ISSN 1756-1841 VOLUME 24 NUMBER 10 2021

International Journal of Rheumatic Diseases

Official journal of the Asia Pacific League of Associations for Rheumatology (APLAR)

WILEY

International Journal of Rheumatic Diseases

Editor-in-Chief

Kevin Pile, *Sydney, Australia*

Senior Editors

Chi-Chiu Mok, *Hong Kong, China*
Debashish Danda, *Vellore, India*
Fereydoun Davatchi, *Tehran, Iran*
Lars Klareskog, *Stockholm, Sweden*
Ramnath Misra, *Lucknow, India*
Zhanguo Li, *Beijing, China*

Associate Editors

Alberta Hoi, *Melbourne, Australia*
Aman Sharma, *Chandigarh, India*
Anand Kumthekar, *New York, USA*
Andrew Harrison, *Wellington, New Zealand*
Anselm Mak, *Singapore*
Atsushi Kawakami, *Nagasaki, Japan*
Benny Samual Eathakkattu Antony, *Hobart, Australia*
Chi-Chen Chang, *Taiwan*
Chin Teck Ng, *Singapore*
Christina Boros, *Adelaide, Australia*
Cho Mar Lwin, *Myanmar*
Dae Hyun Yoo, *Seoul, Korea*
David S. Pisetsky, *Durham, USA*
Dawn Aitken, *Hobart, Australia*
Enrico Tombetti, *London, UK*
Evange Romas, *Melbourne, Australia*
George D. Kitas, *Birmingham, UK*
Gerard Espinosa, *Barcelona, Spain*
Graeme Jones, *Tasmania, Australia*
Haider Mannan, *Sydney, Australia*
Haner Direskeneli, *Istanbul, Turkey*
Ho Ying Chung, *Hong Kong, China*
Ing Soo Lau, *Malaysia*
Ingrid Lundberg, *Stockholm, Sweden*
James Cheng Chung Wei, *Taichung, Taiwan*
Johannes J. Rasker, *Enschede, Netherlands*
Julian Thumboo, *Singapore*
Kanta Kumar, Birmingham, UK
Karina Torralba, *Los Angeles, USA*
Katy Ying Ying Leung, *Singapore*
Keith Lim, *Melbourne, Australia*
Kok Yong Fong, *Singapore*
Lai Shan Tam, *Hong Kong, China*
Latika Gupta, *Lucknow, India*
Lingyun Sun, *Nanjing, China*
Liwei Lu, *Hong Kong, China*
Majda Khoury, *Syria*
Manjari Lahiri, *Singapore*
Marie Feletar, *Melbourne, Australia*
Marwan Adwan, *Jordan*
Maureen Rischmueller, *Adelaide, Australia*
Michael Wiese, *Adelaide, Australia*
Meiying Wang, *China*
Nan Shen, *Shanghai, China*
Nazrul Islam, *Dhaka, Bangladesh*
Nigil Haroon, *Toronto, Canada*
Nina Kello, *New York, USA*
Padmanabha Shenoy, *India*
Paul Bird, *New South Wales, Australia*
Paul Kubler, *Brisbane, Australia*
Paul Wordsworth, *Oxford, UK*
Peter Wong, *Sydney, Australia*
Philip Robinson, *Brisbane, Australia*
Prasanta Padhan, *India*
R Hal Scofield, *Oklahoma, USA*
Ram Pyare Singh, *Los Angeles, USA*
Ram Raj Singh, *Los Angeles, USA*
Robert Lahita, *New Jersey, USA*
Ronald Yip, *Hong Kong, China*
Sam Whittle, *Adelaide, Australia*
Sami Salman, *Baghdad, Iraq*
Sang-Heon Lee, *Seoul, Korea*
Sargunan Sockalingam, *Kuala Lumpur, Malaysia*
Seong-Kyu Kim, *Korea*
Shin-Seok Lee, *Korea*
Sumaira Farman Raja, *Pakistan*
Surjit Singh, Chandigarh, *India*
Syed Atiqul Haq, *Dhaka, Bangladesh*
Tamer Gheita, *Cairo, Egypt*
Tatsuya Atsumi, *Sapporo, Japan*
Temy Mok, *Hong Kong, China*
Tsang Tommy Cheung, *Hong Kong, China*
Tsutomu Takeuchi, *Tokyo, Japan*
Vaidehi Chowdhary, *Rochester, Minnesota, USA*
Vinod Scaria, *New Delhi, India*
VS Negi, *Pondicherry, India*
Wang-Dong Xu, *Luzhou, P.R. China*
Wen-Chan Tsai, *Taiwan*
Worawith Louthrenoo, *Chiang Mai, Thailand*
Yehuda Shoenfeld, *Tel Aviv, Israel*
Yoshiya Tanaka, *Kitakyushu, Japan*
Yuho Kadono, *Japan*

Production Editor

Aishwarya Radhakrishnan (APL@wiley.com)

Editorial Assistant

Lalitha Pari (IJRD.EO@wiley.com)

Past Editors-in-Chief

D Danda, Vellore, India (International Journal of Rheumatic Diseases, 2013–2018)
CS Lau, Hong Kong, China (APLAR Journal of Rheumatology/ International Journal of Rheumatic Diseases, 2004–2012)
PH Feng, Singapore (APLAR Journal of Rheumatology, 1998–2004)
KD Muirden, Australia (APLAR Bulletin)

WILEY

Disclaimer: The Publisher, Asia Pacific League of Associations for Rheumatology and Editors cannot be held responsible for errors or any consequences arising from the use of information contained in this journal; the views and opinions expressed do not necessarily reflect those of the Publisher, Asia Pacific League of Associations for Rheumatology and Editors, neither does the publication of advertisements constitute any endorsement by the Publisher, Asia Pacific League of Associations for Rheumatology and Editors of the products advertised.

International Journal of Rheumatic Diseases @ 2021 Asia Pacific League of Associations for Rheumatology and John Wiley & Sons Australia, Ltd

For submission instructions, subscription and all other information visit http://onlinelibrary.wiley.com/journal/10.1111/(ISSN)1756-185X

View this journal online at wileyonlinelibrary.com/journal/apl

International Journal of Rheumatic Diseases

Volume 24 | Number 10 | October 2021

Contents

Received: 1 July 2021 | Revised: 23 July 2021 | Accepted: 25 July 2021

DOI: 10.1111/1756-185X.14196

EDITORIAL

International Journal of Rheumatic Diseases

WILEY

Online academic community in the Asia-Pacific countries: The paragon of a metamorphic world

1 | INTRODUCTION

There has been a remarkable shift in the ways and means of knowledge exchange in recent times, with an exponential increase in sharing information online while braving widespread lockdowns amid a raging pandemic.[1] The widespread use of social media (SoMe) among the youth (up to 70% in some surveys) opens the case for building an online community for collaborative learning with a global outreach.[2]

Digitalization of medicine has ushered in an era of e-meetings, online mentoring, and e-collaborations, lending a unique enthusiasm and dynamics to an entire generation of scholars.[3-5] Trending scientific information on #MedTwitter and #AcademicTwitter have made the conventional learning models less impactful, especially during the pandemic, which made physical presence an exception to the norm. However, these adaptive measures may be here to stay after the situation returns to normal.[6]

The use of SoMe for learning is notably slower among scholars in the Asia-Pacific region, albeit gaining momentum in recent times.[7,8] Central agencies like APLAR (Asia Pacific League of Associations for Rheumatology) have recorded a total number of 1127 followers on Twitter and 3835 followers on Facebook with a maximum engagement of 1708 people, while BSR (British Society of Rheumatology) has 13.1 k followers on Twitter (as seen in the first quarter of the year 2021). These numbers highlight the importance of increasing awareness about the scholarly use of SoMe among the youth of the Asia-Pacific region.[9] The number of followers may be improved by a charismatic presence; however, the quality and credibility of the content plays a larger role.

Central agencies like APLAR, American College of Rheumatology (ACR), European League Against Rheumatism (EULAR), and so on, hold the potential to be the torchbearers in leading education on SoMe platforms while dispersing information for the lay public. They also may act as the credible sources for reliable engagement with other scholars, practitioners, researchers, allied specialists, allied health professionals, nurse practitioners, and most importantly, patients with chronic diseases. Moreover, an increased presence of academics on such platforms will improve the representation of Asia-Pacific regional experts on a global platform, thus ensuring a holistic approach to shaping global communication and furthering scientific exchange.[10] However, the scholars from the Asia-Pacific countries may potentially face specific limitations in using SoMe.

In this brief, the authors discuss the current landscape of SoMe in the Asia-Pacific and explore solutions to enhance academic engagement on social media platforms (SMPs) for career advancement.

2 | SOCIAL MEDIA FOR EDUCATION

The scholarly use of SMPs includes the collection, dissemination, and promotion of scientific literature and real-time events like conferences and scientific events.[11,12] Facebook is widely used for scientific communications in the Asia-Pacific region while Twitter is seen to have a better hold on the global level.[13-15] This may be due to the open nature of the platform, and the diverse and wide userbase of Twitter which is designed to further professional communications, discussions, and relationships.[16] Therefore, they help enhance the experience of large conferences such as those of ACR and EULAR, enabling quick sifting through content, amplification of breaking news, and highlighting "obscure" sessions that attendees may not be able to get to given the wealth of available content. Dissemination of information using audiovisual aids also helps to get across a large amount of information in a concise manner, allowing for intake of large chunks of information without fatiguing. The pandemic times saw a massive increase in the presence of academic journals on SMPs to reconnect with their reader base and enhance webometrics.[17,18]

SMPs may help to connect with experienced mentors, all over the world, who help to upgrade learning, improve intercommunication and analytical skills of peers in the same field irrespective of their geographical location.[19,20] The EULAR regularly offers e-peer mentoring sessions which are open to rheumatology fellows from all regions. SMPs of central agencies such as APLAR can bust myths to tackle misinformation in brittle times such as now,[21] by deploying their wide reach (Figure 1). A geographically diverse node and hub network of rheumatologists can take the lead in educating young trainees, practitioners, and academics, helping them turn into knowledgeable and skilled practitioners, researchers, and potentially, administrators (Figure 2).

© 2021 Asia Pacific League of Associations for Rheumatology and John Wiley & Sons Australia, Ltd

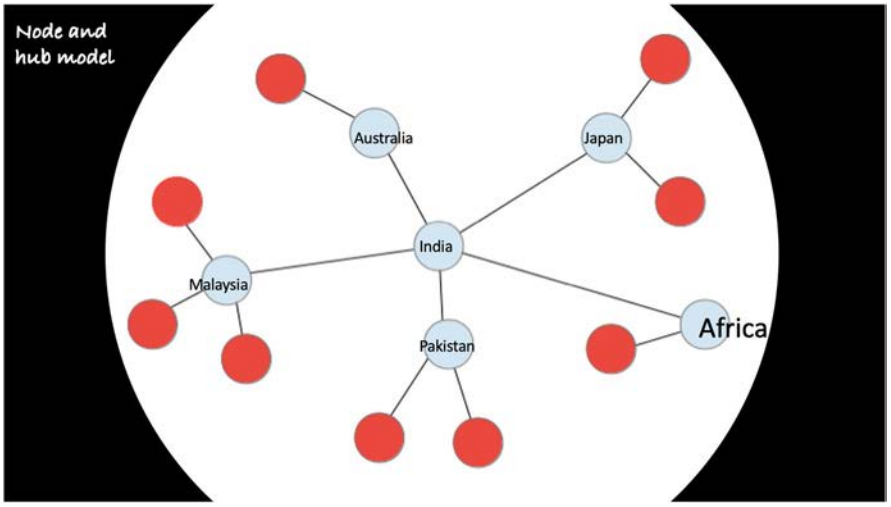

FIGURE 1 Model for a geographically diverse node and hub social media educative network

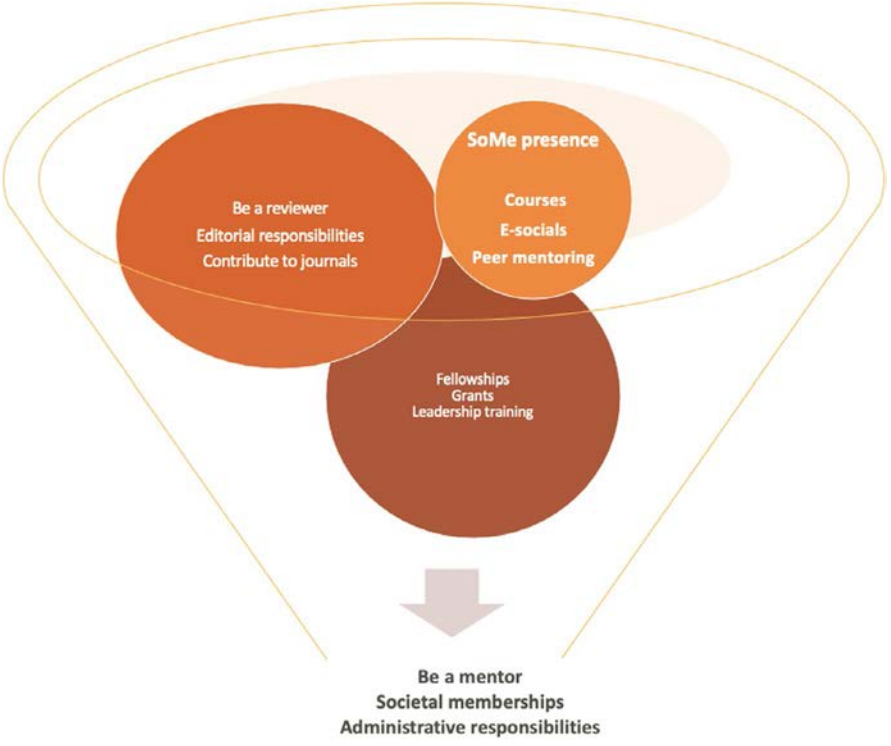

FIGURE 2 FIGURE Social media roadmap for trainee education and career enhancement

3 | SOCIAL MEDIA FOR RESEARCH

Several online tools for research have emerged in recent times, and SMPs assume the central role in reaching out to patients, and colleagues for opinion-based studies.[22,23] Information about open access datasets such as TrinetX were circulated online, as were invitations to join hands for a common rheumatology global alliance for expedited research on the coronavirus disease 2019 (COVID-19) and rheumatic diseases. Movements such as the Plan S and the Open Access Initiative make scientific literature freely available throughout the world.[24] This makes scientific literature accessible to young scholars at no cost and also provides the opportunity to participate in related scientific discussions on SoMe platforms. However, the fee acts a barrier to publish in Open Access Journals and therefore is a mixed blessing.

Citation rates of COVID-19-related papers increased during the COVID-19 pandemic due to the large volume of literature accrued in a short period of time on the subject.[25] However, Altmetric scores assumed a larger role in projecting article visibility, and potential utility for practice, guidelines, and public advice.[26] Infographics used for summarizing research assume a central role in conveying key points in an attempt to communicate better with a wider audience.[27]

SMPs house a large amount of academic information which acts as a haven for the lay public on the lookout for credible sources while dealing with widespread misinformation. However, the potential downside of scientific integrity and authenticity needs to be

guarded.[28] The availability of all information at the click of a button points to the possibility of an infodemic, which the medical fraternity should be wary about. Robust screening systems to allow for calling out misinformation and helping younger professionals identify genuine sources help in the case of an infodemic.

Physicians take to SMPs for patient information, and at times even practice. In India, WhatsApp, due to its wide reach and penetrance, plays an important role in facilitating patient communication with doctors.[29] Further, analysis by researchers of geo-sensed and time-stamped posts helps to identify public discussions on COVID-19 and predict outbreaks in a timely fashion, offering unique insights into the untapped potential of the apparently disorganized information on these platforms.

Technology enthusiasts are exploring the possibility of digital transformation of practice, with an emerging online data bank, and deploying this for artificial intelligence (AI)-based approaches to further medical practice.[30] This may address the gap in physician-patient ratios in developing countries in Asia.

4 | SOCIAL MEDIA IN THE ASIA-PACIFIC REGION

The Asia-Pacific region includes all the countries situated near the western Pacific Ocean, encompassing Central Asia, East Asia, North Asia-Russian Far East, South Asia, Southeast Asia, Central Asia Australasia, Melanesia, Micronesia, and Polynesia. North-East Asia possesses a higher range of internet penetration rate, a stark contrast from South-West Asia.[31] The countries in the Asia-Pacific region are highly populous and have shown a sharp increase in SoMe presence, especially in China, Indonesia, India, and Japan.[32] Facebook is widely used in this region followed by regional SoMe platforms like WeChat, Sina Weibo, Line, and TikTok.[32] Trend shifts in the use of different SoMe platforms do occur as seen by the sudden boom in the use of TikTok in South-East Asia. These trends must be followed to stay relevant among the constantly changing SoMe dynamics. Twitter has very few users from this region as compared to the rest of the world, even though it is a common platform for scientific discussions.[33]

Some countries in this region practice strict regulations and have temporary restrictions on SoMe use which act as an impediment to sustained access to SoMe.[34,35] China constitutes a large percentage of the rheumatology workforce in Asia. SoMe platforms like QQ, WeChat and Sina Weibo are more popular in China.[34] Therefore, platforms like Twitter where scholarly conversations take place on a global platform, perceive the absence of the participation of physicians from China. Additionally, scholars from the Asia-Pacific region have fewer international publications and presence as compared to the developed nations, although these numbers are consistently increasing.[36,37] Moreover, South-Asian journals have a poor social media presence on a global scale, reducing the visibility of their content causing poor publication standards and indexing.[38] This puts the students of the Asia-Pacific region at an inherent disadvantage due to their under-representation on a global scale.

English being the most common medium of conversation on SMPs, students with English as their second language face communication difficulties as they mostly use English secondarily to their native languages.[39] The availability of the translate tool on Twitter has furthered interaction on the platform for non-English speaking (or those with English as a second language) scholars. Available machine translators like Google translator, Yandex, and Bing Translator also facilitate the participation of scholars with poor English fluency. Google translator has the widest range of interpretation, enclosing 107 languages, followed by Yandex and Bing Translator.[40]

Cultural influences may be inhibitive to a free opinion or freedom of expression, and a potential deterrent to the habit of free will and voicing one's thoughts on an open platform.[41] There is a potential risk of miscommunications highlighting the need for a moderator and set of rules to maintain harmony. Moreover, professional avatars may differ from personal handlers, and it is imperative to keep professional accounts clean, follow cyber laws and follow the unsaid rules of the SoMe game. Places like Twitter may have a rapidly flammable environment, making it important to deal with sensitive issues professionally. Misinformation, incivility, cyberbullying, are unwelcome. Moreover, young scholars interacting with professional handlers of organizations or journals may need to be aware of professional ethics and the repercussions of controversial and non-evidence-based opinions. Thus, it is imperative to train scholars and practitioners to diligently use SMPs for the best professional growth and healthy networking. Lastly, the vast sea of social media offers innumerable possibilities, including entertainment, catharsis via art forms, and non-academic writing like poems, cartoons, and viewpoints.[42,43]

The Asia-Pacific region nurtures enthusiastic youth, that has the potential to add to the global academic community by their novel ideas. Enhanced participation of the youth in global scientific exchange may also further individual careers, as well as scientific developments, in respective countries.[44] Engagement of the youth in the research community under the supervision of experienced allies can help them attain full potential.[45]

5 | ROLE OF CENTRAL AGENCIES

Central agencies or professional societies encourage medical professionals and individual members by sponsoring their scientific studies and provide avenues for networking and enhancing scientific knowledge. Events held by the agencies act as opportunities to exhibit leadership skills and contribute to the scientific literature already available. This eventually benefits society at large.[46] Various central societies like ILAR (International League of Associations for Rheumatology), EULAR, PANLAR (Panamerican League of Associations for Rheumatology), AFLAR (African League of Associations for Rheumatology), ACR, and BSR provide a wide array of opportunities for their members.

APLAR is a central agency started in 1963 by 4 nations, Australia, India, Japan, and New Zealand, and is affiliated with ILAR with currently 34 members.[47] APLAR helps to consolidate and propagate rheumatology endeavors in the Asia-Pacific region by providing state-of-the-art care to patients with arthritis and other rheumatic diseases and helping APLAR members with professional development, increasing the understanding and awareness of rheumatic diseases, and promulgating scientific research in the field of rheumatology.[48] It has also helped nurture young scholars with education grants, rewarding ideas, and interest groups under the guidance of experienced mentors. This facilitates the building of an efficient and capable academic community. The online courses, educational projects, and training modules with supportive materials have helped members to build a much-needed medical academic community.[49]

APLAR has SoMe profiles on Twitter and Facebook. The Facebook profile showed an increase in followers by almost 3000 in 3 years. The age of their audience ranges between 25-34 years with 61% males and 38% females. Their largest audience is in Dhaka, Bangladesh, followed by Kathmandu, Nepal with a large majority of them accessing the information in English. The information shared on their profile reaches vast audiences residing in Taiwan, Bangkok, Singapore, Iraq, and South Korea. They also have a COVID updates page with 479 followers.

To improve its outreach APLAR should expand its presence to other SMPs like Instagram and YouTube to connect with a diverse audience. Publishing newsletters, conducting certification courses on social media conduct, like the EULAR Twitter course, and having mentorship programs, allows for building of a vast online community. Young medical students can be involved by allowing them to send in small write-ups, poems, or animations for publishing. Images, including infographics or access to articles, videos with post-publication scientific discussions, and podcasts with mentor-mentee discussions, or young rheumatologist opinions, may help cater to the needs of the vast audience.

Virtual congresses and online learning platforms are not only financially feasible but also have a wider impact showing a huge shift from yesteryear's physical forums. Extracting from the success of specialist trainings held by EULAR, APLAR too can provide for such curricula to improve the practice of rheumatology in the countries of the Asia-Pacific region. However, the impact of such curricula will be seen if there are no bottlenecks in joining central agencies. Intermediate agencies like member national organizations (MNO) play an important role in this sphere. An independent researcher should be allowed to obtain an APLAR membership online without the interference of a MNO, if they fulfill the requirements. This calls for a robust screening process to eliminate false personas and negative elements.

Central agencies can pave the way for the increased participation of young scholars in the medical fraternity and provide them early exposure to the vast global medical community. The concept of intelligent tutoring systems and personalized learning platforms will capture a large component of the Asia-Pacific academic community. This will help ensure that young entrants in the field are updated and have a broad understanding of the rheumatology community.

6 | CONCLUSIONS

The use of SoMe in scholarly communication is the need of the hour with enriching global discussions taking place. Participation of the Asia-Pacific countries in such discussions will enhance the available scientific knowledge and allow for globally uniform healthcare. They will also lead to the formation of strong and sustaining social relationships and eventually help with improving healthcare practice throughout the world. This brief calls to action young scholars to join academic discussions on SMPs, especially Twitter, and identify the need for scientific representation and contribution on a global scale. The improved global scientific contribution will lead to the betterment of rheumatology in particular, but also medicine and humanity in general.

AUTHOR CONTRIBUTIONS

PSG, SS and LG: preparation of the first draft. HA, IL, GH, PW, CYK, BS, DD and AUH: revision of manuscript and critical and intellectual inputs.

KEYWORDS

access to information, communication, developing countries, medicine, social media, youth

Prithvi Sanjeevkumar Gaur[1]
Sreoshy Saha[2]
Himantha Atukorale[3]
Irwin Lim[4]
Cheng Yew Kuang[5]
Priscilla Wong[6]
Ghita Harifi[7]
Babur Salim[8]
Debashish Danda[9]
Atiq Ul Haq[10]
Latika Gupta[11]

[1]*Smt. Kashibai Navale Medical College and General Hospital, Pune, India*
[2]*Mymensingh Medical College, Mymensingh, Bangladesh*
[3]*Ministry of Health, Colombo, Sri Lanka*
[4]*BJC Health, Sydney, NSW, Australia*
[5]*Allergy, Arthritis and Rheumatology Clinic, Farrer Park Hospital, Singapore City, Singapore*
[6]*Prince of Wales Hospital, Hong Kong City, Hong Kong*
[7]*Dr. Humeira Badsha Medical Center, Dubai, United Arab Emirates*
[8]*Fauji Foundation Hospital Rawalpindi, Rawalpindi, Pakistan*
[9]*Department of Rheumatology and Clinical Immunology,*

Christian Medical College Hospital, Vellore, India
[10]*Department of Rheumatology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh*
[11]*Department of Clinical Immunology and Rheumatology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India*

Correspondence
Latika Gupta, Department of Clinical Immunology and Rheumatology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India.
Email: drlatikagupta@gmail.com

ORCID

Babur Salim https://orcid.org/0000-0001-8430-9299
Debashish Danda https://orcid.org/0000-0002-2121-0942
Atiq Ul Haq https://orcid.org/0000-0003-4154-7283
Latika Gupta https://orcid.org/0000-0003-2753-2990

REFERENCES

1. Goel A, Gupta L. Social media in the times of COVID-19. *J Clin Rheumatol*. 2020;26(6):220-223. https://doi.org/10.1097/RHU.0000000000001508
2. Guraya SY. The usage of social networking sites by medical students for educational purposes: a meta-analysis and systematic review. *N Am J Med Sci*. 2016;8(7):268-278. https://doi.org/10.4103/1947-2714.187131
3. Paul J, Jefferson F. A comparative analysis of student performance in an online vs. face-to-face environmental science course from 2009 to 2016. *Front Comput Sci*. 2009;2019(1):7. https://doi.org/10.3389/fcomp.2019.00007
4. Ansari JAN, Khan NA. Exploring the role of social media in collaborative learning the new domain of learning. *Smart Learn Environ*. 2020;7:9. https://doi.org/10.1186/s40561-020-00118-7
5. Nye A. Building an online academic learning community among undergraduate students. *Distance Educ*. 2015;36(1):115-128. https://doi.org/10.1080/01587919.2015.1019969
6. Veletsianos G, Johnson N, Belikov O. Academics' social media use over time is associated with individual, relational, cultural and political factors. *Br J Educ Tech*. 2019;50(4):1713-1728. https://doi.org/10.1111/bjet.12788
7. Hung D, Chen D-T. Online learning and information technology in the Asia-Pacific region: perspectives, issues, and divides. *Educ Tech*. 2003;43(3):5-9.
8. Sinha M, Agarwal V, Gupta L. Human touch in digital education—a solution. *Clin Rheumatol*. 2020;39:3897-3898. https://doi.org/10.1007/s10067-020-05448-y
9. Ahmed S, Gupta L. Perception about social media use by rheumatology journals: survey among the attendees of IRACON 2019. *Indian J Rheumatol*. 2020;15:171-174. https://doi.org/10.4103/injr.injr_15_20
10. Matthews KRW, Yang E, Lewis SW, Vaidyanathan BR, Gorman M. International scientific collaborative activities and barriers to them in eight societies. *Account Res*. 2020;27(8):477-495.
11. Gu F, Widén-Wulff G. Scholarly communication and possible changes in the context of social media: a Finnish case study. *Electron Libr*. 2011;29(6):762-776.
12. Haldule S, Davalbhakta S, Agarwal V, Gupta L, Agarwal V. Post-publication promotion in rheumatology: a survey focusing on social media. *Rheumatol Int*. 2020;40:1865-1872. https://doi.org/10.1007/s00296-020-04700-7
13. Díaz-Faes AA, Bowman TD, Costas R. Towards a second generation of 'social media metrics': characterizing Twitter communities of attention around science. *PLoS One*. 2019;14(5):e0216408. https://doi.org/10.1371/journal.pone.0216408
14. Walter S, Lörcher I, Brüggemann M. Scientific networks on Twitter: analyzing scientists' interactions in the climate change debate. *Public Underst Sci*. 2019;28(6):696-712. https://doi.org/10.1177/0963662519844131
15. Joinson AN. *Looking at, Looking Up or Keeping Up With People? Motives and Use of Facebook*. Proceedings of the SIGCHI Conference on Human Factors in Computing Systems. Association for Computing Machinery; 2008:1027-1036. https://doi.org/10.1145/1357054.1357213
16. Knight CG, Kaye LK. To tweet or not to tweet? A comparison of academics' and students' usage of Twitter in academic contexts. *Innov Educ Teach Int*. 2016;53(2):145-155. https://doi.org/10.1080/14703297.2014.928229
17. Wakefield PMA, Loken PB, Hornik PRC. Use of mass media campaigns to change health behaviour. *Lancet*. 2010;376(9748):1261-1271. https://doi.org/10.1016/S0140-6736(10)60809-4
18. Ahmed S, Gupta L. Social media for medical journals. *Cent Asian J Med Hypotheses Ethics*. 2020;1(1):26-32. https://doi.org/10.47316/cajmhe.2020.1.1.04
19. Gibson C, Gibbs L. Social media experiments: scholarly practice and collegiality. *Dialogues Hum Geogr*. 2013;3(1):87-91.
20. Bhatt NR, Czarniecki SW, Borgmann H, et al. A systematic review of the use of social media for dissemination of clinical practice guidelines. *Eur Urol Focus*. 2020; S2405-4569(20)30292-3.
21. Gupta L, Gasparyan AY, Misra DP, Agarwal V, Zimba O, Yessirkepov M. Information and misinformation on COVID-19: a cross-sectional survey study. *J Korean Med Sci*. 2020;35(27):e256. https://doi.org/10.3346/jkms.2020.35.e256
22. Gupta L, Lilleker JB, Agarwal V, Chinoy H, Aggarwal R. COVID-19 and myositis - unique challenges for patients. *Rheumatology*. 2021;60(2):907-910. https://doi.org/10.1093/rheumatology/keaa610
23. Gupta L, Misra DP, Agarwal V, Balan S, Agarwal V. Management of rheumatic diseases in the time of covid-19 pandemic: perspectives of rheumatology practitioners from India. *Ann Rheum Dis*. 2021;80(1):e1. https://doi.org/10.1136/annrheumdis-2020-217509
24. Gasparyan AY, Yessirkepov M, Voronov AA, Koroleva AM, Kitas GD. Comprehensive approach to open access publishing: platforms and tools. *J Korean Med Sci*. 2019;34(27):e184. https://doi.org/10.3346/jkms.2019.34.e184
25. Gupta L, Gadiwala SF. Coping with the Coronavirus Disease-2019 pandemic: a giant leap towards digital transformation in academic research. *Indian J Rheumatol*. 2021;16:123-126. https://doi.org/10.4103/injr.injr_251_20
26. Hammarfelt B. Using altmetrics for assessing research impact in the humanities. *Scientometrics*. 2014;101:1419-1430. https://doi.org/10.1007/s11192-014-1261-3
27. Huang S, Martin LJ, Yeh CH, et al. The effect of an infographic promotion on research dissemination and readership: a randomized controlled trial. *CJEM*. 2018;20(6):826-833. https://doi.org/10.1017/cem.2018.436
28. Gaur PS, Gupta L. Changing research paradigm in the face of a global pandemic: foreseeable impact and adaptive measures in academic research in the future. *Proc Shevchenko Sci Soc Med Sci*. 2020;62(2):63-68.
29. Perrone G, Zerbo S, Bilotta C, Malta G, Argo A. Telemedicine during Covid-19 pandemic: advantage or critical issue? *Med Leg J*. 2020;88(2):76-77. https://doi.org/10.1177/0025817220926926

30. Bohr A, Memarzadeh K. The rise of artificial intelligence in healthcare applications. In: *Artificial Intelligence in Healthcare*. 2020;25-60: https://doi.org/10.1016/B978-0-12-818438-7.00002-2
31. Active social media user penetration in Asia Pacific as of January 2021, by country. https://www.statista.com/statistics/255235/active-social-media-penetration-in-asian-countries/. Accessed May 2021. Updated May 2021.
32. Social media in Asia Pacific [Internet]. Statista. https://www.statista.com/topics/6606/social-media-in-asia-pacific/. Accessed May 2021. Updated Sep 2020.
33. Leading countries based on number of Twitter users as of January 2021. https://www.statista.com/statistics/242606/number-of-active-twitter-users-in-selected-countries/. Accessed May 2021. Updated Feb 2021.
34. Gaur PS, Gupta L. Social media for scholarly communication in Central Asia and its neighbouring countries. *J Korean Med Sci*. 2021;36(4):e36. https://doi.org/10.3346/jkms.2021.36.e36
35. Shen F, Tsui L. Public opinion toward internet freedom in Asia: a survey of internet users from 11 jurisdictions. 2016. Berkman Center Research Publication No. 2016-8. Available at SSRN: http://dx.doi.org/10.2139/ssrn.2773802
36. Shin JC, Harman G. New challenges for higher education: global and Asia-Pacific perspectives. *Asia Pacific Educ Rev*. 2009;10(1):1-13. https://doi.org/10.1007/s12564-009-9011-6
37. Tunger D, Haustein S. Does an Asia-Pacific research area exist from a bibliometric point of view? Canada Research Chair on the Transformations of Scholarly. *Communication*. 2010;279-281.
38. Akhtar MI, Karam K, Khan FA. Representation of South Asian countries in five high-impact anesthesia journals. *Saudi J Anaesth*. 2018;12(3):379-383. https://doi.org/10.4103/sja.SJA_635_17
39. Nguyen TC. Challenges of learning English in Australia towards students coming from selected Southeast Asian countries: Vietnam, Thailand and Indonesia. *Int Educ Stud*. 2011;4(1):13.
40. Teh H, Ng YS, Foo C. The efficacy of machine translation tools in the translation of technical and non-technical texts: perceptions of undergraduate student users. *Langlit*. 2016;3(2).
41. Macnamara J, Zerfass A, Adi A, Lwin MO. Capabilities of PR professionals for key activities lag: Asia-Pacific study shows theory and practice gaps. *Public Relat Rev*. 2018;44(5):704-716. https://doi.org/10.1016/j.pubrev.2018.10.010
42. Saha S, Bhatia A, Gupta L. Perspectives on poetry in rheumatology. *Indian J Rheumatol*. 2021; https://www.indianjrheumatol.com/preprintarticle.asp?id=315680
43. Wolters FJ, Wijnen-Meijer M. The role of poetry and prose in medical education: the pen as mighty as the scalpel? *Perspect Med Educ*. 2012;1(1):43-50. https://doi.org/10.1007/s40037-012-0008-1
44. Roger C. Youth participation in society. *AEJ*. 2008;5:469-477. https://doi.org/10.1007/s10308-007-0152-0
45. Powers JL, Tiffany JS. Engaging youth in participatory research and evaluation. *J Public Health Manag Pract*. 2006;12:S79-S87. https://doi.org/10.1097/00124784-200611001-00015
46. Beck DE. Role of professional societies in career development. *Clin Colon Rectal Surg*. 2011;24(2):106-108. https://doi.org/10.1055/s-0031-1278406
47. Asia Pacific League Of Associations For Rheumatology APLAR. https://web.archive.org/web/20161101041413/http://asian.cmesociety.org/south-africa/chiang-mai/asia-pacific-league-of-associations-for-rheumatology-aplar. Accessed May 2021.
48. About APLAR. https://www.aplar.org/about_page/about-aplar/. Accessed May 2021.
49. Education-APLAR. https://www.aplar.org/education/. Accessed May 2021.

How to cite this article: Gaur PS, Saha S, Atukorale H, et al. Online academic community in the Asia-Pacific countries: The paragon of a metamorphic world. *Int J Rheum Dis*. 2021;24:1229–1234. https://doi.org/10.1111/1756-185X.14196

Received: 17 May 2021 | Revised: 26 June 2021 | Accepted: 12 July 2021

DOI: 10.1111/1756-185X.14184

INVITED REVIEW

International Journal of Rheumatic Diseases

WILEY

Will rheumatologists ever pick up the arthroscope again?

Robert W. Ike[1] | Kenneth C. Kalunian[2]

[1]Department of Internal Medicine, Division of Rheumatology, University of Michigan Health System, Ann Arbor, MI, USA

[2]Department of Medicine, Division of Rheumatology, Allergy and Immunology, University of California at San Diego, San Diego, CA, USA

Correspondence
Robert W. Ike, Department of Internal Medicine, Division of Rheumatology, University of Michigan Health System, 1611 Harbal Dr, Ann Arbor MI, USA.
Email: scopydoc52@yahoo.com

Abstract

Conditions prompting physicians and surgeons first adapting endoscopes to peer into joints were mainly the sort of synovial conditions that would concern today's rheumatologists. Rheumatologists were among the pre-World War II pioneers developing and documenting arthroscopy. The post-War father of modern arthroscopy, Watanabe, found rheumatologists among his early students, who took back the technique to their home countries, teaching orthopedists and rheumatologists alike. Rheumatologists described and analyzed the intra-articular features of their common diseases in the '60s and '70s. A groundswell of interest from academic rheumatologists in adapting arthroscopy grew considerably in the '90s with development of "needle scopes" that could be used in an office setting. Rheumatologists helped conduct the very trials the findings of which reduced demand for their arthroscopic services by questioning the efficacy of arthroscopic debridement in osteoarthritis (OA) and also developing biological compounds that greatly reduced the call for any resective intervention in inflammatory arthropathies. The arthroscope has proven an excellent tool for viewing and sampling synovium and continues to serve this purpose at several international research centers. While cartilage is now imaged mainly by magnetic resonance imaging, some OA features – such as a high prevalence of visible calcinosis – beg further arthroscopy-directed investigation. A new generation of "needle scopes" with far superior optics awaits future investigators, should they develop interest.

KEYWORDS

arthroscopy, calcinosis, lavage, synovial biopsy, synovium

1 | INTRODUCTION

We authors were the first American rheumatologists to learn arthroscopy from another rheumatologist and apply it exclusively to arthritis patients, including operative interventions. Our mentor Bill Arnold learned the technique in a cooperative venture with orthopedist David Stulberg of Northwestern University beginning in '81, then taught RWI in '85 and KCK in '88, who each subsequently worked with orthopedists before embarking on independent practice at their home institutions. We appreciated from the beginning the tremendous potential for arthroscopy as a tool not only for direct therapy, but for both clinical and research assessment. We've seen the surge of interest among rheumatologists fade into the new century, with arthroscopy employed as a research tool in only a handful of institutions, all outside the USA. Tools for basic assessment of the synovium have grown much more powerful, and arthroscopes themselves have been transformed into tiny inexpensive items ready

We dedicate this work to our mentor, Bill Arnold, who showed us the way.

© 2021 Asia Pacific League of Associations for Rheumatology and John Wiley & Sons Australia, Ltd.

for in-office use. We hypothesize that this combination of factors should be leading to another surge of interest in arthroscopy among rheumatologists. To describe the arc that got us here, and where we might go next, we undertook this review.

2 | SEARCH STRATEGY

We searched literature employing PubMed, Scopus, and Web of Science using search terms "arthroscopy AND rheumatology" plus "arthroscopy AND (synovitis OR synovium)" to find references to supplement our own personal libraries and recollections.

3 | BEGINNINGS

Rheumatologists have had an interest in arthroscopy since its inception. Most of the conditions which the early arthroscopists examined were chronic synovial conditions of the sort that modern rheumatologists would nowadays have a role in managing.[1,2] Those orthopedists who used the scope to evaluate internal derangements, which would make arthroscopy so popular with later generations of orthopedists, eventually abandoned the technique for lack of interest from their peers.[1,3] The first book on arthroscopy was written by German rheumatologist Ernst Vaubel.[4]

World War II paused all investigation into arthroscopy. After the War, Makei Watanabe refined the arthroscope, documented and recorded (with drawing, camera and movie) mechanical and synovial conditions of the knee, and performed the first resective procedures under arthroscopic guidance.[5] Among his many students were rheumatologists from several countries, who took their skills home and trained others.[6-10] Rheumatologists were the main arthroscopists in France[11] and Cuba[12] into the 21st century. Watanabe's most famous student, Canadian orthopedist Bob Jackson, became the prime developer of arthroscopic surgery in North America.[13] He welcomed interest from rheumatologists and helped train Roy Altman (University of Miami) in the '60s, plus Joe Combs (Mayo) and Nathan Wei (Frederick MD) in the '80s.

British,[14,15] Spanish,[16] French,[10] American,[17] Canadian,[18] Mexican[6] and Australian[19] rheumatologists described the arthroscopic features of the chronic conditions they were facing in the '60s and '70s. A Watanabe-trained rheumatologist in Mexico City became the first to use an arthroscope to judge treatment effects, assessing the effect of azathioprine on rheumatoid synovitis.[20] Fiberoptic illumination of the arthroscopic view, replacement of the eyeball with a video camera for capture and recording of that view,[21] and the suction-assisted motorized shaver made arthroscopy a less dangerous and demanding procedure.[22] Explosion of growth in orthopedics was accompanied by growing interest among rheumatologists. Bill Kelley, in his 1987 presidential address to the American Rheumatism Association (ARA: now American College of Rheumatology) outlining ways forward to enhance what he saw as weak interest in rheumatology among students and trainees, stated, "I believe we need to expand the specialty of rheumatology to cover some of the peripheral areas which now are largely ignored and sometimes poorly handled. This would include *…the use of certain technical procedures which are appropriate to our specialty*" (our emphasis).[23] The ARA Board of Directors in June '86 approved guidelines for performance of arthroscopy by rheumatologists.[24] Arthroscopy Association of North America (AANA) guidelines were not published till '93[25] but did include a path for non-orthopedists to perform non-operative arthroscopy and were published in every issue of *Arthroscopy* until January 2019.

Students of the synovium assessed further basic appearances of rheumatologic conditions,[26,27] made correlations between macroscopic and microscopic appearances,[28] including the development of grading scales,[29,30] and described unique characteristics of certain conditions, such as psoriatic arthritis,[31] Behçet's,[32] sarcoidosis,[33] polymyalgia rheumatica,[34] familial Mediterranean fever,[35] and amyloidosis revealing myeloma.[36] Advances in arthroscopic technology that led the procedure out of the operating room into the procedure suite and office made evident the role the arthroscope could play in assessment of synovial disorders. Arthroscopic assessment proved critical in judgment of responses to treatment, both systemic[37,38] and intra-articular[37,39-41] and in further basic investigations of the synovium in various disorders,[42-44] including comparison with imaging modalities.[45,46]

Much of the volume driving use of arthroscopy by rheumatologists in the '80s and '90s concerned use in knee osteoarthritis (OA). Although some basic assessment studies were conducted,[47-49] the major focus was on treatment. The first of many controlled trials questioning the utility of arthroscopy in knee OA came from rheumatologists,[50] as did investigations showing the joint lavage so often ascribed to arthritis improvement following arthroscopy was no more than a placebo effect.[51] Additional investigations sowing the same doubt quelled any use of arthroscopy in OA by rheumatologists but have not yet completely permeated orthopedic practice.[52] Use of arthroscopy in knee OA has shown that magnetic resonance imaging (MRI) assessment is equivalent to direct assessment,[53] and that directed physical exam can predict cartilage abnormalities disclosed at arthroscopy.[54]

4 | THE 21ST CENTURY

In a frank turn-of-the-century discussion of the skills a rheumatologist might possess to face the future, arthroscopy was mentioned at some length.[55] Yet, use of arthroscopy faded among American rheumatologists. RWI did his last case in '01, Bill Arnold in '03 and KCK in '09.[56] However, the new millennium saw an explosion of publications from European and Australian centers using the arthroscope to study synovium, mainly of the idiopathic inflammatory arthropathies. Progress was enhanced by development of mini-arthroscopes capable of examining small joints,[57] establishment of systems to score the macroscopic synovial appearance,[58] and appreciation of the variability of synovial characteristics within any joint,[59] and efficient methods of assessing synovial tissue.[60]

5 | SYNOVIAL DISORDERS

Macroscopic,[61-66] microscopic,[67-73] and molecular[74-82] features of synovium were characterized, with a particular interest in early disease states,[83-96] including pre-clinical[97-100] and even normal synovium.[101] Differences between various disease states were discerned.[102-116] The arthroscope was used extensively to assess effects of various treatments, both intra-articular[117] and systemic.[56,118-159] While orthopedists focused on arthroscopy in infectious arthritis as a treatment modality,[160] rheumatologists utilized the arthroscope to diagnose and monitor Whipples' disease[161] and to characterize features of patients with parvovirus B19 in their synovium.[162]

6 | OA

While use of the arthroscope to treat OA fell out of favor early in the century, it was used to characterize synovium[163,164] and cartilage,[163] including correlation with MRI findings.[164] It was shown that a Jamshidi needle can be applied to sample cartilage at arthroscopy for outcome studies,[165] and that calcinosis is a remarkably prevalent arthroscopic finding in knee OA, even absent radiographic chondrocalcinosis.[166] Synovitis was identified as predictive of cartilage loss.[167] Grading systems for cartilage damage were validated.[168] Two trials comparing intra-articular hyaluronates with corticosteroids demonstrated at arthroscopy that the 2 compounds had equivalent effects on synovitis,[169,170] while progression of cartilage damage was less in hyaluronate-treated knees.[170] A report from Bulgaria described positive effects of arthroscopic debridement and washout in knee OA 2 years after publication of results from controlled trials discrediting these interventions.[171] A recent commentary described positive findings regarding joint washout appearing since the trials which seemingly discredited the procedure, suggesting that washout should be reconsidered as a treatment modality for knee OA.[172] A recent report describing isolation from arthroscopic washout fluid of mesenchymal stem cells that can be encapsulated in a cross-linked hydrogel which can then generate new cartilage matrix in an animal model suggests the therapeutic effect of joint washout may someday extend beyond the immediate effect on the joint.[173]

7 | IMAGING

Arthroscopy served as a gold standard to which MRI[174,175] and ultrasound[176-179] were compared, including descriptions of simultaneous use of ultrasound and arthroscopy to assess synovitis.[180,181] An example of another arthroscopy-directed assessment that cannot be duplicated by an ultrasound-guided procedure, the oxygenation state of the synovial membrane was measured using the Lidox probe, developed to assess brain tissue.[72,152,156,182-184]

TABLE 1 Institutions where a rheumatologist is performing arthroscopy

City	Institution	Arthroscopist	Chief of section	Recent reference(s)	Accepting trainees?	Email
Adelaide	Flinders Medical Centre	Mihir D Wechalekar	Michael Shanahan	75,97	Yes	Mihir.Wechalekar@sa.gov.au
Amsterdam	Amsterdam University Medical Center	Marleen van de Sande	Sander Tas	101	Yes	s.w.tas@amsterdamumc.nl
Barcelona	Hospital Clinic and IDIBAPS	Juan D Cañete	José Alfredo Gómez Puerta	116,117	Yes	JCANETE@clinic.cat
Dublin	St. Vincent's Hospital	Doug Veale	Gerry Wilson	83,192,214	Yes	Douglas.veale@ucd.ie
Leeds	Leeds Institute Rheumatic and Musculoskeletal Medicine University Leeds	Ahmed Zayat* *left Leeds April 2020	Paul Emery		Yes	P.Emery@leeds.ac.uk
Lisbon	Hospital da Santa Maria, CHULN, Instituto de Medicina Molecular Universidade de Lisboa	Elsa Vieira-Sousa	João Eurico Cabral da Fonseca	188-190	Yes	Elsa-sousa@hotmail.com
Louvain	Cliniques Universitaires Saint-Luc Université catholique de Louvain	Adrien Nzeusseu Toukap	Frédéric Houssiau		No	Adrien.Nzeusseu@uclouvain.be
Milan	Niguarda Ca' Granda Hospital	Oscar Masimilliano Epis		183	No	oscar.epis@ospedaleniguarda.it
New Delhi	Army Hospital (Research and Referral) Delhi Cantt	Ved Chaturvedi	Lalit Duggal		No	Ved.chaturvedi@gmail.com
Stockholm	Karolinska Hospital	Erik Af Klint	Marie Wahren-Herlenius		No	erik.af.klint@ki.se

8 | CURRENT STATUS OF INVESTIGATION OF SYNOVIUM

Use of arthroscopy in investigation of synovial disorders has persisted in several international centers (Table 1). While ultrasound-directed biopsy has become popular for obtaining synovium for study,[185] a retrospective review found that patient-related outcomes were no worse following arthroscopic biopsy than the simpler ultrasound-guided procedure.[186] A multicenter retrospective analysis evaluating performance of blind, ultrasound-guided and arthroscopic synovial biopsy techniques in patients with inflammatory arthritis found the amount and quality of tissue procured under ultrasound was as satisfactory as that from arthroscopy, although no small joints were arthroscoped and sublining macrophage number – a marker for the synovial lining layer and thus an indicator of the quality of the specimen – was greater in arthroscopy samples[187] Add to this the capabilities of arthroscopy to provide a larger volume of tissue, assess macroscopic characteristics of tissue, and obtain tissue from joint areas not accessible from ultrasound, and the attractions of arthroscopy become obvious, judged the "gold standard" for synovial biopsy by a panel convened to assess biopsy procedures.[188] Veale, one of the pioneers of modern rheumatologic arthroscopy in Europe, recently re-emphasized the critical role the arthroscope plays in investigations of the synovium.[189] Synovial biopsies and their interpretation will also be augmented by increased use and would evolve the field of synovial histopathology as well. And arthroscopic biopsy may not be without benefit to the patient, with the washout accompanying the procedure conferring benefit,[190] with larger the volume the better,[191] especially if capped with a corticosteroid injection.[192]

While blind, closed synovial biopsy has been possible since the '50s, the procedure never was widely applied.[193] Ultrasound-guided synovial biopsy has become very popular, drawing in many former rheumatologist-arthroscopists. Access is possible in a clinic room, and no operating room politics are involved. However, without being able to visualize the tissue being sampled or obtain fairly large volumes of tissue from such areas, ultrasound-guided biopsy can hardly be considered a comparable substitute for an arthroscopic biopsy. Further, such critical areas in the joint where the synovium may have an important relationship with intra-articular structures, such as the meniscus, the cruciate ligament, and the cartilage-pannus junction[194] are simply out of the reach of any ultrasound-guided procedure.

Chaturvedi et al. recently posited that the very terminology rheumatologists use in describing their use of arthroscopy may be a hindrance to wider acceptance by peers, patients, other physicians and surgeons, and the general public.[195] He proposed we call what we do "medical arthroscopy" to distinguish it from the surgical and operative interventions favored by orthopedists and still perceived by some who wonder what we're doing, and why (Table 2). Moving the procedure fully out of the operating room hasn't been enough, it seems. Mundane administrative factors can impair use of arthroscopy by rheumatologists. For example, while in the US rheumatologists and orthopedists employ the same CPT (Current Procedural Terminology) codes when billing for arthroscopic procedures, in Australia there is an item number for orthopedic procedures associated with renumeration whereas there is no such item number for "medical arthroscopy" and therefore no funding for the procedure.

9 | NEW ARTHROSCOPES

Technological advances in arthroscopy have produced a new generation of "scopes" even more suited to the office environment than their predecessors (Figure 1).[196] Each has combined small size with modern image processing power of the sort that has made your cell phone camera the equivalent of an SLR. The old dark blurry needle scope images of the '90s have been replaced with images worthy of a 4.0 mm glass lens operating room scope. The images are projected to the equivalent of a tablet, so the whole unit is much more compact and much cheaper than an old office unit or operating room setup. These "scopes" are primarily promoted as diagnostic instruments, although one of the manufacturers has developed a line of hand-operated and motorized instruments for tissue resection suitable for use with the new small scope.[197] These arthroscopes beg to be deployed in rheumatology offices, but the interest has yet to develop. Orthopedists are taking notice.[198]

10 | WAYS FORWARD

It has recently been written that orthopedists "are falling out of love with arthroscopy",[199] as commonly performed arthroscopic surgical procedures fall victim to the scrutiny of prospective controlled trials. Use of arthroscopic surgery is truly falling off.[200]

TABLE 2 Summary of indications for and benefits of medical arthroscopy (from reference 195, with permission)

Indication for arthroscopy	Benefits of arthroscopy
Does the patient have synovial inflammation?	Distinguishing inflammatory arthritis, eg, psoriatic arthritis from osteoarthritis. Investigation of persistent swelling of one joint with otherwise well-controlled inflammatory arthritis
What is the etiology of synovial inflammation?	Diagnostic histopathology: sarcoidosis, crystal arthritis, atypical infections, eg, mycobacterial, fungal, parasitic
Research	Using histopathologic features to stratify therapeutic choice, eg, use of rituximab in rheumatoid arthritis

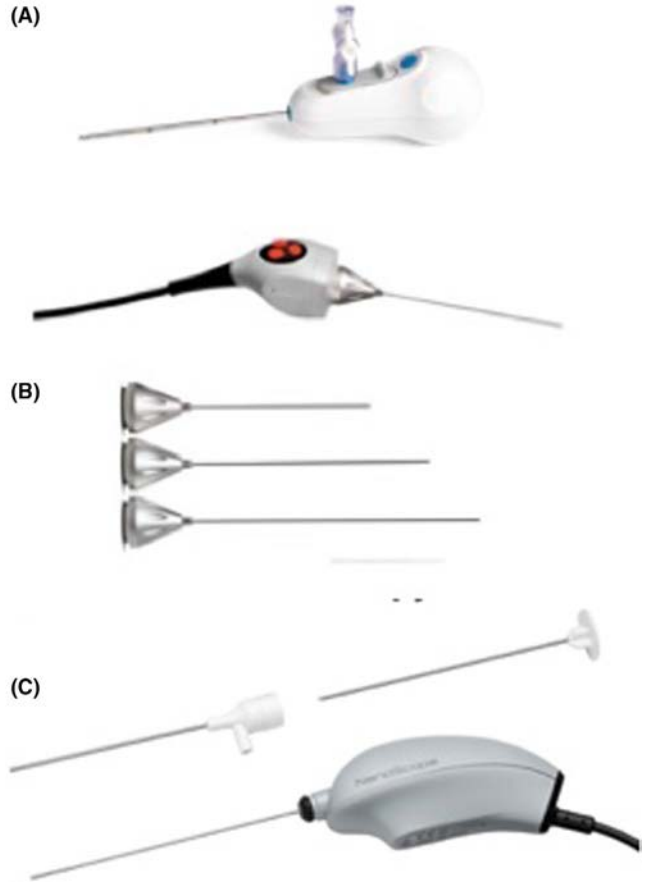

FIGURE 1 Needle arthroscopes for in-office use. (A) MiEye 2 (Trice Medical, Malvern, PA, USA), 1.9 mm disposable scope and camera with 2.2 mm inflow cannula and 120^0 field of view. https://tricemedical.com/mi-eye/. (B) VisionScope (VisionScope Technologies, Littleion, MA, USA), 1.4 mm reusable scope available in 4 lengths (60 mm, 95 mm, 125 mm, and 160 mm). Utilizes 1.9 mm disposable cannula and reusable camera. https://visionscope-tech.com/. (C) NanoScope (Arthrex, Inc Naples, FL, USA), 1.9 mm disposable scope and camera with 2.2 mm inflow cannula and 120° field of view. https://www.arthrex.com/what-surgeons-are-talking-about/78CC3845-4F4A-4F8A-A867-016B995DFC52. Images of arthroscopes obtained directly from their respective manufacturers, who also granted permission to use the images in this publication

Rheumatologists fell into a similar pit, after first seeing their procedure as a help with OA or an intervention for rheumatoid arthritis (where biologics have made it unnecessary). Yet the utility of arthroscopy as a tool to assess synovium remains incredibly underutilized. Tools to evaluate synovial tissue have become ever more powerful.[201] Rheumatologists have not entirely put the arthroscope down. There are many reasons for them to pick it up again. Access to arthroscopy is easier and cheaper than ever. Learning how to do it is admittedly a challenge. Not everyone has the unique set of psychomotor skills necessary to manipulate the scope and instruments in 3 dimensions. Some will never get it, even as some orthopedists find out.[202] Apparently, it helps if you're good at video games.[203] Virtual reality-based arthroscopy simulators have been developed[204-206] and have been used successfully in orthopedic surgery training programs.[207] The range of skills required for the uses a rheumatologist might have for an arthroscope are not as broad as those required to perform arthroscopic surgery. Use of a simulator could accelerate the rate at which an interested rheumatologist might acquire those skills. And applying those skills can certainly add to job satisfaction. There is joy in the successful application of hand-eye coordination that comes with doing arthroscopy, and in seeing directly the pathologies about which one had only been inferring for years; while too serious to be called a game, those who do it always get a big kick out of it, every time. And is there something bad about bringing some fun to the practice of medicine?[208,209]

11 | CONCLUSIONS

In part due to lessons learned from arthroscopy, rheumatology stands on the brink of true "precision medicine", with treatments tailored to specific individual characteristics of each patient.[210,211] It remains generally accepted that arthroscopy is the gold standard for assessing and obtaining the synovium that would guide such therapy,[212,213] particularly since the variability in synovial characteristics cannot be accounted for by externally guided sampling.[214] Means to assess synovial tissue are about to take another quantum leap.[215] The future for treatment of inflammatory joint disorders looks bright, with arthroscopy possibly a very big part of that future. Barriers to performance of this procedure have been broken down by newly available instruments. It's time for rheumatologists to pick up the arthroscope again.

CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose, including any with the arthroscope manufacturers.

ORCID

Robert W. Ike https://orcid.org/0000-0003-4715-4384
Kenneth C. Kalunian https://orcid.org/0000-0003-0261-3102

REFERENCES

1. Jackson RW. A history of arthroscopy. *Arthroscopy*. 2010;26(1):91-103. https://doi.org/10.1016/j.arthro.2009.10.005
2. Ike RW, Arnold WJ, Kalunian KC. Arthroscopy in rheumatology: where have we been? Where might we go? *Rheumatology*. 2021;60(2):518-528. https://doi.org/10.1093/rheumatology/keaa560
3. Burnam MS. Arthroscopy or direct visualization of joints. *J Bone Joint Surg*. 1931;13:669-695.
4. Kieser C. [Ernst Vaubel M. D. German pioneer in the field of arthroscopy 1902-1989]. *Unfallchirurg*. 103(1):93-97. [in German]. https://doi.org/10.1007/s001130050018
5. Watanabe M. Memories of the early days of arthroscopy. *Arthroscopy*. 1986;2(4):209-214. https://doi.org/10.1016/s0749-8063(86)80073-1
6. Gil JR, Katona G. Arthroscopy as a means of diagnosis and research: review of 80 arthroscopies. Proceedings of the Fourth Pan

American Congress of Rheumatology, Mexico City. *Excerpta Med Intern Congress*. 165:209-215.
7. Marqués J, Santamaría A, Gómez Martínez G, Barceló P. Arthroscopy. *Rev Esp Reum Enferm Osteoartic*. 1971;14(1):47-58. [in Spanish].
8. Andersen RB, Rossel I. Arthroscopy of the knee joint in rheumatic diseases. *Ugeskr Laeger*. 1973;135(2):71-73. [in Danish].
9. Torres-Moya R. La artroscopia en Cuba, sus inicios en el Servicio de reumatología del Hospital Docente Clínico Quirúrgico 10 de Octubre [Arthroscopy in Cuba, its beginnings in the Rheumatology Service of the Teaching Clinical Surgical Hospital October 10]. *Revista Cubana de Reumatología*. 2013;13:1-3. [in Spanish].
10. Dorfman H, de Seze S. Nouvelles observations sur l'arthroscopie du genou. Resultat d'une experience personelle. [New observations on knee arthroscopy. Result of a personal experience]. *Sem Hop*. 1972;48:3011-3019. [In French].
11. Ayral X, Bonvarlet JP, Simonnet J, Amor B, Dougados M. Arthroscopy-assisted synovectomy in the treatment of chronic synovitis of the knee. *Rev Rhum Engl Ed*. 1997;64(4):215-226.
12. Reyes Llerena GA, Toledano MG, Martinez AH. Rheumatology and care for the rheumatic diseases in Cuba. *J Clin Rheumatol*. 1995;15(5):289-292. https://doi.org/10.1097/00124743-199910000-00010
13. Jackson RW. Memories of the early days of arthroscopy: 1965–1975: The formative years. *Arthroscopy*. 1987;1:1-3. https://doi.org/10.1016/s0749-8063(87)80002-6
14. Jayson MIV, Dixon AS. Arthroscopy of the knee in rheumatic diseases. *Ann Rheum Dis*. 1968;27:503-511. https://doi.org/10.1136/ard.27.6.503
15. Yates DB, Scott JT. Rheumatoid synovitis and joint disease. *Ann Rheum Dis*. 1975;34:1-6.
16. Marqués J, Barcelóy GP. *La artroscopia [The arthroscopy*]. Pher Laboratories; 1977. [in Spanish].
17. Altman RD. Arthroscopic findings of the knee in patients with pseudogout. *Arthritis Rheum*. 1978;19:286-292.
18. Camerlain M. Arthroscopy in rheumatological perspectives [L'arthroscopie et ses perspectives rhumatologiques]. *Union Med Can*. 1974;103(7):1262-1265. [in French].
19. Henderson DRF, Tribe CR, Dixon ASJ. Synovitis in polymyalgia rheumatica. *Rheumatol Rehab*. 1975;14(4):244-250. https://doi.org/10.1093/rheumatology/14.4.244
20. Katona G, Larraza O, Isai M. Objective evaluation of an anti-inflammatory effect of azathioprine in rheumatoid arthritis. *Eur J Rheum Inflamm*. 1978;1(3):232-236.
21. Jackson DW. Videoarthroscopy: a permanent medical record. *Am J Sports Med*. 1978;6(5):213-216. https://doi.org/10.1177/036354657800600501
22. Johnson LL. *Arthroscopic Surgery: Principles and Practice*. C. V. Moseby; 1986.
23. Kelley WN. A new role for the ARA in guiding our destiny. *Arthritis Rheum*. 1987;30(11):1201-1204. https://doi.org/10.1002/art.1780301101
24. Arnold WJ, Kalunian K. Arthroscopic synovectomy by rheumatologists: time for a new look. *Arthritis Rheum*. 1989;32(1):109-111. https://doi.org/10.1002/anr.1780320120
25. Morris AH, Jennings JE, Stone RG, Katz JA, Garroway RY, Hendler RC. Guidelines for privileges in arthroscopic surgery. *Arthroscopy*. 1993;9(1):125-127.
26. Frassica FJ, Combs JJ. Sim FH (1985) Synovial proliferative disorders: differential diagnosis. *Arthroscopy*. 1985;1(3):183-189.
27. Myers SL, Brandt KD, Ehlich JW, et al. Synovial inflammation in patients with early osteoarthritis of the knee. *J Rheumatol*. 1990;12:1662-1669.
28. Lindblad S, Hedfors E. Intraarticular variation in synovitis. Local macroscopic and microscopic signs of inflammatory activity are significantly correlated. *Arthritis Rheum*. 1985;28(9):977-986. https://doi.org/10.1002/art.1780280904
29. Lindblad S. Recent progress in the study of synovitis by macroscopic and microscopic examination – a review. *Scand J Rheumatol Suppl*. 1988;76:27-32. https://doi.org/10.3109/03009748809102949
30. Ayral X, Mayoux-Benhamou A, Dougados M. Proposed scoring system for assessing synovial membrane abnormalities at arthroscopy in knee osteoarthritis. *Br J Rheumatol*. 1996;35(Suppl 3):14-17. https://doi.org/10.1093/rheumatology/35.suppl_3.14
31. Reece RJ, Canete JD, Parsons WJ, Emery P, Veale DJ. Distinct vascular patterns of early synovitis in psoriatic, reactive, and rheumatoid arthritis. *Arthritis Rheum*. 1999;42(7):1481-1484.
32. Moll C, Bogas M, Gómez-Puerta JA, et al. Macroscopic features of knee synovitis in early untreated Behçet disease and psoriatic arthritis. *Clin Rheumatol*. 2009;28(9):1053-1057. https://doi.org/10.1007/s10067-009-1205-0
33. Scott DG, Porto LO, Lovell CR, Thomas GO. Chronic sarcoid synovitis in the Caucasian: an arthroscopic and histological study. *Ann Rheum Dis*. 1981;40:121-123. https://doi.org/10.1136/ard.40.2.121
34. Douglas WAC, Martin BA, Morris JH. Polymyalgia rheumatica: An arthroscopic study of the shoulder joint. *Ann Rheum Dis*. 1983;42(3):311-316. https://doi.org/10.1136/ard.42.3.311
35. Langer HE, Huth F, Behar S, Zeidler H. Synovitis of familial Mediterranean fever [Die synovitis des familiaren mittelmeerfiebers]. *Deutsche Med Wochen*. 1985;110(44):1695-1700. [in German]. https://doi.org/10.1055/s-2008-1069072
36. Krause E, Argiles A, Bataille R, et al. Synovial amyloidosis revealing a myeloma. Clinical arthroscopic and immunochemical aspects. *Rev Rhum*. 1988;55(9):689-692.
37. Veale DJ, Reece RJ, Parsons W, et al. Intra-articular primatised anti-CD4: efficacy in resistant rheumatoid knees. A study of combined arthroscopy, magnetic resonance imaging, and histology. *Ann Rheum Dis*. 1999;58(6):342-349. https://doi.org/10.1136/ard.58.6.342
38. Smeets TJ, Kraan MC, Versendaal J, Breedveld FC, Tak P. Analysis of serial synovial biopsies in patients with rheumatoid arthritis: description of a control group without clinical improvement after treatment with interleukin 10 or placebo. *J Rheumatol*. 1999;26(10):2089-2093.
39. Yates DB, Scott JT, Ramsey N. Double-blind trial of ^{90}Y for chronic inflammatory synovitis of the knee. *Rheumatology*. 1979;XVIII(suppl):46-47. https://doi.org/10.1093/rheumatology/xviii.suppl.46
40. Lindblad S, Hedfors E, Malmborg A-S. Rifamycin SV in local treatment of synovitis. A clinical, arthroscopic and pharmacologic evaluation. *J Rheumatol*. 1985;12(5):900-903.
41. Oliunin IA, Manuïlova LS. The clinico-morphological assessment of the efficacy of local radiation therapy in rheumatoid arthritis | [Kliniko-morfologicheskaia otsenka éffektivnosti lokal'noï luchevoï terapii pri revmatoidnom artrite.]. *Ter Arkh*. 1991;63(11):122-125. [in Russian].
42. Frizziero L, Georgountzos A, Zizzi F, Focherini MC. Microarthroscopic study of the morphologic features of normal and pathological synovial membrane. *Arthroscopy*. 1992;8(4):504-509. https://doi.org/10.1016/0749-8063(92)90016-5
43. Benerbaum F, Rajzbaum G, Amor B, Toubert A. Evidence for GM-CSF receptor expression in synovial tissue – an analysis by semiquantitative polymerase chain reaction on rheumatoid arthritis and osteoarthritis synovial biopsies. *European Cytokine Net*. 1994;5(1):43-46.
44. Youssef P, Roth J, Frosch M, et al. Expression of myeloid related proteins (MRP) 8 and 14 and the MRP 8/14 heterodimer in rheumatoid arthritis synovial membrane. *J Rheumatol*. 1999;26(12):2523-2528.

45. Rubaltelli L, Fiocco U, Cozzi L, et al. Prospective sonographic and arthroscopic evaluation of proliferative knee joint synovitis. *J Ultrasound Med*. 1994;13(11):855-862. https://doi.org/10.7863/jum.1994.13.11.855
46. Nielsen P, Volck B, Jensen CH, Lorenzen IB. Magnetic resonance imaging-determined synovial membrane and joint effusion volumes in rheumatoid arthritis and osteoarthritis - Comparison with the macroscopic and microscopic appearance of the synovium. *Arthritis Rheum*. 1997;40(10):1856-1867. https://doi.org/10.1002/art.1780401020
47. Frizziero L, Zizzi F. Arthroscopic and microarthroscopic study of the synovial membrane in osteoarthrosis. *Min Ortop Traum*. 1988;39(7):497-500.
48. Fernandez-Madrid F, Karkoven RL, Teitge RA, Miller PR, An T, Negendank WG. Synovial thickening detected my MR imaging in osteoarthritis confirmed by biopsy as synovitis. *Mag Reson Imag*. 1995;13(2):177-183. https://doi.org/10.1016/0730-725X(94)00119-N
49. Smith MD, Triantafillou S, Parker A, Youssef PP. Coleman M (1997) Synovial membrane inflammation and cytokine production in patients with early osteoarthritis. *J Rheumatol*. 1997;24(2):365-371.
50. Chang RW, Falconer J, David Stulberg S, Arnold WJ, Manheim LM, Dyer AR. A randomized, controlled trial of arthroscopic surgery versus closed-needle joint lavage for patients with osteoarthritis of the knee. *Arthritis Rheum*. 1993;36(3):289-296. https://doi.org/10.1002/art.1780360302
51. Bradley JD, Heilman DK, Katz B, Gsell P, Wallick JE, Brandt KD. Tidal irrigation as treatment for knee osteoarthritis: a sham-controlled, randomized, double-blinded evaluation. *Arthritis Rheum*. 2002;46:100-108.
52. Katz JN, Brownlee SA, Jones MH. The role of arthroscopy in the management of knee osteoarthritis. *Best Pract Res Clin Rheumatol*. 2014;28:143-156. https://doi.org/10.1016/j.berh.2014.01.008
53. Brodenick LS, Turner DA, Renfrew DL, Schnitzer TJ, Huff JP, Harris C. Severity of articular cartilage abnormality in patients with osteoarthritis: Evaluation with fast spin-echo MR vs arthroscopy. *Am J Roentgen*. 1994;162(1):99-103. https://doi.org/10.2214/ajr.162.1.8273700
54. Ike RW, O'Rourke KS. Compartment directed physical exam of the knee can predict articular cartilage abnormalities disclosed by needle arthroscopy. *Arthritis Rheum*. 1995;38:917-925. https://doi.org/10.1002/art.1780380707
55. Fraser A, Veale DJ. What practical skills do rheumatologists of the future need? *Best Pract Res Clin Rheumatol*. 2000;14(4):635-648.
56. Rosengren S, Wei N, Kalunian KC, Kavanaugh A, Boyle DL. CXCL13: a novel biomarker of B-cell return following rituximab treatment and synovitis in patients with rheumatoid arthritis. *Rheumatology (Oxford)*. 2011;50:603-610. https://doi.org/10.1093/rheumatology/keq337
57. Ostendorf B, Dann P, Wedekind F, et al. Miniarthroscopy of metacarpophalangeal joints in rheumatoid arthritis. Rating of diagnostic value in synovitis staging and efficiency of synovial biopsy. *J Rheumatol*. 1999;26(9):1901-1908.
58. af Klint E, Catrina AI, Matt P, et al. Evaluation of arthroscopy and macroscopic scoring. *Arthritis Res Ther*. 2009;11(3):R81. https://doi.org/10.1186/ar2714
59. Lindberg J, Af Klint E, Ulfgren A-K, et al. Variability in synovial inflammation in rheumatoid arthritis investigated by microarray technology. *Arthritis Res Ther*. 2006;8(2):R47. https://doi.org/10.1186/ar1903
60. Kraan MC, Haringman JJ, Ahern MJ, Breedveld FC, Smith MD, Tak PP. Quantification of the cell infiltrate in synovial tissue by digital image analysis. *Rheumatol*. 2000;39(1):43-49. https://doi.org/10.1093/rheumatology/39.1.43
61. Fiocco U, Cozzi L, Chieco-Bianci F, et al. Vascular changes in psoriatic knee joint synovitis. *J Rheumatol*. 2001;28(11):2480-2486.
62. Van den Bosch F, Baeten D, Kruithof E, De Keyser F, Veys EM. Characteristic macro- and microscopic aspect of the synovial membrane in crystal induced arthritis. *J Rheumatol*. 2001;28(2):392-393.
63. Kuzmanova SI, Zaprianov ZN, Solakov P. Correlations between arthroscopic findings and synovial membrane histology in patients with rheumatoid synovitis of the knee joint. *Folia Medica (Plovdiv)*. 2003;45(3):60-65.
64. Salvador G, Sanmartí R, Gil-Torregrosa B, García Peiró A, Rodríguez-Cros JR, Cañete JD. Synovial vascular patterns and angiogenic factors expression in synovial tissue and serum of patients with rheumatoid arthritis. *Rheumatology (Oxford)*. 2006;45(8):966-971. https://doi.org/10.1093/rheumatology/kel043
65. Moll C, Bogas M, Gomez-Puerta CR, et al. Macroscopic features of knee synovitis in early untreated Behçet disease and psoriatic arthritis. *Clin Rheumato*. 2009;28(9):1053-1077. https://doi.org/10.1007/s10067-009-1205-0
66. Vordenbaeumen S, Sewerin P, Loegters T, et al. Inflammation and vascularization markers of arthroscopically-guided finger joint synovial biopsies reflect global disease activity in rheumatoid arthritis. *Clin Exp Rheumatol*. 2014;32(1):117-120.
67. Smeets TJM, Kraan MC, Galjaard S, Youssef PP, Smith MD, Tak PP. Analysis of the cell infiltrate and expression of matrix metalloproteinases and granzyme B in paired synovial biopsy specimens from the cartilage-pannus junction in patients with RA. *Ann Rheum Dis*. 2001;60(6):561-565. https://doi.org/10.1136/ard.60.6.561
68. Van Kuijk AWR, Reinders-Blankert P, Smeets TJM, Dijkmans B, Tak PP. Detailed analysis of the cell infiltrate and the expression of mediators of synovial inflammation and joint destruction in the synovium of patients with psoriatic arthritis: Implications for treatment. *Ann Rheum Dis*. 2006;65(12):1551-1557. https://doi.org/10.1136/ard.2005.050963
69. Thuerlings RM, Wijbrandt CA, Mebius RE, et al. Synovial lymphoid neogenesis does not define a specific clinical rheumatoid arthritis phenotype. *Arthritis Rheum*. 2008;58(6):1582-1589. https://doi.org/10.1002/art.23505
70. Jones E, Churchman SM, English A, et al. Mesenchymal stem cells in rheumatoid synovium: Enumeration and functional assessment in relation to synovial inflammation level. *Ann Rheum Dis*. 2001;69(2):450-457. https://doi.org/10.1136/ard.2008.106435
71. Moran EM, Heydrich R, Ng CT, et al. IL-17A Expression Is Localised to Both Mononuclear and Polymorphonuclear Synovial Cell Infiltrates. *PLoS One*. 2011;6(8):e24048. https://doi.org/10.1371/journal.pone.0024048
72. Benham H, Norris P, Goodall J, et al. Th17 and Th22 cells in psoriatic arthritis and psoriasis. *Arthritis Res Ther*. 2013;15(5):R136. https://doi.org/10.1186/ar4317
73. Musters A, Klarenbeek PL, Doorenspleet ME, et al. In rheumatoid arthritis, synovitis at different inflammatory sites is dominated by shared but patient-specific T cell clones. *J Immunol*. 2018;201(2):417-422. https://doi.org/10.4049/jimmunol.1800421
74. Murray-Brown W, Wilsdon TD, Weedon H, et al. Nivolumab-induced synovitis is characterized by florid T cell infiltration and rapid resolution with synovial biopsy-guided therapy. *J ImmunoTher Cancer*. 2020;8:e000281. https://doi.org/10.1136/jitc-2019-000281
75. Chen S, Noordenbos T, Blijdorp I, et al. Histologic evidence that mast cells contribute to local tissue inflammation in peripheral spondyloarthritis by regulating interleukin-17A content. *Rheumatology (Oxford)*. 2019;58(4):617-627. https://doi.org/10.1093/rheumatology/key331
76. Baeten D, Peene I, Union A, et al. Specific presence of intracellular citrullinated proteins in rheumatoid arthritis synovium:

Relevance to antifilaggrin autoantibodies. *Arthritis Rheum*. 2001;44(10):2255-2262.
77. Lories RJU, Derese I, Ceuppens JL, Luyten FP. Bone morphogenetic proteins 2 and 6, expressed in arthritic synovium, are regulated by proinflammatory cytokines and differentially modulate fibroblast-like synoviocyte apoptosis. *Arthritis Rheum*. 2003;48(10):2807-2818. https://doi.org/10.1002/art.11389
78. Kane D, Roth J, Frosch M, Vogl T, Bresnihan B, FitzGerald O. Increased perivascular synovial membrane expression of myeloid-related proteins in psoriatic arthritis. *Arthritis Rheum*. 2003;48(6):1676-1685. https://doi.org/10.1002/art.10988
79. Bresnihan B, Gogarty M, FitzGerald O, Dayer J-M, Burger D. Apolipoprotein A-I infiltration in rheumatoid arthritis synovial tissue: a control mechanism of cytokine production? *Arthritis Res Ther*. 2004;6:R563-R566. https://doi.org/10.1186/ar1443
80. Roelofs MF, Weninck MH, Brentano F, et al. Type I interferons might form the link between Toll-like receptor (TLR) 3/7 and TLR4-mediated synovial inflammation in rheumatoid arthritis (RA). *Ann Rheum Dis*. 2009;68(9):1486-1493. https://doi.org/10.1136/ard.2007.086421
81. Guo Y, Walsh AM, Canavan M, et al. Immune checkpoint inhibitor PD-1 pathway is down-regulated in synovium at various stages of rheumatoid arthritis disease progression. *PLoS One*. 2018;13(2):e0192704. https://doi.org/10.1371/journal.pone.0192704
82. Canavan M, Marzaoil V, McGarry T, et al. Rheumatoid arthritis synovial microenvironment induces metabolic and functional adaptations in dendritic cells. *Clin Exp Immunol*. 2020;202(2):226-238. https://doi.org/10.1111/cei.13479
83. Tajik N, Frech M, Schulz O, et al. Targeting zonulin and intestinal epithelial barrier function to prevent onset of arthritis. *Nat Commun*. 2020;11(1):1995. https://doi.org/10.1038/s41467-020-15831-7
84. Cunnane G, FitzGerald O, Hummel KM, Gay RE, Gay S, Bresnihan B. Collagenase, cathepsin B and cathepsin L gene expression in the synovial membrane of patients with early inflammatory arthritis. *Rheumatology*. 1999;38(1):34-42. https://doi.org/10.1093/rheumatology/38.1.34
85. Cunnane G, Fitzgerald O, Hummel KM, et al. Synovial tissue protease gene expression and joint erosions in early rheumatoid arthritis. *Arthritis Rheum*. 2001;44(8):1744-1753.
86. Fraser A, Fearon U, Reece R, Emery P, Veale DJ. Matrix metalloproteinase 9, apoptosis, and vascular morphology in early arthritis. *Arthritis Rheum*. 2001;44(9):2024-2028.
87. Fearon U, Griosios K, Fraser A, Emery P, Veale DJ. Angiopoietins, growth factors, and vascular morphology in early arthritis. *J Rheumatol*. 2003;30(2):260-268.
88. Ali M, Veale DJ, Reece R, et al. Overexpression of transcripts containing LINE-1 in the synovia of patients with rheumatoid arthritis. *Ann Rheum Dis*. 2003;62(7):663-666. https://doi.org/10.1136/ard.62.7.663
89. Fraser A, Fearon U, Billinghurst RC, et al. Turnover of type II collagen and aggrecan in cartilage matrix at the onset of inflammatory arthritis in humans - Relationship to mediators of systemic and local inflammation. *Arthritis Rheum*. 2003;48(11):3085-3095. https://doi.org/10.1002/art.11331
90. Steenvoorden MMC, Tolboom TCA, van der Pluijm G, et al. Transition of healthy to diseased synovial tissue in rheumatoid arthritis is associated with gain of mesenchymal/fibrotic characteristics. *Arthritis Res Ther*. 2006;8(6):R165. https://doi.org/10.1186/ar2073
91. Walker JG, Ahern MJ, Coleman M, et al. Characterisation of a dendritic cell subset in synovial tissue which strongly expresses Jak/STAT transcription factors from patients with rheumatoid arthritis. *Ann Rheum Dis*. 2007;66(8):992-999. https://doi.org/10.1136/ard.2006.060822
92. Wenink MH, Brentano F, Abdollahi-Roodsaz S, et al. Type I interferons might form the link between Toll-like receptor (TLR) 3/7 and TLR4-mediated synovial inflammation in rheumatoid arthritis (RA). *Ann Rheum Dis*. 2009;68(9):1486-1493. https://doi.org/10.1136/ard.2007.086421
93. Rosu A, Ciurea P, Simionescu C, et al. The study of angiogenesis in early rheumatoid arthritis–clinical, immunohistochemical and immunological correlations. *J Med Life*. 2008;1(3):287-294.
94. Dubikov AI, Kalinichenko SG. Small molecules regulating apoptosis in the synovium of rheumatoid arthritis. *Scan J Rheum*. 2010;39(5):368-372. https://doi.org/10.3109/03009741003742771
95. de Hair MJH, Harty LC, Gerlag DM, Pitzalis C, Veale DJ, Tak PP. Synovial tissue analysis for the discovery of diagnostic and prognostic biomarkers in patients with early arthritis. *J Rheumatol*. 2011;38(9):2068-2072. https://doi.org/10.3899/jrheum.110426
96. Wang JJ, Lee AYS, Colella AD, Chataway TK, Gordon TP, Wechalekar MD. Proteomic mapping of rheumatoid factors in early rheumatoid arthritis. *Arthritis Rheumatol*. 2020;72(12):2159-2161. https://doi.org/10.1002/art.41446
97. Maijer KI, Noort AR, De Hair MJH, et al. Nuclear factor-κB-inducing kinase is expressed in synovial endothelial cells in patients with early arthritis and correlates with markers of inflammation: A prospective cohort study. *J Rheumatol*. 2015;42(9):1573-1581. https://doi.org/10.3899/jrheum.150245
98. De Hair MJH, Leclerc P, Newsum EC, et al. Expression of prostaglandin E_2 enzymes in the synovium of arthralgia patients at risk of developing rheumatoid arthritis and in early arthritis patients. *PLoS One*. 2015;10(7):e0133669. https://doi.org/10.1371/journal.pone.0133669
99. Maijer KI, Neumann E, Mäller-Ladner U, et al. Serum vaspin levels are associated with the development of clinically manifest arthritis in autoantibody-positive individuals. *PLoS One*. 2015;10(12):e0144932. https://doi.org/10.1371/journal.pone.0144932
100. De Hair MJH, Van De Sande MGH, Ranwahadoede R, et al. Features of the synovium of individuals at risk of developing rheumatoid arthritis : Implications for understanding preclinical rheumatoid arthritis. *Arthritis Rheum*. 2014;66(3):513-522. https://doi.org/10.1002/art.38273
101. Smith MD, Barg E, Weedon H, et al. Microarchitecture and protective mechanisms in synovial tissue from clinically and arthroscopically normal knee joints. *Ann Rheum Dis*. 2003;62(4):303-307. https://doi.org/10.1136/ard.62.4.303
102. Baeten D, De Keyser F, Demetter P, et al. Comparative study of the synovial histology in rheumatoid arthritis, spondyloarthropathy, and osteoarthritis: Influence of disease duration and activity. *Ann Rheum Dis*. 2000;59(12):945-953. https://doi.org/10.1136/ard.59.12.945
103. Smeets TJM, Barg EC, Kraan MC, Smith MD, Breedveld FC, Tak PP. Analysis of the cell infiltrate and expression of proinflammatory cytokines and matrix metalloproteinases in arthroscopic synovial biopsies: comparison with synovial samples from patients with end stage, destructive rheumatoid arthritis. *Ann Rheum Dis*. 2003;62:635-638. https://doi.org/10.1136/ard.62.7.635
104. Haynes DR. Osteoprotegerin expression in synovial tissue from patients with rheumatoid arthritis, spondyloarthropathies and osteoarthritis and normal controls. *Rheumatology*. 2003;42(1):123-134. https://doi.org/10.1093/rheumatology/keg047
105. Baeten D, Kruithof E, De Rycke L, et al. Diagnostic classification of spondylarthropathy and rheumatoid arthritis by synovial histopathology: A prospective study in 154 consecutive patients.

Arthritis Rheum. 2004;50(9):2931-2941. https://doi.org/10.1002/art.20476
106. Kane D, Jensen L, Grehan S, Whitehead AS, Bresnihan B, Fitzgerald O. Quantitation of metalloproteinase gene expression in rheumatoid and psoriatic arthritis synovial tissue distal and proximal to the cartilage-pannus junction. *J Rheumatol*. 2004;31(7):1274-1280.
107. Salvador G, Sanmarti R, Garcia-Peiró A, Rodríguez-Cros JR, Muñoz-Gómez J, Cañete JD. p53 expression in rheumatoid and psoriatic arthritis synovial tissue and association with joint damage. *Ann Rheum Dis*. 2005;4(2):183-187. https://doi.org/10.1136/ard.2004.024430
108. Tilleman K, Van Beneden K, Dhondt A, et al. Chronically inflamed synovium from spondyloarthropathy and rheumatoid arthritis investigated by protein expression profiling followed by tandem mass spectrometry. *Proteonomics*. 2005;5(8):2247-2257. https://doi.org/10.1002/pmic.200401109
109. Van Holten J, Smeets TJM, Blankert P, Tak P-P. Expression of interferon β in synovial tissue from patients with rheumatoid arthritis: Comparison with patients with osteoarthritis and reactive arthritis. *Ann Rheum Dis*. 2005;64(12):1780-1782. https://doi.org/10.1136/ard.2005.040477CD55
110. Chapuy-Regaud S, Sebbag M, Baeten D, et al. Fibrin deimination in synovial tissue is not specific for rheumatoid arthritis but commonly occurs during synovitides. *J Immunol*. 2005;174(8):5057-5064. https://doi.org/10.4049/jimmunol.174.8.5057
111. Nzeusseu Toukap A, Galante C, Theate I, et al. Identification of distinct gene expression profiles in the synovium of patients with systemic lupus erythematosus. *Arthritis Rheum*. 2007;56(5):1579-1588. https://doi.org/10.1002/art.22578
112. Van Oosterhout M, Bajema I, Levahrt EWN, Toes REM, Huizinga TWJ, Van Laar JM. Differences in synovial tissue infiltrates between anti–cyclic citrullinated peptide–positive rheumatoid arthritis and anti–cyclic citrullinated peptide–negative rheumatoid arthritis. *Arthritis Rheum*. 2008;58(1):53-60. https://doi.org/10.1002/art.23148
113. Cañete JD, Celis R, Noordenbos T, et al. Distinct synovial immunopathology in Behçet disease and psoriatic arthritis. *Arthritis Res Ther*. 2009;11(1):R17. https://doi.org/10.1186/ar2608
114. Gómez-Puerta JA, Celis R, Hernández MV, et al. Differences in synovial fluid cytokine levels but not in synovial tissue cell infiltrate between anti-citrullinated peptide/protein antibody-positive and -negative rheumatoid arthritis patients. *Arthritis Res Ther*. 2013;15(6):R182. https://doi.org/10.1186/ar4372
115. Celis R, Cuervo A, Ramírez J, Cañete JD. Psoriatic Synovitis: Singularity and Potential Clinical Implications. *Front Med*. 2019;6:1-7. https://doi.org/10.3389/fmed.2019.00014
116. Cuervo A, Celis R, Julià A, et al. Synovial Immunohistological Biomarkers of the Classification of Undifferentiated Arthritis Evolving to Rheumatoid or Psoriatic Arthritis. *Front Ed (Lausanne)*. 2021;8:1-8. https://doi.org/10.3389/fmed.2021.656667
117. Af Klint E, Grundtman C, Engström CAI, et al. Intraarticular glucocorticoid treatment reduces inflammation in synovial cell infiltrations more efficiently than in synovial blood vessels. *Arthritis Rheum*. 2005;52(12):3880-3889. https://doi.org/10.1002/art.21488
118. Kraan MC, Reece RJ, Barg E, et al. Modulation of inflammation and metalloproteinase expression in synovial tissue by leflunomide and methotrexate in patients with active rheumatoid arthritis: Findings in a prospective, randomized, double-blind, parallel-design clinical trial in thirty-nine patients at two centers. *Arthritis Rheum*. 2000;43(8):1820-1830.
119. Smith MD, Kraan MC, Slavotinek J, et al. Treatment-induced remission in rheumatoid arthritis patients is characterized by a reduction in macrophage content of synovial biopsies. *Rheumatology (Oxford)*. 2001;40(4):367-374.
120. Wong PKK, Cuello C, Bertouch J, et al. Effects of pulse methylprednisolone on macrophage chemotactic protein-1 and macrophage inflammatory protein-1α in rheumatoid synovium. *J Rheumatol*. 2001;28(12):2634-2636.
121. Bingham S, Veale D, Fearon U, et al. High-dose cyclophosphamide with stem cell rescue for severe rheumatoid arthritis: Short-term efficacy correlates with reduction of macroscopic and histologic synovitis. *Arthritis Rheum*. 2002;46(3):837-839. https://doi.org/10.1002/art.10093
122. Kraan MC, van Kuijk AWR, Dinant HJ, et al. Alefacept treatment in psoriatic arthritis: Reduction of the effector T cell population in peripheral blood and synovial tissue is associated with improvement of clinical signs of arthritis. *Arthritis Rheum*. 2002;46(10):2776-2784. https://doi.org/10.1093/rheumatology/40.4.367
123. Haringman JJ, Kraan MC, Smeets TJM, Zwinderman KH, Tak PP. Chemokine blockade and chronic inflammatory disease: Proof of concept in patients with rheumatoid arthritis. *Ann Rheum Dis*. 2003;62(8):715-721. https://doi.org/10.1136/ard.62.8.715
124. Smeets TJM, Kraan MC, Van Loon ME, Tal P-P. Tumor necrosis factor α blockade reduces the synovial cell infiltrate early after initiation of treatment, but apparently not by induction of apoptosis in synovial tissue. *Arthritis Rheum*. 2003;48(8):2155-2162. https://doi.org/10.1002/art.11098
125. Buch MH, Conaghan PG, Bingham SJ, Veale D, Emery P. True infliximab resistance in rheumatoid arthritis: A role for lymphotoxin α? *Ann Rheum Dis*. 2004;63(10):1344-1346. https://doi.org/10.1136/ard.2003.014878
126. Cañete JD, Pablos JL, Sanmarti MC, et al. Antiangiogenic effects of anti-tumor necrosis factor a therapy with infliximab in psoriatic arthritis. *Arthritis Rheum*. 2004;50(5):1636-1641. https://doi.org/10.1002/art.20181
127. Kane D, Gogarty M, O'Leary J, et al. Reduction of synovial sublining layer inflammation and proinflammatory cytokine expression in psoriatic arthritis treated with methotrexate. *Arthritis Rheum*. 2004;50(10):3286-3295. https://doi.org/10.1002/art.20518
128. Gerlag DM, Haringman JJ, Smeets TJM, et al. Effects of oral prednisolone on biomarkers in synovial tissue and clinical improvement in rheumatoid arthritis. *Arthritis Rheum*. 2004;50(12):3783-3791. https://doi.org/10.1002/art.20664
129. Haringman JJ, Gerlag DM, Zwinderman AH, et al. Synovial tissue macrophages: A sensitive biomarker for response to treatment in patients with rheumatoid arthritis. *Ann Rheum Dis*. 2005;64(6):834-838. https://doi.org/10.1136/ard.2004.029751
130. Van Holten J, Pavelka K, Vencovsky J, et al. A multicentre, randomised, double blind, placebo controlled phase II study of subcutaneous interferon beta-1a in the treatment of patients with active rheumatoid arthritis. *Ann Rheum Dis*. 2005;64(1):64-69. https://doi.org/10.1136/ard.2003.020347
131. Van Oosterhaut M, Levarht EWN, Sont JK, Huizinga TWJ, Toes REM, Van Laar JM. Clinical efficacy of infliximab plus methotrexate in DMARD naive and DMARD refractory rheumatoid arthritis is associated with decreased synovial expression of TNFα and IL18 but not CXCL12. *Ann Rheum Dis*. 2005;64(4):537-543. https://doi.org/10.1136/ard.2004.024927
132. Baeten D, Houbiers J, Kruithof E, et al. Synovial inflammation does not change in the absence of effective treatment: Implications for the use of synovial histopathology as biomarker in early phase clinical trials in rheumatoid arthritis. *Ann Rheum Dis*. 2006;65(8):990-997. https://doi.org/10.1136/ard.2005.047852
133. Ernestam S, Klint EA, Catrina AI, et al. Synovial expression of IL-15 in rheumatoid arthritis is not influenced by blockade of tumour necrosis factor. *Arthritis Res Ther*. 2006;8(1):R18.
134. Lindberg J, af Klint E, Catrina AL, et al. Effect of infliximab on mRNA expression profiles in synovial tissue of rheumatoid

arthritis patients. *Arthritis Res Ther*. 2006;8(6):R179. https://doi.org/10.1186/ar2090
135. Vergunst CE, Gerlag DM, Dinant H, et al. Blocking the receptor for C5a in patients with rheumatoid arthritis does not reduce synovial inflammation. *Rheumatology (Oxford)*. 2007;46(12):1773-1778.
136. Haynes D, Crotti T, Weedon H, et al. Modulation of RANKL and osteoprotegerin expression in synovial tissue from patients with rheumatoid arthritis in response to disease-modifying antirheumatic drug treatment and correlation with radiologic outcome. *Arthritis Care Res*. 2008;59(7):911-920. https://doi.org/10.1002/art.23818
137. Lebre MC, Jongbloed SL, Tas SW, Smeets TJM, McInnes IB, Tak PP. Rheumatoid arthritis synovium contains two subsets of CD83 ˉDC-LAMPˉ dendritic cells with distinct cytokine profiles. *Am J Clin Path*. 2008;172(4):940-950. https://doi.org/10.2353/ajpath.2008.070703
138. Lories RJU, Derese I, Luyten FP, de Vlam K. Activation of nuclear factor kappa B and mitogen activated protein kinases in psoriatic arthritis before and after etanercept treatment. *Clin Exp Rheumatol*. 2008;26(1):96-102.
139. Sundberg E, Grundtman C, af Klint E, et al. Systemic TNF blockade does not modulate synovial expression of the pro-inflammatory mediator HMGB1 in rheumatoid arthritis patients – a prospective clinical study. *Arthritis Res Ther*. 2008;10:R33. https://doi.org/10.1186/ar2387
140. Kavanaugh A, Rosengren S, Lee S, et al. Assessment of rituximab's immunomodulatory synovial effects (ARISE trial). 1: clinical and synovial biomarker results. *Ann Rheum Dis*. 2008;67(3):402-408. https://doi.org/10.1136/ard.2007.074229
141. Van Der Pouw Kraan TCM, Wijbrandts CA, Van Baarsen LG, et al. Responsiveness to anti-tumour necrosis factor α therapy is related to pre-treatment tissue inflammation levels in rheumatoid arthritis patients. *Ann Rheum Dis*. 2008;67(4):563-566. https://doi.org/10.1136/ard.2007.081950
142. Walsh CAE, Fearon U, FitzGerald O, Veale DJ, Bresnihan B. Decreased CD20 expression in rheumatoid arthritis synovium following 8 weeks of rituximab therapy. *Clin Exp Rheumatol*. 2008;26(4):656-658.
143. Rosengren S, Wei N, Kalunian KC, Zvaifler NJ, Kavanaugh A, Boyle D. Elevated autoantibody content in rheumatoid arthritis synovia with lymphoid aggregates and the effect of rituximab. *Arthritis Res Ther*. 2008;10:R105. https://doi.org/10.1186/ar2497
144. Vergunst CE, Gerlag DM, Lopantinskaya L, et al. Modulation of CCR2 in rheumatoid arthritis: A double-blind, randomized, placebo-controlled clinical trial. *Arthritis Rheum*. 2008;58(7):1931-1939. https://doi.org/10.1002/art.23591
145. Bresnihan B, Pontifex E, Thurlings RM, et al. Synovial tissue sublining CD68 expression is a biomarker of therapeutic response in rheumatoid arthritis clinical trials: Consistency across centers (Conference Paper). *J Rheumatol*. 2009;36(8):1800-1802. https://doi.org/10.3899/jrheum.090348
146. Van Kuijk AWR, Gerlag DM, Vos K, et al. A prospective, randomised, placebo-controlled study to identify biomarkers associated with active treatment in psoriatic arthritis: Effects of adalimumab treatment on synovial tissue. *Ann Rheum Dis*. 2009;68(8):1303-1309. https://doi.org/10.1136/ard.2008.091389
147. Lindberg J, Wijbrandts CA, van Baarsen LG, et al. The gene expression profile in the synovium as a predictor of the clinical response to infliximab treatment in rheumatoid arthritis. *PLoS One*. 2010;5(6):e11310. https://doi.org/10.1371/journal.pone.0011310
148. Roone T, Roux-Lombard P, Veale DJ, FitzGerald O, Dayer J-M, Bresnihan B. Synovial tissue and serum biomarkers of disease activity, therapeutic response and radiographic progression: analysis of a proof-of-concept randomised clinical trial of cytokine blockade. *Ann Rheum Dis*. 2010;69(4):706-714. https://doi.org/10.1136/ard.2009.108324
149. Smith MD, Weedon H, Papangelis V, et al. Apoptosis in the rheumatoid arthritis synovial membrane: modulation by disease-modifying anti-rheumatic drug treatment. *Rheumatology (Oxford)*. 2010;49(5):862-887. https://doi.org/10.1093/rheumatology/kep467
150. Cañete JD, Celis R, Hernández V, Pablos JL, Sanmartí R. Synovial immunopathologic changes associated with successful abatacept therapy in a case of severe refractory psoriatic arthritis. *Ann Rheum Dis*. 2011;69(5):935-936. https://doi.org/10.1136/ard.2009.113233
151. Pontifex EK, Gerlag DM, Gogarty M, et al. Change in CD3 positive T-cell expression in psoriatic arthritis synovium correlates with change in DAS28 and magnetic resonance imaging synovitis scores following initiation of biologic therapy - a single centre, open-label study. *Arthritis Res Ther*. 2011;13(1):R7. https://doi.org/10.1186/ar3228
152. Kennedy A, Teck Ng C, Cheng Chang T, et al. Tumor necrosis factor blocking therapy alters joint inflammation and hypoxia. *Arthritis Rheum*. 2011;63(4):923-932. https://doi.org/10.1002/art.30221
153. Revu S, Neregård P, af Klint E, Korotkova M, Catrina A. Synovial membrane immunohistology in early-untreated rheumatoid arthritis reveals high expression of catabolic bone markers that is modulated by methotrexate. *Arthritis Res Ther*. 2013;15(6):R205. https://doi.org/10.1186/ar4398
154. Neregard P, Krishnamurthy A, Revu S, Engström M, Af Klint E, Catrina AI. Etanercept decreases synovial expression of tumour necrosis factor-α and lymphotoxin-α in rheumatoid arthritis. *Scan J Rheum*. 2014;43(2):85-90. https://doi.org/10.3109/03009742.2013.834964
155. De Groof A, Ducreux J, Humby F, et al. Higher expression of TNFα-induced genes in the synovium of patients with early rheumatoid arthritis correlates with disease activity, and predicts absence of response to first line therapy. *Arthritis Res Ther*. 2016;18:19. https://doi.org/10.1186/s13075-016-0919-z
156. Fisher BA, Donatien P, Filer A, et al. Decrease in articular hypoxia and synovial blood flow at early time points following infliximab and etanercept treatment in rheumatoid arthritis. *Clin Exp Rheum*. 2016;34(6):1072-1076.
157. Szentpetery A, Heffernan E, Gogarty M, et al. Abatacept reduces synovial regulatory T-cell expression in patients with psoriatic arthritis. *Arthritis Res Ther*. 2017;19:158. https://doi.org/10.1186/s13075-017-1364-3
158. Walsh AM, Wechalekar MD, Guo Y, et al. Triple DMARD treatment in early rheumatoid arthritis modulates synovial T cell activation and plasmablast/plasma cell differentiation pathways. *PLoS One*. 2017;12(9):e0183928. https://doi.org/10.1371/journal.pone.0183928
159. Humby F, Durez P, Buch MH, et al. Rituximab versus tocilizumab in anti-TNF inadequate responder patients with rheumatoid arthritis (R4RA): 16-week outcomes of a stratified, biopsy-driven, multicentre, open-label, phase 4 randomised controlled trial. *Lancet*. 2021;397(10271):305-317. https://doi.org/10.1016/S0140-6736(20)32341-2
160. Peres LR, Marchitto RO, Pereira GS, Yoshino FS, Fernandes MDC, Matsumoto MH. Arthrotomy versus arthroscopy in the treatment of septic arthritis of the knee in adults: a randomized clinical trial. *Knee Surg Sports Traumatol Arthrosc*. 2016;24(10):3155-3162. https://doi.org/10.1007/s00167-015-3918-8
161. Brühlmann P, Michel BA, Altwegg M. Diagnosis and therapy monitoring of Whipple's arthritis by polymerase chain reaction. *Rheumatology (Oxford)*. 2000;39(12):1427-1428. https://doi.org/10.1093/rheumatology/39.12.1427

162. Schmid S, Bossart W, Michel BA, Brühlmann P. Outcome of patients with arthritis and parvovirus B19 DNA in synovial membranes. *Rheumatol Int*. 2007;27(8):747-751. https://doi.org/10.1007/s00296-007-0337-2
163. Frizziero L. Arthroscopic study of joint cartilage damage and synovial membrane in osteoarthritis of the knee | [Valutazione artroscopica della sofferenza cartilaginea e della membrana sinoviale nell'artrosi del ginocchio]. *Prog Reumatol*. 2003;4(2):193-202. [in Italian].
164. Loueuille D, Chary-Valckenaere I, Champignuelle J. Macroscopic and microscopic features of synovial membrane inflammation in the osteoarthritic knee: Correlating magnetic resonance imaging findings with disease severity. *Arthritis Rheum*. 2005;52(11):3492-3501. https://doi.org/10.1002/art.21373
165. Wei N, Johnson LL, Seeley BL, Delauter SK. Arthroscopically guided Jamshidi biopsy of articular cartilage: potential in the evaluation of disease-modifying osteoarthritis drugs (DMOADS). *J Appl Res*. 2003;3(3):329-338.
166. Ike R, Baskaran A, Chao J, et al. Prevalence of crystalline disease in knee osteoarthritis: experience from patients undergoing arthroscopic procedures. *J Clin Rheumatol*. 25(1):51-53.
167. Ayral X, Pickering EH, Woodworth TG. Synovitis: A potential predictive factor of structural progression of medial tibiofemoral knee osteoarthritis - Results of a 1 year longitudinal arthroscopic study in 422 patients. *Osteoarthritis Cartilage*. 2005;13(5):361-367.
168. Wu CW, Morrell MR, Heinze E, et al. Validation of American College of Rheumatology classification criteria for knee osteoarthritis using arthroscopically defined cartilage damage scores. *Semin Arthritis Rheum*. 2005;35(3):197-201. https://doi.org/10.1016/j.semarthrit.2005.06.0
169. Pasquali Ronchetti I, Guerra D, et al. Morphological analysis of knee synovial membrane biopsies from a randomized controlled clinical study comparing the effects of sodium hyaluronate (Hyalgan®) and methylprednisolone acetate (Depomedrol®) in osteoarthritis. *Rheumatology*. 2001;40(2):158-169. https://doi.org/10.1093/rheumatology/40.2.158
170. Frizziero L, Pasquali Ronchetti I. Intra-articular treatment of osteoarthritis of the knee: An arthroscopic and clinical comparison between sodium hyaluronate (500–730 kDa) and methylprednisolone acetate. *J Orthop Traumatol*. 2002;3(2):89-96.
171. Kuzmanova S, Andrees S, Atanassov A, Batalov A, Solakov P. Arthroscopic synovectomy, debridement and tidal lavage of the knee joint in osteoarthritis - long term results. *Revmatologiia*. 2004;12(4):42-47.
172. Ike RW, Kalunian KC, Arnold WJ (2021) Why not wash out the OA knee? *J Clin Rheumatol*. 27(2):43-45.
173. Li J, Huang Y, Song J, et al. Cartilage regeneration using arthroscopic flushing fluid-derived mesenchymal stem cells encapsulated in a one-step rapid cross-linked hydrogel. *Acta Biomater*. 2018;79:202-215. https://doi.org/10.1016/j.actbio.2018.08.029
174. Ostendorf B, Peters R, Dann P, et al. Magnetic resonance imaging and miniarthroscopy of metacarpophalangeal joints - Sensitive detection of morphologic changes in rheumatoid arthritis. *Arthritis Rheum*. 2001;44(11):2492-2502.
175. Coumbaras M, Le Hir P, Sautet A, Jomaah N, Tubiana JM, Arrivé L. Reactive synovitis: MRI features with arthroscopic correlation [Synovites réactionnelles: Aspects en IRM et corrélations arthroscopiques]. *J Radiologie*. 2005;86(5):481-486. https://doi.org/10.1016/S0221-0363(05)81393-9
176. Ostergaard M, Stoltenberg M, Lovgreen FU, et al. Contrast medium in power Doppler ultrasound for assessment of synovial vascularity: Comparison with arthroscopy. *J Rheumatol*. 2003;30(10):2170-2176.
177. Karim Z, Wakefield RJ, Quinn M, et al. Top of validation and reproducibility of ultrasonography in the detection of synovitis in the knee - A comparison with arthroscopy and clinical examination. *Arthritis Rheum*. 2004;50(2):387-394. https://doi.org/10.1002/art.20054
178. Komarova EB. Correlation between joint ultrasound data and clinical, laboratory and instrumental indices in patients with rheumatoid arthritis. *Sov Tehn Med*. 2017;9(1):92-96. https://doi.org/10.17691/stm2017.9.1.11
179. Najm A, Orr C, Gallagher L, et al. Knee joint synovitis: Study of correlations and diagnostic performances of ultrasonography compared with histopathology. *RMD Open*. 2018;4(1):e000616. https://doi.org/10.1136/rmdopen-2017-000616
180. De Lucia O, Paresce E, Murgo A, et al. Simultaneous ultrasonography and arthroscopy for the study of the joint environment: Indications and limits | [Ecografia e artroscopia in contemporanea per lo studio dell'ambiente articolare: Indicazioni e limiti]. *Reumatismo*. 2007;59(2):146-152. [in Italian].
181. Paresce E, De Lucia O, Bruschi E, Giacomelli L, Epis OM. Use of ultrasound-assisted arthroscopy in rheumatology: an experience in 11 patients with different rheumatic diseases. *Expert Opin Med Diagn*. 2013;7(4):309-312. https://doi.org/10.1517/17530059.2013.79413
182. Ng CT, Binieka M, Kennedy A, et al. Synovial tissue hypoxia and inflammation in vivo. *Ann Rheum Dis*. 2010;69(7):1389-1395. https://doi.org/10.1136/ard.2009.119776
183. Kennedy A, Ng CT, Binieka M, et al. Angiogenesis and blood vessel stability in inflammatory arthritis. *Arthritis Rheum*. 2010;62(3):711-721. https://doi.org/10.1002/art.27287
184. Binieka M, Fox E, Gao W, et al. Hypoxia induces mitochondrial mutagenesis and dysfunction in inflammatory arthritis. *Arthritis Rheum*. 2011;63(8):2172-2182. https://doi.org/10.1002/art.30395
185. Romão VC, Polido-Pereira J, Barros R, et al. Efficacy, Safety, and Sample Quality of Ultrasound-Guided Synovial Needle Biopsy in Clinical Practice and Research: A Prospective Observational Study. *Arthritis Care Res (Hoboken)*. 2020;72(10):1497-1505. https://doi.org/10.1002/acr.24050
186. Just SA, Humby F, Lindegaard H, et al. Patient-reported outcomes and safety in patients undergoing synovial biopsy: comparison of ultrasound-guided needle biopsy, ultrasound-guided portal and forceps and arthroscopic-guided synovial biopsy techniques in five centres across Europe. *RMD Open*. 2018;4(2):e000799. https://doi.org/10.1136/rmdopen-2018-000799
187. Humby F, Romão VC, Manzo A, et al. A Multicenter Retrospective Analysis Evaluating Performance of Synovial Biopsy Techniques in Patients With Inflammatory Arthritis. *Arthritis Rheumatol*. 2018;70(5):702-710. https://doi.org/10.1002/art.40433
188. van de Sande MGH, Gerlag DM, Lodde BM, et al. Evaluating antirheumatic treatments using synovial biopsy: a recommendation for standardisation to be used in clinical trials. *Ann Rheum Dis*. 2011;70(3):423-427. https://doi.org/10.1136/ard.2010.139550
189. Veale DJ. Synovial tissue biopsy research. *Front Med*. 2019;6:1-4. https://doi.org/10.3389/fmed.2019.00072
190. Sharma A, Baethge BA, Acebes JC, Lisse JR. Arthroscopic lavage treatment in rheumatoid arthritis of the knee. *J Rheumatol*. 1996;11:1872-1874.
191. Tanaka N, Sakahashi H, Hirose K, Ishima T, Ishii S. Volume of a wash and the other conditions for maximum therapeutic effect of arthroscopic lavage in rheumatoid knees. *Clin Rheumatol*. 2006;25(1):65-69. https://doi.org/10.1007/s10067-005-1143-4
192. van Oosterhout M, Sont JK, Bajema IM, Breedveld FC, van Laar JM. Comparison of efficacy of arthroscopic lavage plus administration of corticosteroids, arthroscopic lavage plus administration of placebo, and joint aspiration plus administration of corticosteroids in arthritis of the knee: A randomized controlled trial. *Arthritis Rheum*. 2006;55(6):964-970. https://doi.org/10.1002/art.22340

193. Johnsson H, Najm A. Synovial biopsies in clinical practice and research: current developments and perspectives. *Clin Rheumatol*. 2021;40:2593-2600. https://doi.org/10.1007/s10067-020-05512-7
194. Youssef PP, Kraan M, Breedveld F, et al. Quantitative microscopic analysis of inflammation in rheumatoid arthritis synovial membrane samples selected at arthroscopy compared with samples obtained blindly by needle biopsy. *Arthritis Rheum*. 1998;41(4):663-669.
195. Chaturvedi V, Thabah MM, Ravindran V, Kiely PD. Medical arthroscopy: A tool for diagnosis and research in rheumatology. *Int J Rheum Dis*. 2017;20:145-153. https://doi.org/10.1111/1756-185X.12951
196. McMillan S, Saini S, Alyea E, Ford E. Office-based needle arthroscopy: a standardized diagnostic approach to the knee. *Arthroscop Tech*. 2017;6(4):e1119-e1124. https://doi.org/10.1016/j.eats.2017.03.031
197. https://www.arthrex.com/knee/nano-arthroscopic-instruments
198. Zhang K, Crum RJ, Samuelsson K, Cadet E, Ayeni OR, de Sa D. In-office needle arthroscopy: a systematic review of indications and clinical utility. *Arthroscopy*. 2019;9:2709-2721.
199. Teppo LN, Järvinen N, Guyatt GH. Falling out of love with knee arthroscopy. *Nature Rev Rheumatol*. 2017;13(9):515-516. https://doi.org/10.1038/nrrheum.2017.106
200. Howard DH. Trends in the use of knee arthroscopy in adults. *JAMA Intern Med*. 2018;178(11):1557-1558. https://doi.org/10.1001/jamainternmed.2018.4175
201. Orr C, Vieira-Sousa E, Boyle DL, et al. Synovial tissue research: a state-of-the-art review. *Nat Rev Rheumatol*. 2017;13(8):463-475.
202. Alvand A, Auplish S, Gill H, Rees J. Innate arthroscopic skills in medical students and variation in learning curves. *J Bone Joint Surg Am*. 2011;93(19):1-9. https://doi.org/10.2106/JBJS.K.00199
203. Cychosz CC, Tofte JN, Johnson A, Carender C, Gao Y, Phisitkul P. Factors impacting initial arthroscopy performance and skill progression in novice trainees. *Iowa Orthop J*. 2019;39(1):7-13.
204. https://www.toltech.net/medical-simulators/products/arthrosim-arthroscopy-simulator
205. https://www.virtamed.com/en/medical-training-simulators/arthros/
206. https://simbionix.com/simulators/arthro-mentor/
207. Vaughan N, Dubey VN, Wainwright TW, Middleton RG. A review of virtual reality based training simulators for orthopaedic surgery. *Med Eng Phys*. 2016;38(2):59-71. https://doi.org/10.1016/j.medengphy.2015.11.021
208. Guze SB. Can the practice of medicine be fun for a lifetime? *JAMA*. 1979;241(19):2021-2023. https://doi.org/10.1001/jama.1979.03290450019016
209. Colaianni CA. Fun. *N Engl J Med*. 2020;382(5):402-403. https://doi.org/10.1056/NEJMp1909360
210. Traille C, Lauwery BR. Synovial tissue: turning the page to precision medicine in arthritis. *Front Med (Lausanne)*. 2019;6:46. https://doi.org/10.3389/fmed.2019.00046
211. Small A, Wechalekar MD. Synovial biopsies in inflammatory arthritis: precision medicine in rheumatoid arthritis. *Exp Rev Mol Diagnostic*. 2020;20(3):315-325. https://doi.org/10.1080/14737159.2020.1707671
212. Humby FC. Synovial tissue sampling in rheumatological practice-past developments and future perspectives. *Front Med (Lausanne)*. 2019;6:4. https://doi.org/10.3389/fmed.2019.00004
213. Orr CK, Vieira-Sousa E, Fonseca JE, Veale D. Arthroscopic Guided Synovial Biopsies. *Front Med*. 2021;7:1-7. https://doi.org/10.3389/fmed.2020.604582
214. Ouboussad L, Burska AN, Melville A. Synovial tissue heterogeneity in rheumatoid arthritis and changes with biologic and targeted synthetic therapies to inform stratified therapy [Mini Review]. *Front Med (Lausanne)*. 2019;6:45. https://doi.org/10.3389/fmed.2019.00045
215. Veale DJ, Fearon U. Next-generation analysis of synovial tissue architecture. *Nat Rev Rheumatol*. 2019;16(2):67-69. https://doi.org/10.1038/s41584-019-0357-9

How to cite this article: Ike RW, Kalunian KC. Will rheumatologists ever pick up the arthroscope again? *Int J Rheum Dis*. 2021;24:1235–1246. https://doi.org/10.1111/1756-185X.14184

Received: 21 April 2021 | Revised: 4 July 2021 | Accepted: 10 July 2021

DOI: 10.1111/1756-185X.14183

ORIGINAL ARTICLE

International Journal of Rheumatic Diseases | WILEY

Epidemiology of Takayasu arteritis in Shanghai: A hospital-based study and systematic review

Ying Sun[1] | Meng-meng Yin[1] | Li-li Ma[1] | Xiao-min Dai[1] | Liang-jing Lv[2] | Xiao-xiang Chen[2] | Shuang Ye[3] | Ting Li[3] | Jie Chen[3] | Dong-bao Zhao[4] | Rui-na Kong[4] | Qiang-hua Wei[5] | Guang-hui Yang[6] | Su-gang Gong[7] | Cheng-de Yang[8] | Hong-lei Liu[8] | Yu Xue[9] | Jian-ping Tang[10] | Run Feng[10] | Ai Peng[11] | Ling Qin[11] | Hua Liu[12] | Xiao Su[13] | Hui-ping Huang[13] | Jian-long Guan[14] | Dan Luo[14] | Sheng-Ming Dai[15] | Fu-tao Zhao[16] | Zhen-Hang Zhu[16] | Xiao-yan Zhang[17] | Jie Han[18] | Jia-yi Wang[18] | Chun-yuan Xiao[18] | Hu-ji Xu[19] | Xin Wu[19] | Dong-yi He[20] | Jian-chun Mao[21] | Zhu-jing Zhu[21] | Luan Xue[22] | Ben Li[22] | Jiang Lin[23] | Jian-zhou Zou[24] | Xiao-ning Sun[25] | Jing Ding[26] | Zhi-hui Dong[27] | Xiang-fei Wang[28] | Jun-Ying[29] | Lin-di Jiang[1,30]

[1]Department of Rheumatology, Zhongshan Hospital, Fudan University, Shanghai, China

[2]Department of Rheumatology, Renji Hospital, Shanghai JiaoTong University School of Medicine, Shanghai, China

[3]Department of Rheumatology, Renji Hospital South Campus, Shanghai JiaoTong University School of Medicine, Shanghai, China

[4]Department of Rheumatology and Immunology, Changhai Hospital, Second Military Medicine University, Shanghai, China

[5]Department of Rheumatology, Shanghai General Hospital, Shanghai, China

[6]Department of Rheumatology, Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Shanghai, China

[7]Department of Cardio-Pulmonary Circulation, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, China

[8]Department of Rheumatology and Immunology, Shanghai JiaoTong University School of Medicine Affiliated Ruijin Hospital, Shanghai, China

[9]Department of Rheumatology, Huashan Hospital, Fudan University, Shanghai, China

[10]Division of Rheumatology and Immunology, Tongji Hospital of Tongji University School of Medicine, Shanghai, China

[11]Department of Nephrology & Rheumatology, Shanghai Tenth People's Hospital, Tongji University School of Medicine, Shanghai, China

[12]Department of Cardiology, Shanghai Chest Hospital, Shanghai JiaoTong University School of Medicine, Shanghai, China

[13]Department of Rheumatology, Shanghai municipal Hospital of Traditional Chinese Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai, China

[14]Department of Rheumatology, Huadong Hospital, Fudan University, Shanghai, China

[15]Department of Rheumatology & Immunology, Shanghai JiaoTong University Affiliated Sixth People's Hospital, Shanghai, China

[16]Department of Rheumatology and Immunology, Shanghai Ninth People's Hospital, School of Medicine, Shanghai JiaoTong University, Shanghai, China

[17]Department of Renal and Rheumatology, Xinhua Hospital Affiliated To Shanghai JiaoTong University School of Medicine, Shanghai, China

[18]Department of Rheumatology, Shanghai East Hospital, Tongji University, Shanghai, China

[19]Department of Rheumatology and Immunology, Changzheng Hospital, Secondary Military Medicine University, Shanghai, China

[20]Department of Rheumatology, Shanghai Guanghua Hospital of Integrated Traditional and Western Medicine, Shanghai, China

[21]Department of Rheumatology, Longhua Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Shanghai, China

[22]Department of Rheumatology and Immunology, Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai, China

[23]Department of Radiology, Zhongshan Hospital, Fudan University, Shanghai, China

[24]Department of Nephrology, Zhongshan Hospital, Fudan University, Shanghai, China

[25]Department of Cardiac Surgery, Zhongshan Hospital, Fudan University, Shanghai, China

Sun and Yin contributed equally to this work.

© 2021 Asia Pacific League of Associations for Rheumatology and John Wiley & Sons Australia, Ltd.

[26]Department of Neurology, Zhongshan Hospital, Fudan University, Shanghai, China
[27]Department of Vascular Surgery, Zhongshan Hospital, Fudan University, Shanghai, China
[28]Department of Cardiology, Zhongshan Hospital, Fudan University, Shanghai, China
[29]Fudan University Library, Shanghai, China
[30]Evidence-Based Medicine Center, Fudan University, Shanghai, China

Correspondence
Lin-di Jiang, Department of Rheumatology, Zhongshan Hospital, Fudan University, 180 Fenglin Road, Shanghai 200032, China.
Email: zsh-rheum@hotmail.com

Funding information
This work was supported by the National Natural Science Foundation of China (NSFC 81771730 and 81901639)

Abstract

Background: Takayasu arteritis (TAK) is a rare large vessel vasculitis, and epidemiological data on TAK are lacking in China. Thus, we designed this study to estimate the TAK prevalence and incidence in residential Shanghai, China.

Methods: Data on diagnosed TAK cases aged over 16 years were retrieved from 22 tertiary hospitals in Shanghai through hospital electronic medical record systems between January 1, 2015 and December 31, 2017 to estimate the prevalence and incidence. A systematic literature review based on searches in PubMed, Ovid-Medline, Excerpta Medica Database (EMBASE), Web of Science, and China National Knowledge Infrastructure (CNKI) was performed to summarize TAK distribution across the world.

Results: In total 102 TAK patients, with 64% female, were identified. The point prevalence (2015-2017) was 7.01 (95% CI 5.65-8.37) cases per million, and the mean annual incidence was 2.33 (1.97-3.21) cases per million. The average age of TAK patients was 44 ± 16 years, with the highest prevalence (11.59 [9.23-19.50] cases per million) and incidence (3.55 [0.72 3.74] cases per million) in the 16 to 34 years population. Seventeen reports were included in the system review, showing that the epidemiology of TAK varied greatly across the world. The incidence and prevalence were both relatively higher in Asian countries, with the prevalence ranging 3.3-40 cases per million and annual incidence ranging 0.34-2.4 cases per million.

Conclusions: The prevalence and incidence of TAK in Shanghai was at moderate to high levels among the previous reports. The disease burden varied globally among racial populations.

KEYWORDS
China, incidence, prevalence, system review, Takayasu arteritis

1 | INTRODUCTION

Takayasu arteritis (TAK) is a chronic and granulomatous vasculitis that mainly involves the aorta and its primary branches. Stenosis, obstruction or dilation might lead to important organ dysfunctions and reduce quality of life.[1-3] Thus, although TAK is a rare disease, it deserves great concern. This disease was first reported in Japan[4] and is more commonly seen in East Asia. Although the prevalence and incidence have been reported in some regions, the global distribution characteristics of TAK are still unclear.

Currently, the identification of TAK patients is most widely performed according to the 1990 American College of Rheumatology (ACR) classification criteria.[5] Other diagnostic criteria include the initial 1994 definition in the Chapel Hill consensus and its 2012 revision,[6,7] the Ishikawa criteria,[8] as well as Sharma's criteria.[9] According to the 1990 ACR classification criteria, the diagnosis of TAK needs professional knowledge and imaging techniques. Hence, a definitive diagnosis is usually made in large-scale comprehensive hospitals. For most diseases, epidemiological surveys are mainly based on population data; however, for TAK, the survey of population-based data are scarce because of its low prevalence as well as the complicated diagnostic criteria.[3,10-13] Hospital-based investigation is an effective method for obtaining TAK epidemiological data.

Epidemiological data on TAK are still lacking in China. Shanghai, on the east coast of China, is one of the country's most important metropolises. There are in total 22 large-scale comprehensive hospitals, the catchment areas of which cover the whole city, providing all primary and secondary care for TAK to its residents. These hospitals have sufficient facilities and multidisciplinary specialist teams that were required by TAK for diagnosis, treatment and clinical

assessment. Thus, we designed this research using the diagnosed cases based on the electronic medical records systems in 22 comprehensive hospitals in combination with local population data to estimate the prevalence of TAK in Shanghai, China. Furthermore, a systematic review was performed to describe the global distribution and disease burden of TAK.

2 | MATERIALS AND METHODS

2.1 | Study design

A multidisciplinary team (MDT), comprised of rheumatologists, vascular surgeons, cardiologists, cardiac surgeons, nephrologists, neurologists, and imaging specialists, was established to discuss and draft the study protocol. This panel was also responsible for overseeing the process, the training of investigators, and the review of the TAK diagnosis. Data on TAK in Shanghai were collected from the electronic medical record systems of 22 comprehensive hospitals between January 1, 2015 and December 31, 2017. The electronic medical records comprise of both outpatients and inpatients.

A systematic literature search was also conducted. PubMed, Ovid-Medline, Excerpta Medica Database (EMBASE), Web of Science as well as China National Knowledge Infrastructure (CNKI) were searched before December 31, 2018 with terms involving TAK, incidence, and prevalence. Two researchers independently reviewed the reports and extracted the information according to the inclusion criteria. Disagreements were resolved by discussion.

2.2 | Ethics approval of the study protocol

The procedures were in accordance with the tenets of the 1975 Helsinki Declaration and its later amendments. The study protocol was approved by the Ethics Committees of Zhongshan Hospital, Fudan University, Shanghai, China (B2013-115[3]). Written informed consent was obtained from all patients to use their data.

2.3 | Data collection

2.3.1 | Study population

There are in total 22 large-scale comprehensive hospitals, the catchment areas of which could cover the whole city (Shanghai). The International Classification of Diseases (ICD)–10 code I177.601 was used to screen the electronic databases of the above 22 hospitals for identifying TAK cases diagnosed from January 1, 2015 to December 31, 2017. In addition, manual searches using key words including aortic ulceration, stenosis, occlusion, dilation, aneurysm, dissection, and pseudoaneurysm were also conducted. What is more, young patients (<40 years old) with hypertension, cerebrovascular accident/stroke, and limb claudication/pulselessness were also screened. The national personal identification number with the first 3 digits "310" was used to identify indigenous Shanghainese. Medical records of all TAK patients, who had been registered as Shanghainese with age over 16 years, were retrieved. Rehospitalization cases were excluded from the analysis.

The population of total indigenous Shanghainese (the national identity document [ID] also with the first digits "310") during the study period, was provided by the Shanghai Statistics Bureau. At the end of December 31, 2015, the total Shanghainese population was 14 429 700 and increased to 14 551 300 at the end of December 31, 2017.

2.3.2 | Diagnosis and angiographic classification of TAK

The diagnosis of TAK was confirmed by the MDT with reference to the 1990 ACR classification criteria.[5] All confirmed TAK cases were cross-matched against the Shanghai mortality database to identify survival status on December 31, 2017.

The angiographic classification referred to the 1996 Numano criteria: type I (branches of the aortic arch), type IIa (ascending aorta, aortic arch and its branches), type IIb (ascending aorta, aortic arch and its branches, and thoracic descending aorta), type III (thoracic descending aorta, abdominal aorta, and/or renal arteries), type IV (abdominal aorta and/or renal arteries), and type V (combined features of types IIb and IV).[14]

2.4 | Systematic literature review

The search strategy used Medical Subject Heading (MeSH) search terms for "Takayasu arteritis", "aortic arch syndrome" and "large vessel vasculitis" in combination with keyword terms for epidemiology or incidence or prevalence – ("Takayasu Arteritis" [MeSH] OR "Aortic Arch Syndromes" [MeSH] OR "Large vessel vasculitis" [MeSH]) AND ("epidemiology" OR "incidence" OR "prevalence"). The databases searched included PubMed, Ovid-Medline, EMBASE, Web of Science, and CNKI before December 31, 2018.

All articles were downloaded and selected on the basis of title and then the abstract for full review. Articles were included if they were written in English or Chinese language and were about the incidence or prevalence of TAK in human subjects. Exclusion criteria were review articles, conference proceedings, abstracts or editorials, articles in press, and observational studies unrelated to epidemiology. Information on author, journal, year of publication, country, region, diagnosis, study period, number of incidents or prevalent cases, incidence (per million person-years) or prevalence (per million persons) was collected. In addition, any age-, gender-, or ethnic group-specific incidence or prevalence rates reported were collected in detail. Age-adjusted or standardized results were presented whenever available. The screening process is shown in Figure 1. In the end, 17 reports with either population-based or hospital-based epidemiological data

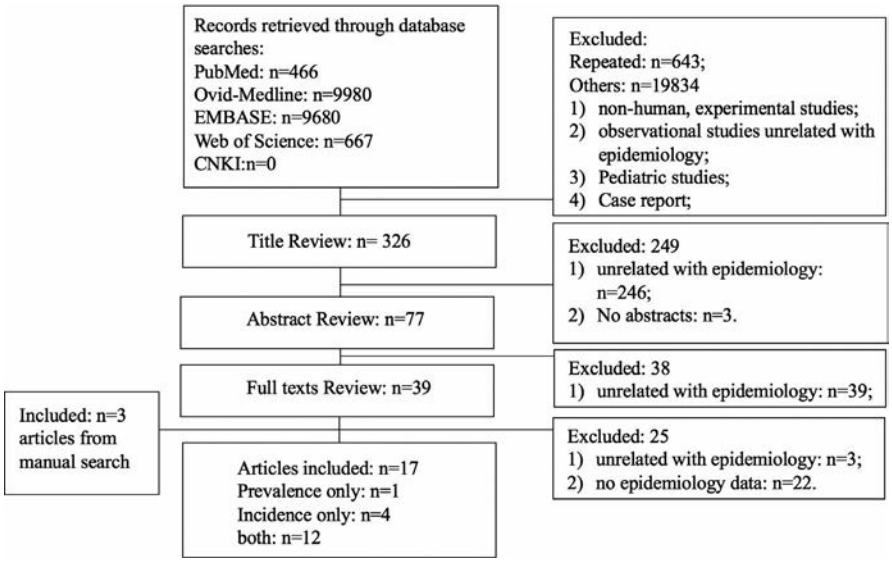

FIGURE 1 Flow chart of systematic literature review. A systematic literature search was conducted. PubMed, Ovid-Medline, Excerpta Medica Database (EMBASE), Web of Science as well as China National Knowledge Infrastructure (CNKI) were searched before December 31, 2018 with terms involving Takayasu arteritis, incidence, and prevalence. In the end, 17 reports with either population-based or hospital-based epidemiological data on Takayasu arteritis were included

on TAK were included. The quality of all included articles was graded as low to moderate according to the agency for healthcare research and quality tools (Table S1).[15]

2.5 | Statistical analysis

The general characteristics of TAK patients were summarized, including age, gender ratio, and imaging classification. The point prevalence (2015-2017) was estimated using the corresponding TAK case numbers as numerator and the population number at the end of December 31, 2017 as the denominator. For annual incidence estimation, the newly diagnosed cases between 2016 and 2017, referred to those diagnosed in 2015, were used as numerator and the average population number between 2016 and 2017 was used as the denominator. The rates of prevalence and incidence were defined as per million persons. We also calculated the prevalence by age (the age at enrollment) and gender groups, respectively. Poisson distribution was used for uncertainty estimation, reported as 95% confidence intervals (CI). Epidemiological data of the system review were presented as a histogram.

SPSS Statistics v25.0 (IBM, Armonk, NY, USA) was used for all analyses.

3 | RESULTS

3.1 | Epidemiology of TAK in Shanghai

In total, 270 suspected TAK patients, were identified from the electronic medical records systems of 22 comprehensive hospitals in Shanghai after the first screening. Thirty-four rehospitalization cases were excluded, and then the suspected cases were screened manually by 2 rounds of MDT review. One hundred and thirty-four cases, who only had a single vascular lesion without any systemic symptoms and systemic as well as local inflammation, were also excluded. Finally, 102 patients were confirmed (Figure 2). The average age of TAK patients at enrollment was 44 ± 16 years, and the gender ratio (female:male) was 1.8:1. Given the imaging classification, type V was the most commonly seen (38.2%), followed by type I (22.6%), type II (20.6%: IIa, 9.8%; IIb, 10.8%), type IV (11.8%), and type III (6.8%).

Of the 102 confirmed TAK patients, 68 were diagnosed between 2016 and 2017 (incident cases), and the remaining 34 cases were diagnosed in 2015, but were all still alive and living within the study area on the date of overall prevalence estimation. The point prevalence (2015-2017) was 7.01 (95% CI 5.65-8.37) cases per million, while based on the 68 patients newly diagnosed between 2016 and 2017, the mean annual incidence of TAK was 2.33 (95% CI 1.97-3.21) cases per million total population. The prevalence (8.99 [95% CI 6.86-11.2]) and incidence (3.00 [95% CI 2.13-4.76]) were both higher in the female population and was highest in the 16-34 years subgroup (prevalence 11.59 [95% CI 9.23-19.50] cases per million; incidence 3.55 [95% CI 0.72 3.74] cases per million) (Table 1).

3.2 | Prevalence of TAK worldwide

Among 13 TAK prevalence studies, 5 were population-based[3,10-13] and 8 were hospital-based.[16-23] According to population-based data from Japan up to 2012, the prevalence is over 40 per million, which is the highest in our review.[3] Compared with Asia, the prevalence of TAK in Europe was much lower, ranging from 4.7 to 8 per million based on different time spans[10-12] (Table 2 and Figure 3).

From hospital-based studies, the prevalence in Turkey was higher than in other countries in Asia: 33 cases per million in Edirne, 2014.[16] In Europe, the highest prevalence was reported in southeastern

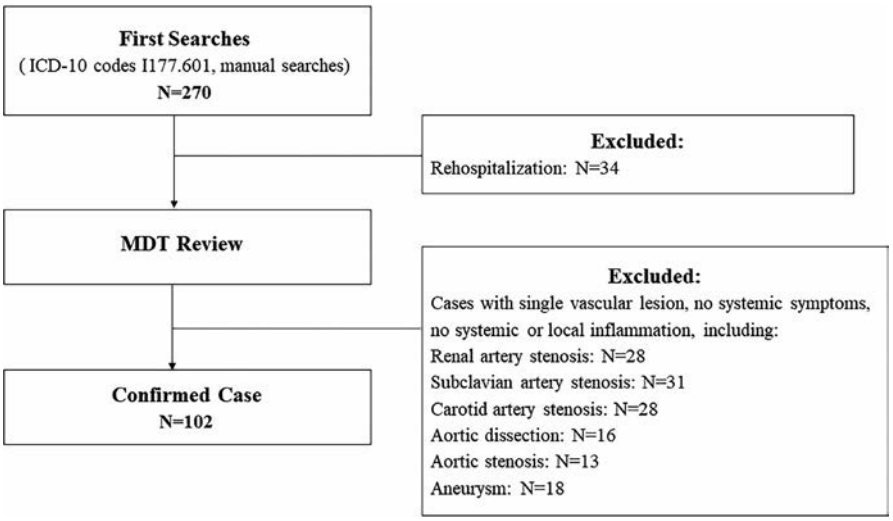

FIGURE 2 Flow chart of study case screening and confirmed diagnosis. In total, 270 suspected Takayasu arteritis patients, were identified from the electronic medical records systems of 22 comprehensive hospitals in Shanghai using the International Classification of Diseases (ICD)−10 code I177.601 or manual searches. First, 34 rehospitalization cases were excluded, and then the suspected cases were screened manually by 2 rounds of multidisciplinary team (MDT) review. One hundred and thirty-four cases, who only had a single vascular lesion without any systemic symptoms and systemic as well as local inflammation, were also excluded. Finally, 102 patients were confirmed

TABLE 1 The epidemiology of Takayasu arteritis in Shanghai during 2015 and 2017

Year	Subgroup	No. of cases	Population size	Prevalence (2015-2017) Cases per million (95% CI)	Mean annual incidence (2016-2017) Cases per million (95% CI)
2015	Total	34	14 429 700		
	Female	22	7 266 000		
	Male	12	7 163 700		
	16-34 y old	11	2 914 000		
	35-59 y old	14	5 535 700		
	>60 y old	9	4 359 500		
2016	Total	33	14 660 000		
	Female	26	7 306 500		
	Male	7	7 193 500		
	16-34 y old	14	2 755 900		
	35-59 y old	14	5 482 400		
	>60 y old	5	4 578 000		
2017	Total	35	14 551 300	7.01 (5.65 8.37)	2.33 (1.97 3.21)
	Female	18	7 338 400	8.99 (6.86-11.2)	3.00 (2.13 4.76)
	Male	17	7 212 900	4.99 (3.37-6.64)	1.66 (0.98 3.14)
	16-34 y old	5	2 589 700	11.59 (9.23-19.50)	3.55 (0.72 3.74)
	35-59 y old	20	5 415 000	8.86 (6.28-11.20)	3.12 (1.47 5.11)
	>60 y old	10	4 816 100	4.98 (3.14-7.33)	1.59 (1.04 3.29)

Norway up to 2012, 25.2 per million according to the Ishikawa diagnostic criteria, and 22.0 per million according to 1990 ACR criteria.[19] One study from Western Australia reported TAK prevalence in 1992 was 3.2 cases per million in Caucasians[22] (Table 2 and Figure 3).

Three studies reported prevalence in age subgroups, and indicated that the prevalence in young people (<40 years old) was higher,[10,18] except the survey in Izmir, Turkey, 2010[17] (Table 2).

3.3 | Incidence of TAK worldwide

Among the 15 included TAK incidence studies, 4 were population-based[10-13] and 11 were hospital-based.[16-26] According to population-based data, the highest incidence was reported in Korea, where it was up to 2.4 cases per million per year and the ratio of female:male was 4.44:1.[13] The incidence in Europe was

TABLE 2 The prevalence of Takayasu arteritis in different countries and regions

Study	Population	Design	Diagnosis	Case no.	Prevalence per million (95% CI)			
					Total	Male	Female	<40 y old
Watts R 2009	England (Norfolk region, UK, annual)	Population-based (UKGPRD)	UKGPRD or ICD: G575.11	16	4.7 (3.1-8.5)	-	-	
Dreyer L 2011	Denmark (1990-2009)[a]	Population-based (NHR)	ICD8: 446.90 and 446.91; ICD10: M31.4	19	8 (5.08-12.48)	-	-	12
Terao 2014	Japan (2012)	Population-based	1990 ACR classification criteria	5881	40	-	-	-
Park S J 2017	Korea (2012)	Population-based	ICD 10	1438	28.2	9	47	-
Kanecki K 2018	Poland (2011-2015)	Population-based	ICD10: M31.4	177	4-6	-	-	-
Waern AU 1983	Sweden (Uppsala County, 1969-1976)	Hospital-based	Angiography	15	0.64 (yearly)	-	-	-
El-Reshaid K 1995	Kuwait (nationwide)	Hospital-based	Angiography	19	7.8	-	-	9.5
Mohammad A J 2015	Sweden (Skane, 2012)	Hospital-based	1990 ACR classification criteria	13	10.2 (3.1-117.2) (Swedish) 25.5 (3.2-47.9) (Non-Swedish)	0	26.2 (11.9-40.4)	-
Carlos 2015	Spain (Marbella, 2010)	Hospital-based	Hospital diagnosis	5	10.5	-	-	-
Saritas F 2016	Turkey (Edirne, 2014)	Hospital-based	1990 ACR classification criteria	23	33 (19-48)	9 (1-19)	58 (31-85)	-
Birlik M 2016	Turkey (Izmir, 2010)	Hospital-based	1990 ACR classification criteria	41	12.8 (12-13.6)	1.9 (1.5-2.4)	23.5 (21.9-25)	4 (3.5-4.6)
Birgir G 2017	Norway (Southeast, 2012)	Hospital-based	1990 ACR classification criteria /Ishikawa in 1995	78	22 (17-29) (northern European)	-	-	-
					78.1 (38-152) (Asian whites)	-	-	-
					108.3 (46-254) (Africans)	-	-	-
Makin K 2017	Western Australia (2014)	Hospital-based	ICD 10: M31.4, I77.6; Keywords; Doctors diagnosis	14	3.9 (overall) 3. 2 (Caucasians) 15 (Asians)	-	-	-

Abbreviations: ACR, American College of Rheumatology; HIRA, the Health Insurance Review and Assessment Service; NHR, The Danish National Hospital Register; UK, United Kingdom; UKGPRD, The UK General Practice Research Database.

[a]Capital region, the Zealand region, the Island of Bornholm, and Christians Island.

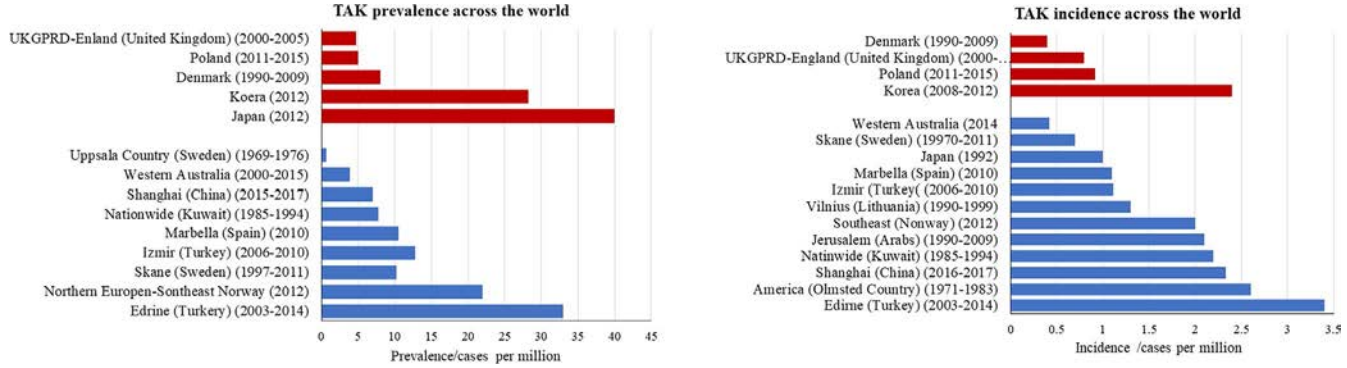

FIGURE 3 The prevalence and incidence of Takayasu arteritis (TAK) across the world

relatively low (0.4-0.92 cases per million per year)[10-12] (Table 3 and Figure 3).

Analysis in hospital-based studies showed that the incidence of TAK worldwide was 0.42-3.4 cases per million per year. The highest incidence was 3.4 cases per million per year reported in Edirne, Turkey.[16] In the US, the yearly incidence of TAK was 2.6 cases per million, second highest in the world.[25] In a Western Australian study from 2000 to 2015, the incidence in Caucasians was 0.3 cases per million per year[22] (Table 3 and Figure 3).

There were only 3 articles mentioning the concrete data about gender, pointing out that the incidence in males was much lower than that in females.[13,16,21] In addition, 3 reports indicated that the incidence was higher in young people (<40 years),[10,17,21] although another 2 studies in Turkey and Sweden showed no difference in different age groups[16,18] (Table 3).

4 | DISCUSSION

To our knowledge, this is the first study to estimate the epidemiology of TAK in a Chinese population in a defined geographical area, Shanghai, supporting approximately 24 183 300 people (approximately 14 million indigenous Shanghainese). Shanghai is one of the most important megalopolises in China, and has 22 large-scale comprehensive hospitals, which covered all the 16 administrative regions and provide medical support for the overwhelming majority of Shanghai residents. Due to the complicated diagnostic requirements, it is most likely that TAK patients among Shanghai residents would be identified and followed in these 22 comprehensive hospitals. Thus, we designed this study to estimate the TAK epidemiology through the electronic medical record systems of these 22 comprehensive hospitals in Shanghai.

In summary, the point prevalence (2015-2017) was 7.01 cases per million, with mean annual incidence of 2.33 cases per million, which was both at moderate to high levels among the previous reports. The incidence reported in our study was higher than the reports during the same period from Western countries. Analysis of gender and age subgroups were also performed to further identify the disease burden. The highest prevalence (11.59 cases per million) and incidence (3.55 cases per million) was both demonstrated in the 14-34 years old population. Furthermore, our results also indicated gender difference in the prevalence and incidence, which was both much higher in females than that in males, and was in accordance with results in former research.[13,16,21]

In the present study, we also made a comprehensive literature review in order to clarify the TAK burden across the world. High heterogeneity was found. In Asia, the annual incidence was 0.34-2.4 cases per million, while the prevalence ranged 3.3-40 cases per million. In European countries, America, Australia, and other countries and regions, the annual incidence rate was about 0.4-2.6 cases per million, with the prevalence of 0.64-22 cases per million. The etiology of TAK remains unclear. The discrepancy of regional distribution may be attributable to inherent and acquired risk factors, such as genetic susceptibility, infection-related factors, and environmental and economic factors. Various investigation intervals in the reports may also contribute to the high heterogeneity. Further study was needed to clarify the features of TAK epidemiology during the same period.

In addition, the incidence of TAK in Asia showed an increasing trend, while there was no changed trend in incidence in Europe and America from the 1980s to 2010s. Furthermore, female patients were predominant, while there was no obviously higher incidence in the subgroup aged <40 years than in other age subgroups. This may be related with the delay of diagnosis from disease onset. Most patients with TAK manifest occult onset and complain of mild symptoms, which results in ignoring the existence of this special disease in its early stage, especially in the regions with underdeveloped systems of public health. Once there is appearance of typical manifestations, TAK can be correctly identified and classified. However, in order to obtain precise epidemic data, the age at diagnosis or survey was always used instead of onset age. What is more, the reported incidence showed significant differences between population-based and hospital-based data. These differences may be attributed to the especially strict diagnostic procedure used and some potential patients with few manifestations may have been missed in the hospital-based study.

TABLE 3 The incidence of Takayasu arteritis in different countries and regions

Author	Population	Database	Diagnosis	Case no.	Incidence per million per year (95% CI)			
					Total	Male	Female	<40 y old
Watts R 2009	England (Norfolk region, UK, 2000-2005)	Population-based (UKGPRD)	Read code: G575.11	14	0.8 (0.4-1.3)	-	-	-
Dreyer L 2011	Denmark (1990-2009)[a]	Population-based (NHR)	ICD8: 446.90 and 446.91; ICD10: M31.4	19	0.4 (0.25-0.62)	-	-	0.6 (0.36-1.12)
Park S J 2017	Korea (2008-2012)	Population-based (HIRA database)	ICD 10	612	2.4	0.9	4	-
Kanecki K 2018	Poland (2011-2015)	Population-based	ICD10: M31.4	177	0.92 (0.68-1.16)	-	-	-
Hall S 1985	America (Olmsted County, 1971-1983)	Hospital-based	Angiography	15	2.6	-	-	-
Koide K 1992	Japan	Hospital-based	Experts diagnosis	2148 (1973-1975) 2606 (1982-1984)	1 (1973-1975) 1.1 (1982-1984)	-	-	-
El-Reshaid K 1995	Kuwait (nationwide, 1985-1994)	Hospital-based	Angiography	19	2.2	-	-	3.3
Dadoniene 2005	Lithuania (Vilnius, 1990-1999)	Hospital-based	1990 ACR classification criteria	6	1.3 (1.2-4.3)	-	-	-
Mohammad A J 2015	Sweden (Skane, 1997-2011)	Hospital-based	1990 ACR classification criteria	10	0.7 (0.3-1.2) (Total) 0.6 (0.2-1.1) (Swedish) 1.4 (0-2.9) (Non-Swedish)	0	1.5 (0.6-2.4)	1.1 (0.3-1.9)
Carlos 2015	Spain (Marbella)	Hospital-based	Hospital diagnosis	5	1.1	-	-	-
Saritas F 2016	Turkey (Edirne, 2003-2014)	Hospital-based	1990 ACR classification criteria	23	0.34	0.11	0.56	-
Birlik M 2016	Turkey (Izmir, 2006-2010)	Hospital-based	1990 ACR classification criteria	41	1.11 (0.54-1.67)	0.15 (0-0.56)	2.06 0.88-3.23)	0.83 (0-1.67)
Nesher 2016	Arabs (Jerusalem, 1990-2009)	Hospital-based (hospital registry system)	Not mentioned	11	2.1 (1.2-2.9)	-	-	-
Birgir G 2017	Norway (Southeast, 1999-2012)	Hospital-based	1990 ACR classification criteria/ Ishikawa in 1995	55	1.5 (1.2-2.0)	-	-	-
Makin K 2017	Western Australia (2000-2015)	Hospital-based	ICD 10: M31.4, I77.6; Keywords: Doctors diagnosis	18	0.42 (overall) 0.3 (Caucasians) 1.1 (Asians)	-	-	-

Abbreviations: ACR, American College of Rheumatology; HIRA, the Health Insurance Review and Assessment Service; ICD, International Classification of Diseases; NHR, The Danish National Hospital Register; UK, United Kingdom; UKGPRD, The UK General Practice Research Database.

[a]Capital region, the Zealand region, the Island of Bornholm, and Christians Island.

There are some limitations in the present study. First, our data was hospital-based instead of population-based, so any patients who did not visit one of the 22 study hospitals, would be missed in our data sources. Second, the prevalence we calculated was from 2015 to 2017, and 3 years might not be enough to confidently conclude epidemiological data. Third, we only estimated the mean annual incidence between 2016-2017 using the new diagnosed cases after 2015, which might lead to some bias. Further epidemiological studies with larger samples and longer time spans, are needed to identify the incidence and prevalence of TAK in Chinese populations.

5 | CONCLUSIONS

In conclusion, this is the first report about the epidemiology of TAK in Shanghai China and provides a comprehensive summary of the disease burden worldwide. We estimated the point prevalence (2015-2017) of TAK in Shanghai as 7.01 cases per million, with the mean annual incidence of 2.33 cases per million, which are higher than that in some Western countries.

ACKNOWLEDGEMENTS

None.

CONFLICT OF INTEREST

The authors declare they have no conflicts of interests.

AUTHOR CONTRIBUTIONS

Ying Sun and Meng-meng Yin were responsible for the data analysis and writing the paper; Li-li Ma and Xiao-min Dai were responsible for the case collection of Zhongshan Hospital and system review; Liang-jing Lv, Xiao-xiang Chen, Shuang Ye, Ting Li, Jie Chen, Dong-bao Zhao, Rui-na Kong, Qiang-hua Wei[5], Guang-hui Yang, Su-gang Gong, Cheng-de Yang, Hong-lei Liu, Yu Xue, Jian-ping Tang, Run Feng, Ai Peng, Ling Qin, Hua Liu, Xiao Su, Hui-ping Huang, Jian-long Guan, Dan Luo, Sheng-ming Dai, Fu-tao Zhao, Zhen-Hang Zhu, Xiao-yan Zhang, Jie Han, Jia-yi Wang, Chun-yuan Xiao, Hu-ji Xu, Xin Wu, Dong-yi He, Jian-chun Mao, Zhu-jing Zhu, Luan Xue, and Ben Li were responsible for the case collection of the other 21 hospitals in Shanghai; Jiang Lin, Jian-zhou Zou, Xiao-ning Sun, Jing Ding, Zhi-hui Dong, and Xiang-fei Wang were the members of the MDT; Jun-Ying was the adviser for the literature review; Lin-di Jiang was response for study design.

ORCID

Ting Li https://orcid.org/0000-0001-6800-6650
Sheng-Ming Dai https://orcid.org/0000-0001-8876-4205
Lin-di Jiang https://orcid.org/0000-0001-7747-7788

REFERENCES

1. Kerr GS. Takayasu's arteritis. *Rheum Dis Clin North Am*. 1995;21:1041-1058.
2. Kerr GS, Hallahan CW, Giordano J, et al. Takayasu arteritis. *Ann Intern Med*. 1994;120:919-929.
3. Terao C, Yoshifuji H, Mimori T. Recent advances in Takayasu arteritis. *Int J Rheum Dis*. 2014;17:238-247.
4. Koide K. Takayasu arteritis in Japan. *Heart Vessels Suppl*. 1992;7:48-54.
5. Arend WP, Michel BA, Bloch DA, et al. The American College of Rheumatology 1990 criteria for the classification of Takayasu arteritis. *Arthritis Rheum*. 1990;33:1129-1134.
6. Jennette JC, Falk RJ, Andrassy K, et al. Nomenclature of systemic vasculitides. Proposal of an international consensus conference. *Arthritis Rheum*. 1994;37:187-192.
7. Jennette JC, Falk RJ, Bacon PA, et al. 2012 revised international Chapel Hill Consensus Conference nomenclature of vasculitides. *Arthritis Rheum*. 2013;65:1-11.
8. Ishikawa K. Diagnostic approach and proposed criteria for the clinical diagnosis of Takayasu's arteriopathy. *J Am Coll Cardiol*. 1988;12:964-972.
9. Sharma BK, Jain S, Suri S, Numano F. Diagnostic criteria for Takayasu arteritis. *Int J Cardiol*. 1996;54(Suppl):S141-S147.
10. Dreyer L, Faurschou M, Baslund B. A population-based study of Takayasu's arteritis in eastern Denmark. *Clin Exp Rheumato*. 2011;29:40-42.
11. Watts RA, Al-Taiar A, Mooney J, Scott DG, Macgregor AJ. The epidemiology of Takayasu arteritis in the UK. *Rheumatology (Oxford)*. 2009;48:1008-1011.
12. Kanecki K, Nitsch-Osuch A, Tyszko PZ, Gorynski P, Smolarczyk R, Suchta K. Takayasu's arteritis: a rare disease in Poland. *Ann Agric Environ Med*. 2018;25:469-472.
13. Park SJ, Kim HJ, Park H, et al. Incidence, prevalence, mortality and causes of death in Takayasu Arteritis in Korea-a nationwide, population-based study. *Int J Cardiol*. 2017;235:100-104.
14. Numano F, Kobayashi Y. Takayasu Arteritis-beyond Pulselessness. *Int Med*. 1999;38:226-232.
15. Zeng X, Zhang Y, Kwong JSW, et al. The methodological quality assessment tools for preclinical and clinical studies, systematic review and meta-analysis, and clinical practice guideline: a systematic review. *J Evid Based Med*. 2015;8:2-10.
16. Saritas F, Donmez S, Direskeneli H, Pamuk ON. The epidemiology of Takayasu arteritis: a hospital-based study from northwestern part of Turkey. *Rheumatol Int*. 2016;36:911-916.
17. Birlik M, Kücükyavas Y, Aksu K, et al. Epidemiology of Takayasu's arteritis in Turkey. *Clin Exp Rheumatol*. 2016;34:S33-S39.
18. el-Reshaid K, Varro J, Al-Duwairi Q, Anim JT. Takayasu's arteritis in Kuwait. *J Trop Med Hyg*. 1995;98:299-305.
19. Gudbrandsson B, Molberg Y, Garen T, Palm Y. Prevalence, incidence and disease characteristics of Takayasu Arteritis by ethnic background: data from a large, population based cohort resident in Southern Norway. *Arthritis Care Res (Hoboken)*. 2017;69:278-285.
20. Urban Waern A, Andersson P, Hemmingsson A. Takayasu's arteritis: a hospital-region based study on occurrence, treatment and prognosis. *Angiology*. 1983;34:311-320.
21. Mohammad AJ, Mandl T. Takayasu arteritis in Southern Sweden. *J Rheumatol*. 2015;42:853-858.
22. Romero-Gómez C, Aguilar-García JA, García-de-Lucas MD, et al. Epidemiological study of primary systemic vasculitides among adults in Southern Spain and review of the main epidemiological studies. *Clin Exp Rheumatol*. 2015;33:S11-S18.
23. Makin K, Isbel M, Nossent J. Frequency, presentation, and outcome of Takayasu arteritis in Western Australia. *Mod Rheumatol*. 2017;27:1-5.
24. Nesher G, Ben-Chetrit E, Mazal B, Breuer G. The incidence of primary systemic vasculitis in Jerusalem: a 20-year hospital-based retrospective study. *J Rheumatol*. 2016;43:1072-1077.
25. Hall S. Takayasu arteritis: A study of 32 North American patients. *Medicine (Baltimore)*. 1985;64:89-99.

26. Dadoniene J, Kirdaite G, Mackiewicz Z, Rimkevicius A, Haugeberg G. Incidence of primary systemic vasculitides in Vilnius: a university hospital population based study. *Ann Rheum Dis*. 2005;64:335-336.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Sun Y, Yin M-M, Ma L-L, et al. Epidemiology of Takayasu arteritis in Shanghai: A hospital-based study and systematic review. *Int J Rheum Dis*. 2021;24:1247–1256. https://doi.org/10.1111/1756-185X.14183

Received: 30 June 2021 | Revised: 27 July 2021 | Accepted: 2 August 2021

DOI: 10.1111/1756-185X.14205

International Journal of Rheumatic Diseases

WILEY

REVIEW

The current role of NLRP3 inflammasome polymorphism in gout susceptibility

Denise Clavijo-Cornejo[1] | Olivia Hernández-González[2] | Marwin Gutierrez[1]

[1]Division of Musculoskeletal and Rheumatic Diseases, Instituto Nacional de Rehabilitación, Mexico City, Mexico

[2]Electron Microscopy Laboratory, Instituto Nacional de Rehabilitación, Mexico City, Mexico

Correspondence
Denise Clavijo-Cornejo, Division of Musculoskeletal and Rheumatic Diseases, Instituto Nacional de Rehabilitación Luis Guillermo Ibarra Ibarra, Calzada México-Xochimilco 289, Colonia Arenal de Guadalupe, CP 143898, Mexico City, Mexico.
Email: dence.cc@gmail.com

Funding information
This study was funded by CONACYT: Fondo Sectorial de Investigación en Salud y Seguridad Social Convocatoria: S0008-2016-2; Solicitud: 273143, Instituto Nacional de Rehabilitación "Luis Guillermo Ibarra" (INRLGII)

Abstract

Introduction: The NLR family pyrin domain containing 3 (NLRP3) signaling pathway has an important role in inflammation mediated by monosodium urate crystals in gout, and the characterization of single nucleotide polymorphisms (SNPs) have helped to recognize disease susceptibility.

Objective: The aim of this review is to provide an overview of the potential role of the inflammasome gene SNPs as a susceptibility factor for gout, discussing the current evidence available.

Methods: This review analyzes the relevant literature in the field of inflammasome SNPs and gout published in the last 10 years. The systematic research was performed in 16 articles, including both the SNPs associated and those not associated with gout, with the goal to have a complete overview.

Results: Sixty-nine SNPs from 10 different genes have been reported in the literature. Of these, 13 SNPs present association with gout susceptibility in different populations, while 56 have been established as not being associated with the disease.

Conclusions: This review is a summary of the potential role of inflammasome gene SNPs and their association with gout risk, all of them related with NLRP3 inflammasome signaling, suggesting these polymorphisms are susceptibility candidates and genetic markers for gout. From the 69 SNPs analyzed in the literature, 13 of them have been associated with gout as follows: NLRP3 (rs3806268 and rs10754558), CARD8 (rs2043211), TLR4 (rs2149356), CD14 (rs2569190), IL-1β (rs1143623), P2RX7 (rs2230911, rs1653624, rs7958316 and rs17525809) and PPARGC1B (rs45520937, rs10491360 and rs7712296) in different populations.

KEYWORDS
gout, inflammasome, Inflammation, NLRP3, SNPs

1 | INTRODUCTION

Gout is a common chronic inflammatory disease which results from an increase in elevated serum uric acid, which can lead to recurrent acute attacks of arthritis, renal failure, hypertension and cardiovascular disease as a result of the precipitation of monosodium urate (MSU) crystals.[1,2] The pathogenesis of gout has not been fully determined, but it is influenced by various factors including the environmental and the genetic ones.[3]

A main characteristic of gout is the presence of inflammation and particularity NLR family pyrin domain containing 3 (NLRP3) inflammasome activation, which leads the production and release of

© 2021 Asia Pacific League of Associations for Rheumatology and John Wiley & Sons Australia, Ltd.

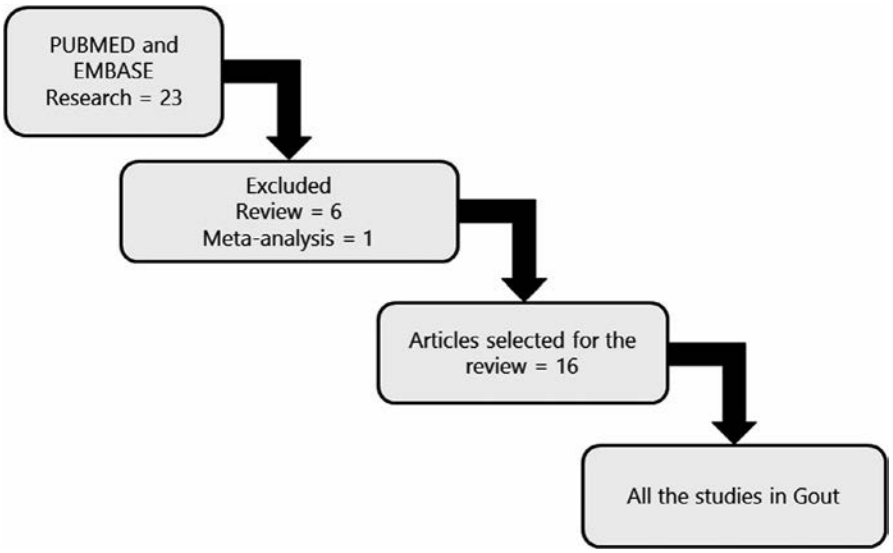

FIGURE 1 Flow chart of research strategy

inflammatory cytokines as interleukin (IL)-1β.[4] After MSU crystals are precipitated, they are recognized by the membrane-bound Toll-like receptor (TLR), mainly TLR2 and TLR4, and CD14 as an adaptor molecule, that activates the inflammasome.[5] NLRP3, also known as NACHT, LRR and PYD Domains-containing protein 3 (NALP3), is a multiproteic complex which include the apoptosis-associated speck-like protein (ASC) and the caspase recruitment domain containing protein 8 (CARD8). The NLRP3 inflammasome activates caspase-1 which proteolytically processes the pro-IL-1β into its active form.[6] It was proposed that changes in adenosine triphosphate (ATP) concentration activates NLRP3. ATP is a ligand of the Purinergic receptor P2X ligand-gated ion channel 7 (P2X7R) which has a vital function in immunity and autoimmunity and modulates the immune cell differentiation and triggers cytokine release, activating inflammation processes.[7] To regulate the inflammatory processes, the peroxisome proliferator-activated receptor gamma (PPARγ) is activated and acts as an anti-inflammatory response, inhibiting the proinflammatory cytokine products.[8] Taking into account that single nucleotide polymorphisms (SNPs) are part of the underlying mechanisms of the innate immune response, the aim of this review is to summarize and provide an overview of the potential role of the inflammasome gene polymorphisms as a susceptibility factor for gout, discussing the current evidence available.

2 | METHODS

2.1 | Literature review criteria and research strategy

All relevant literature in the field of inflammasome polymorphism and gout published in the last 10 years have been reviewed. We included original articles concerning studies in humans, published between April 2010 to November 2020. To identify all available studies, a detailed research was conducted according to PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines.[9] A systematic research was performed in the electronic databases (PubMed, and EMBASE), using the following search terms in all possible combinations: gout AND single nucleotide polymorphism AND one of the follow genes: single nucleotide polymorphism, gout, inflammasome, NALP3 (NLRP3) or TLR4 or TLR2 or CARD8 or IL-1β or P2RX7 or PPARGC1b or CD14 or IL-18. In addition, the reference lists of all retrieved articles were manually reviewed. Two independent authors analyzed each article and performed the data extraction independently. In case of disagreement, a third investigator was consulted. Discrepancies were resolved by consensus.

2.2 | Inclusion and exclusion criteria

We excluded from this review the following types of publications: reviews and meta-analysis and articles not in English. Research results were screened to avoid duplicates. Titles, abstracts, and full reports of articles identified were systematically screened with regard to inclusion and exclusion criteria.

3 | RESULTS

A total of 23 publications were identified in PUBMED and EMBASE databases. Sixteen articles were finally included in our review. The results of the research strategy are illustrated in Figure 1. The present review includes both the SNPs associated and those not associated with gout, with the goal to have a complete overview; the description of all the SNPs are summarized in Table 1.

3.1 | NLRP3 inflammasome polymorphism described in the literature

3.1.1 | NLRP3 polymorphism

Meng et al.[10] analyzed 17 polymorphisms from Qingdao (China) mentioned in Table 1, and no significant differences were identified for all

TABLE 1 Inflammasome gene polymorphism and gout association

Gene	dbSNP ID	Gout association (yes/no)	Population	Cohort		References
				Gout	Control	
NLRP3	rs7512998 rs7525979 rs4925651 rs4925650 rs4925648 rs4612666 rs3806268 rs3806266 rs3738448 rs12565738 rs12239046 rs12143966 rs12137901 rs10925019 rs10754557 rs10754555 rs10159239	No	Qingdao, China	480	480	Meng et al.[10]
	rs3806268	Yes	Eastern China	247	247	Deng et al.[11]
	rs4612666 rs7512998 rs10754558 rs12137901 rs12239046 rs12565738	No				
	rs7512998 rs10754558 rs35829419	No	European	1494	10 942	McKinney et al.[12]
			New Zealand Polynesian	863	1030	
	rs7512998 rs10754558 rs12137901	No	Eastern China	320	320	Wang et al.[13]
	rs35829419	No	Taiwan	448	943	Chang et al.[14]
	rs10754558	Yes	Sichuan, China	583	459	Zhang et al.[15]
	rs4612666 rs1539019	No				
CARD8	rs2043211	Yes	Qingdao, China	396	403	Chen et al.[16]
			European	1494	10 942	McKinney et al.[12]
			New Zealand Polynesian	863	1030	
		No	Korea	242	280	Lee et al.[17]
TLR2	rs5743708 (Arg677Trp, Arg753Gln and −196 to −174 deletion)	No	Nanchong, China	215	216	Cai et al.[18]
	rs4696480	No	European	1494	10 942	McKinney et al.[12]
			New Zealand Polynesian	863	1030	
CD14	rs2569190	Yes	European	1494	10 942	McKinney et al.[12]
			New Zealand Polynesian	863	1030	

(Continues)

TABLE 1 (Continued)

Gene	dbSNP ID	Gout association (yes/no)	Population	Cohort		References
				Gout	Control	
TLR4	Asp299Gly Thr399Ile	No	Sichuan, Chinese	218	226	Qing et al.[19]
	s2149356	Yes	Sichuan, China	459	669	Qing et al.[20]
			European	1614	13 005	Rasheed et al.[21]
			New Zealand Polynesian	636	920	
	rs2149356	No	Spain	125	300	Torres et al.[22]
IL-1β	rs1143623	Yes	European	1494	10 942	McKinney et al.[12]
			New Zealand Polynesian	863	1,030	
IL-18	rs1946518 rs187238	No	Qingdao University	202	493	Li et al.[13]
P2RX7	rs17525809	No	European	1494	10 942	McKinney et al.[12]
			New Zealand Polynesian	863	1030	
	rs3751142	No	Korea	242	280	Lee et al.[17]
	rs2230911	Yes	Ningbo, China	293	269	Ying et al.[24]
	rs208294 rs435309 rs28360447 rs1718119 rs28360457 rs3751143	No				
	rs1653624 rs7958316 rs17525809	Yes	Anhui, China	117	95 (Hyperuricemia)	Tao et al.[25]
	rs208294 rs10160951 rs1718119 rs16950860 rs2230912	No				
PPARGC1B	rs45520937 rs10491360 rs7712296	Yes	Taiwan	448	943	Chang et al.[14]
	rs10515638 rs76097064 rs10515638 rs10491361 rs7732671	No				
PPARγ	rs10510410 rs10510411 rs10510412 rs10510417 rs2938392 rs2292101 rs10510418 rs1801282 rs1899951 rs1805192 rs4135268 rs72551363 rs709157	No				

Note: dbSNP ID, National Center for Biotechnology Information database of genetic variation.

the SNPs. After a few years, Deng et al.[11] analyzed 7 SNPs (Table 1) from eastern China, showing that individuals with the GG (odds ratio [OR] = 1.83) genotype of NLRP3 rs3806268 were associated with increased risk of primary gout when compared with the A/A genotype (Table 2), while no significant associations were described for the remaining SNPs cited in Table 1. Mckinney et al.[12] analyzed 3 SNPs (rs7512998, rs10754558 and rs35829419) from European and New Zealand Polynesian (Māori and Pacific Island) populations; the polymorphisms were genotyped in both populations, finding no significant association. In the same year, Wang et al.[13] explored 3 NLRP3 SNPs (rs7512998, rs10754558 and rs12137901) in Eastern China and they did not find a significant association between NLRP3 polymorphisms and the risk of gout. Two years later, Chang et al.[14] screened the SNP NLRP3 rs35829419 in a population from Taiwan (Han Chinese population) and reported similar results as Mckinney et al.,[12] finding no significant association with gout. Zhang et al.[15] analyzed 3 NALP3 polymorphisms (rs10754558, rs4612666 and rs1539019) in a Han Chinese population, finding that the allelic frequency G (OR = 1.30) of rs10754558 was significantly increased in the gout patients compared with the group control, while people carrying the G/G genotype (adjusted OR = 2.66) had a higher risk for developing gout than those carrying the C/C genotype (Table 2).

3.1.2 | CARD8 polymorphism

Chen et al.[16] analyzed the CARD8 rs2043211 polymorphism in a Chinese population concluding that individuals carrying the A allele had a greater risk for developing gout compared to those carrying the T allele (OR = 0.84) (Table 2); additionally they described an association between rs2043211 and gout under the recessive model, finding that patients carrying genotype A/A had lower risk for gout compared to TT/TA genotypes (OR = 0.65) as shown in Table 2. Mckinney et al.[12] in the same year focused their attention on CARD8 rs2043211 polymorph<<<ism in European and New Zealand Polynesian populations, showing a nominal allelic association of T allele with gout when analyzing the populations together by a meta-analysis (OR = 1.12), but even more it was an association with gout just in Europeans (OR = 1.11) (Table 2). On the other hand, Won Lee et al.[17] did not find a difference in genotypic frequency of the CARD8 rs2043211 between gout and control patients in a Korean population.

3.1.3 | TLR2 and TLR4 and CD14 polymorphism

Cai et al.[18] analyzed 3 SNPs, Arg677Trp, Arg753Gln and the 196 to −174 deletion (rs5743708), demonstrating no significant differences in genotype and allele frequencies between the study groups, which suggests no association with susceptibility to gout in their Chinese population. Mckinney et al.[12] analyzed the TLR2 rs4696480 and showed no significant associations with gout, either in European or New Zealand populations, but interestingly they found a nominal allelic association of the CD14 rs2569190, concluding that A allele is significantly associated with gout (OR = 1.08) (Table 2).

Four TLR4 SNPs were analyzed (Table 1); Qing et al,[19] analyzed the genotype of 2 functional variants within the TLR4 gene (Asp299Gly and Thr399Ile) showing no evidence for involvement of this polymorphism in the susceptibility to develop gout in a Han Chinese population (North Sichuan).

Lately, Qing et al.[20] analyzed the TLR4 rs2149356 polymorphism and described that the frequencies of T allele were significantly different between the gout and control groups (OR = 1.42), and the multivariate logistic regression analysis showed a significant increased risk of gout associated with the T/T genotype (OR = 1.96) as shown in Table 2. Further, Rasheed et al.[21] replicated this observation in people of European and New Zealand Polynesian (Māori and Pacific) ancestry; they found that the T allele increased the risk of gout in the clinically ascertained European samples (OR = 1.2), but it has an opposing association in Polynesians (OR = 0.80). Also, the T/T genotype was associated with gout in European and Polynesian populations (OR = 1.32 and 0.63 respectively) as shown in the Table 2. Recently Torres[22] replicated the analysis of TLR4 rs2149356 polymorphism in a Spanish cohort, but contrary to Qing and Rasheed, no significant association with the risk of gout was found even when the allele frequency for rs2149356 in the Spanish population was similar to other populations studied.

3.1.4 | IL polymorphism

Li et al.[23] analyzed the participation of 2 IL-18 polymorphisms in a case-control study including a Chinese cohort, finding no significant association between the polymorphisms −607C/A and −137G/C with the risk of gout disease (Table 1). However, Mckinney et al.[12] found a nominal allelic association for Il-1β rs1143623 in the combined European and Polynesian populations for the G allele (OR = 1.10), but there was not a risk association when analyzing the 2 populations separately.

3.1.5 | P2X7R polymorphism

To date there are 16 SNPs analyzed related to the P2X7R gene. In 2015 Mckinney et al.[12] reported no association of rs17525809 among European and New Zealand Polynesian populations (Table 1). One year later Lee et al.[17] analyzed the association of P2X7R rs3751142 and similarly they did not find difference in the genotypic frequency between groups (Table 1), but they mentioned that the genotype C/A had a trend toward a higher risk of gout if it was combined with the T/T genotype in a male Korean population (data not shown). Ying et al.[24] analyzed the rs2230911 polymorphism in a Han Chinese population, and they found that G allele was highly associated with the risk of gout compared with the C allele (OR = 1.755), and there was greater risk in genotype C/G + G/G when it was compared with the genotype CC

TABLE 2 Association of the allelic and genotypic frequencies of inflammasome gene polymorphisms among primary gout and controls

Gene	dbSNP ID	SNP type	SNP alleles, DNA substitution	MAF, dbSNP	Allele	OR (95% CI)	*P* value	Genotype	OR (95% CI)	*P* value	Reference
NLRP3	rs3806268	SV	A/G, transition substitution	0.39 (A)	NS	NS	NS	G/G	1.83 (1.03-3.26)	>.03	Deng et al.[11]
	rs10754558	3' UTR	C/G, Transversion substitution	0.35 (G)	G	1.30 (1.06-1.84)	.003	G/G	2.68 (1.13-7.2)	.006	Zhang et al.[15]
CARD8	rs2043211	MV	A/T, transversion substitution	0.32 (T)	T	1.12 (SE 0.042)	.007	NS	NS	NS	McKinney et al.[12]
					A	0.84 (0.69-1.02)	.08	A/A	0.65 (0.47-0.88)	.006	Chen et al.[16]
TLR4	rs2149356	IV	G/T, transversion substitution	0.48 (T)	T	1.42 (1.20-1.69)	4.1×10^{-5}	T/T	1.96 (1.40-2.74)	7.9×10^{-5}	Qing et al.[20]
					T	1.12 (1.025-1.227) European	.012	T/T	1.32 (1.082-1.605) European	.006	Rasheed et al.[21]
					T	0.80 (0.674-0.949) Polynesian	.011	T/T	0.63 (0.450-0.895) Polynesian	.009	
CD14	rs2569190	IV	A/G, transition substitution	0.47 (A)	A	1.08 (SE 0.036)	.036	NS	NS	NS	McKinney et al.[12]
IL-1β	rs1143623	IgV	C/G, transversion substitution	0.29 (G)	G	1.10 (SE 0.042)	.020	NS	NS	NS	McKinney et al.[12]
P2RX7	rs2230911	MV	C/G, transition substitution	0.16 (G)	G	1.755 (1.278, 2.410)	.001	C/G+G/G	1.876 (1.303, 2.701)	.001	Ying et al.[24]
	rs1653624	MV	T/A, transversion substitution	0.05 (A)	A	1.608 (1.077-2.400)	.02	A/A	3.214 (1.247-8.283)	.013	Tao et al.[25]
	rs7958316	MV	A/G, transition substitution	0.01 (A)	A	1.698 (1.147-2.514)	.008	A/A	3.391 (1.402-8.204)	.006	
	rs17525809	MV	T/C, transition substitution	0.05 (C)	T	2.728 (1.545-4.817)	.000	T/T	3.338 (1.763-6.320)	.000	
PPARGC1B	rs45520937	MV	A/G, transition substitution	0.07 (A)	A	1.85 (1.51, 2.28)	6.66×10^{-9}	G/G	1.96 (1.59, 2.42)	4.0×10^{-10}	Chang et al.[14]
	rs10491360	IV	T/C, transition substitution	0.12 (C)	C	3.06 (1.58, 5.91)	.021	NS	NS	NS	
	rs7712296	3' UTR	C/A, transversion substitution	0.11 (A)	A	3.44 (1.99, 5.95)	1.14×10^{-4}	NS	NS	NS	

Note: SNP types: Synonymous variant (SV), a sequence variant where there is no resulting change to the encoded amino acid; 3 prime UTR variant (3' UTR), a UTR variant of the 3'UTR; Missense variant (MV), a sequence variant that chances one or more bases resulting in a different amino acid sequence but where the length is preserved; Intron variant (IV), a transcript variant occurring within an intron; Intergenic Variant (IgV), a sequence variant located in the intergenic region, between genes.

DNA substitution mutations: transition substitution, interchanges of 2-ring purines (A↔G) or of one-ring pyrimidines (C↔T); transversion substitution, interchanges of purine for pyrimidine bases, which therefore involve exchange of 1-ring and 2-ring structures.

Abbreviations: SNP, single nucleotide polymorphism; MAF, minor allele frequency; dbSNP, the National Center for Biotechnology Information database of genetic variation; NS, not specified; UTR, untranslated region.

between groups (OR = 1.876) as shown in Table 2. They concluded that P2RX7 rs2230911 may be associated with primary gout risk in a Chinese Han male population (Table 2). On the other hand, Tao et al.[25] studied 8 SNPs as mentioned in Table 1, finding that rs1653624, rs7958316 and rs17525809 were associated with a risk of gout in a Chinese population. As shown in Table 2, the A allele frequency of the rs1653624 polymorphism was higher versus T in the gout group compared with the hyperuricemic group (OR = 1.608). As well, the genotype frequencies were significantly different between groups, with the A/A genotype exhibiting a higher risk of gout (OR = 3.214) compared with T/T, and the genotypes A/A + A/T are in risk too compared with T/T (OR = 2.456). With respect to rs7958316, the A allele frequency was higher in the gout group compared with the hyperuricemic group (OR = 1.698). The authors even describe that it was significantly different in the genotype frequencies between groups as follows: the A/A genotype exhibited a higher risk of gout compared with G/G (OR = 3.391) while A/A + A/G were gout susceptibility genotypes compared to G/G (OR =2.140) and A/A is in risk with gout compared to A/G + G/G genotypes (OR = 2.229). Regarding rs17525809, the T allele was more frequent in the gout group compared to C (OR = 2.728), and the genotype T/T is associated with gout susceptibility compared to C/T + C/C (OR = 3.338).

3.1.6 | PPARγ polymorphism

Chang et al.[14] studied PPARγ gene SNPs in a Taiwanese population. As a preliminary data they analyzed 71 SNPs of genes NLRP3, CASP1, PPARγ, PPARGC1A and PPARGC1 (26, 1, 30, 4 and 11 SNPs for each gene respectively), and excluded 45 SNPs for different criteria as well described by the authors (data not show). Finally, 21 SNPs were included for the association analysis (Table 1), resulting in the identification of 10 SNPs ($P < .05$). The authors describe 3 SNPs of PPARGC1B associated with gout: rs10491360, rs45520937 and rs7712296 (Table 2). When comparing the allele frequencies between cases and controls, it was described that the A allele frequency of rs10491360 is higher in the gout group compared to T allele (OR = 3.06), while in the rs7712296 SNP the A allele frequency is higher than C allele (OR = 3.44); this data showed the association of these alleles with the risk of gout. The rs45520937 of PPARGC1B gene causes Arg265Gln (p.R265Q) substitution in the exon 5 of PPARGC1B, showing a strong association between the risk of gout in the A allele compared to G allele (OR = 1.85). Analyzing the 3-additive model (OR = 1.96), dominant model (OR = 1.58) and recessive model (OR = 2.74), it was shown that rs45520937 is associated with gout risk.

4 | DISCUSSION

Gout is a chronic disease with a multifactorial pathogenesis and the advances in the identification of genes involved in the susceptibility and SNP characterization help to better understand disease development at the molecular and genetic levels.

Our review shows the summary of reports on the inflammasome-related gene SNPs and their potential association with gout susceptibility. The NLRP3 inflammasome has relevance in the gout pathophysiology because it supports the inflammation response mediated by MSU recognition. To date, few reports have focused their attention to assess the potential association between the inflammasome gene SNPs and the risk of gout susceptibility. However, their preliminary results are encouraging and open new research avenues on the potential association of SNPs with gout which may assume a relevant clinical impact.

From our literature review emerged the analysis of 10 different genes in the inflammasome, including 69 SNPs that provide helpful information for future research. From the 69 SNPs analyzed, 13 of them present association with the risk to develop gout in different populations, while 56 have demonstrated not to be associated with gout development (Table 1). The importance in the study of the SNPs of NLRP3 is the alteration in the IL-1β concentration, that is involved in chronic autoinflammatory syndromes.

NLRP3 has a role in innate immunity; this protein is expressed mainly in dendritic cells and phagocytes in response to invading pathogens,[26] and play a central role in the maturation and secretion of the proinflammatory cytokines IL-1β and IL-18. The genetic variants within the NLRP3 gene might be an important determinant affecting the immune inflammatory response.[15] To date, 21 different NLRP3 gene polymorphisms have been analyzed. They were case-control studies including mainly Chinese, European and Polynesian population. Only 2 SNPs showed association with gout risk (rs3806268 and rs10754558) as described in Table 2, while 32 SNPs were reported with no association (Table 1).

NLRP3 includes CARD8 (also named TUCAN/CARDINAL) which is involved in apoptosis, nuclear factor kappa-B (NFκB) activation, and cytokine regulation in inflammation. CARD8 as a component of the inflammasome interacts with caspase-1 and negatively regulates NLRP3.[27] Today 1 SNP has been analyzed in the CARD8 gene. The association between rs2043211 polymorphism and gout was studied in Chinese, European, Polynesian and Korean populations, showing that the rs2043211 SNP has an association with the risk of gout in all the populations studied, except in the Korean population that only shows a trend (Tables 1 and 2). The rs2043211 SNP results in a truncated protein and the association with gout was demonstrated by the enhance of the inflammatory response mediated by the high expression of IL-1β, not only in gout but also in rheumatoid arthritis, inflammatory bowel disease and cryopyrin-associated periodic syndromes,.[28,29]

The MSU crystals are recognized by the transmembrane protein called TLRs that play an important role in the innate immune response since they recognize pathogen-associated molecular pattern (PAMPs) and damage-associated molecular patterns (DAMPs). In gout, once the MSU crystals are precipitated they are recognized by TLR2 and CD14 as lipopolysaccharide-binding protein in the chondrocyte; this canonical pathway activates the inflammasome.[30] The

review shows that 4 TLR2 SNPs analyzed, in 2 different populations, had no association with gout risk (Table 1). However, the rs2569190 SNP of the adaptor molecule CD14 was significantly associated with the risk of gout in European and Polynesia populations (Table 2), suggesting that TLR2 together with CD14 SNPs can be involved in gout risk. The TLR4 receptor activates the NLRP3 inflammasome via the NFκB signaling pathway.[31] Four TLR4 gene SNPs were analyzed, and only rs2149356 SNP was associated in the Chinese and Polynesian populations but not in the Spanish population (Table 1).

Inflammasome signaling activation triggers the IL-1β maturation and release. In the literature there is only one IL-1β SNP associated and correlated with the increase in the expression of the IL-1β gene. The rs2149356 was associated in Chinese, European and New Zealand Polynesian populations (Table 2). The interleukins are a group of cytokines that have complex immunological functions including proliferation, migration, growth and differentiation of cells and play a central role in the generation and regulation of inflammatory responses, in both innate and adaptive immunity. The SNP of IL-1 genes are linked to human diseases like gout, and their study may allow new directions in early diagnosis and effective treatment.[32]

In addition to the TLRs, the NLRP3 inflammasome signaling is activated by the ATP concentration that activates P2X7R and induces downstream events including inflammatory molecule release like IL-1β, IL-18 and tumor necrosis factor-α (TNF-α). Sixteen P2X7R polymorphisms were analyzed in 4 different populations, reporting that 1 SNP has an association with gout and 3 of them were associated with a hyperuricemic state in a Chinese population (Tables 1 and 2). The data reported suggest that the P2X7R gene polymorphisms can affect the formation of the P2X7R membrane pores and the efflux of K+ ions altering the activation of NLRP3.[25]

The NALP3 inflammasome is regulated by PPARγ which is a key regulator controlling both metabolism and inflammatory response.[33] There were 71 SNPs of this gene analyzed (Table 1), including the transcriptional coactivators PPARGC1A and PPARGC1B, but only 3 polymorphisms (Table 2) of the PPARGC1B gene present an association with the risk of gout development. The relevance in SNP study of PPARγ and its transcriptional coactivators (PPARGC1A and PPARGC1B) is because of their effect in anti-inflammation by inhibiting the proinflammatory cytokine products.

This review has some limitations. First, there are few studies available in the literature, followed by the evidence that some studies include small cohorts and then the variables taken in the statistics analysis are not the same in all of them; in addition, the allele frequency and genotype distribution of polymorphisms are different between the different populations studied; finally, the studies do not indicate the analysis of the ancestry-informative marker (AIM) SNP panel for each population.

Despite these limitations, the information provided is of interest in order to understand better the mechanisms involved in the pathogenesis of gout. Future research might be focused on the determination of a genetic profile for early diagnosis and susceptibility to gout and the analysis of the functional variants within the NLRP3 inflammasome gene that affect the protein structure and its function.

5 | CONCLUSIONS

In conclusion, this review showed an overview of the potential role of the inflammasome gene SNPs and their association with gout risk. All of them related with the NLRP3 inflammasome signaling, suggesting these polymorphisms as susceptibility candidates and genetic markers for gout. From the 69 SNPs analyzed in the literature, 13 of them have been associated with gout as follows: NLRP3 (rs3806268 and rs10754558), CARD8 (rs2043211), TLR4 (rs2149356), CD14 (rs2569190), IL-1β (rs1143623), P2RX7 (rs2230911, rs1653624, rs7958316 and rs17525809) and PPARGC1B (rs45520937, rs10491360 and rs7712296) in different population. This information could open new frontiers of research in order to understand better the pathogenesis of gout including potential prevention strategies and new bases for their treatment.

ACKNOWLEDGEMENTS

We wish to thank to Gabriela Fuentes Moreno for her support in reviewing the table data.

CONFLICT OF INTEREST

The authors declare no conflict of interests regarding the publication of this paper.

AUTHORS' CONTRIBUTIONS

DCC had the idea for the article, DCC, OHG and MG performed the literature search and data analysis, DCC and MG critically revised the work.

ORCID

Denise Clavijo-Cornejo https://orcid.org/0000-0002-6399-9865
Olivia Hernández-González https://orcid.org/0000-0003-1343-4732
Marwin Gutierrez https://orcid.org/0000-0002-7995-1110

REFERENCES

1. Neogi T, Jansen TLTA, Dalbeth N, et al. Gout classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheumatol*. 2015;67(10):2557-2568.
2. Lee S-S, Lee SW, Oh DH, Kim H-S, Chae S-C, Kim S. Genetic Analysis for rs2241880 (T> C) in ATG16L1 Polymorphism for the Susceptibility of Gout. *J Clin Rheumatol*. 2019;25(7):e113-e115.
3. Reginato AM, Mount DB, Yang I, Choi HK. The genetics of hyperuricaemia and gout. *Nat Rev Rheumatol*. 2012;8(10):610.
4. Martinon F, Pétrilli V, Mayor A, Tardivel A, Tschopp J. Gout-associated uric acid crystals activate the NALP3 inflammasome. *Nature*. 2006;440(7081):237-241.
5. Xiao J, Zhang X-L, Fu C, et al. Soluble uric acid increases NALP3 inflammasome and interleukin-1β expression in human primary renal proximal tubule epithelial cells through the Toll-like receptor 4-mediated pathway. *Int J Mol Med*. 2015;35(5):1347-1354.
6. Bae JY, Park HH. Crystal structure of NALP3 protein pyrin domain (PYD) and its implications in inflammasome assembly. *J Biol Chem*. 2011;286(45):39528-39536.
7. Di Virgilio F, Dal Ben D, Sarti AC, Giuliani AL, Falzoni SJI. The P2X7 receptor in infection and inflammation. *Immunity*. 2017;47(1):15-31.

8. Youssef J, Badr MJ. Role of peroxisome proliferator-activated receptors in inflammation control. *Biotechnology*. 2004;2004(3):156-166.
9. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg*. 2010;8(5):336-341.
10. Meng D-M, Zhou Y-J, Wang L, et al. Polymorphisms in the NLRP3 gene and risk of primary gouty arthritis Corrigendum in/mmr/8/6/1888. *Mol. Med. Rep*. 2013;7(6):1761-1766.
11. Deng J, Lin W, Chen Y, et al. rs3806268 of NLRP3 gene polymorphism is associated with the development of primary gout. *Int J Clin Exp Pathol*. 2015;8(10):13747.
12. McKinney C, Stamp LK, Dalbeth N, et al. Multiplicative interaction of functional inflammasome genetic variants in determining the risk of gout. *Arthritis Res Ther*. 2015;17(1):288.
13. Wang L, Ding Y, Zhao Q, Zhang X. Investigation on the association between NLRP3 gene polymorphisms and susceptibility to primary gout. *Genet Mol Res*. 2015;14(4):16410-16414.
14. Chang W-C, Jan Wu Y-J, Chung W-H, et al. Genetic variants of PPAR-gamma coactivator 1B augment NLRP3-mediated inflammation in gouty arthritis. *Rheumatology*. 2017;56(3):457-466.
15. Zhang Q-B, Qing Y-F, He Y-L, Xie W-G, Zhou J-G. Association of NLRP3 polymorphisms with susceptibility to primary gouty arthritis in a Chinese Han population. *Clin Rheumatol*. 2018;37(1):235-244.
16. Chen Y, Ren X, Li C, et al. CARD8 rs2043211 polymorphism is associated with gout in a Chinese male population. *Cell Physiol Biochem*. 2015;35(4):1394-1400.
17. Lee SW, Lee S-S, Oh DH, et al. Genetic association for P2X7R rs3751142 and CARD8 rs2043211 polymorphisms for susceptibility of gout in Korean men: multi-center study. *J Korean Med Sci*. 2016;31(10):1566-1570.
18. Cai Y, Peng YH, Tang Z, et al. Association of Toll-like receptor 2 polymorphisms with gout. *Biomed Rep*. 2014;2(2):292-296.
19. Qing Y-F, Zhou J-G, Li M, et al. No evidence for involvement of the toll-like receptor (TLR) 4 gene Asp299Gly and Thr399Ile polymorphisms in susceptibility to primary gouty arthritis. *Rheumatol Int*. 2013;33(11):2937-2941.
20. Qing Y-F, Zhou J-G, Zhang Q-B, et al. Association of TLR4 Gene rs2149356 polymorphism with primary gouty arthritis in a case-control study. *PLoS One*. 2013;8(5):e64845.
21. Rasheed H, McKinney C, Stamp LK, et al. The toll-like receptor 4 (TLR4) variant rs2149356 and risk of gout in European and Polynesian sample sets. *PLoS One*. 2016;11(1):e0147939.
22. Torres RJ. Toll-Like receptor 4 (TLR4) polymorphism rs2149356 and risk of gout in a Spanish cohort. *Nucleosides Nucleotides Nucleic Acids*. 2020;39(10-12):1424-1431.
23. Li C, Yuan Y, Wang X, et al. Lack of association of-607 C/A and-137 G/C polymorphisms in interleukin 18 gene with susceptibility to gout disease in Chinese Han male population. *Rheumatol Int*. 2012;32(6):1805-1807.
24. Ying Y, Chen Y, Li Z, Huang H, Gong Q. Investigation into the association between P2RX7 gene polymorphisms and susceptibility to primary gout and hyperuricemia in a Chinese Han male population. *Rheumatol Int*. 2017;37(4):571-578.
25. Tao J-H, Cheng M, Tang J-P, et al. Single nucleotide polymorphisms associated with P2X7R function regulate the onset of gouty arthritis. *PLoS One*. 2017;12(8):e0181685.
26. Martinon F, Mayor A, Tschopp J. The inflammasomes: guardians of the body. *Annu Rev Immunol*. 2009;27:229-265.
27. Razmara M, Srinivasula SM, Wang L, et al. CARD-8 protein, a new CARD family member that regulates caspase-1 activation and apoptosis. *J Biol Chem*. 2002;277(16):13952-13958.
28. Kastbom A, Johansson M, Verma D, Soderkvist P, Rantapaa-Dahlqvist S. CARD8 p. C10X polymorphism is associated with inflammatory activity in early rheumatoid arthritis. *Ann Rheum Dis*. 2010;69(4):723-726.
29. Sayaka I, Yukichi H, Kubota T. CARD8 is a negative regulator for NLRP3 inflammasome, but mutant NLRP3 in cryopyrin-associated periodic syndromes escapes the restriction. *Arthritis Res Ther*. 2014;16(1):R52.
30. Da Silva TA, Zorzetto-Fernandes ALV, Cecilio NT, Sardinha-Silva A, Fernandes FF, Roque-Barreira MC. CD14 is critical for TLR2-mediated M1 macrophage activation triggered by N-glycan recognition. *Sci Rep*. 2017;7(1):7083.
31. Liu-Bryan R, Scott P, Sydlaske A, Rose DM, Terkeltaub R. Innate immunity conferred by Toll-like receptors 2 and 4 and myeloid differentiation factor 88 expression is pivotal to monosodium urate monohydrate crystal-induced inflammation. *Arthritis Rheum*. 2005;52(9):2936-2946.
32. Khazim K, Azulay EE, Kristal B, Cohen I. Interleukin 1 gene polymorphism and susceptibility to disease. *Immunol Rev*. 2018;281(1):40-56.
33. Kersten S, Desvergne B, Wahli W. Roles of PPARs in health and disease. *Nature*. 2000;405(6785):421-424.

How to cite this article: Clavijo-Cornejo D, Hernández-González O, Gutierrez M. The current role of NLRP3 inflammasome polymorphism in gout susceptibility. *Int J Rheum Dis*. 2021;24:1257–1265. https://doi.org/10.1111/1756-185X.14205

Received: 14 March 2021 | Revised: 15 July 2021 | Accepted: 16 July 2021

DOI: 10.1111/1756-185X.14189

ORIGINAL ARTICLE

International Journal of Rheumatic Diseases | WILEY

Serial administration of rhBMP-2 and alendronate enhances the differentiation of osteoblasts

Sang-Hyon Kim[1] | Hye-Jung Choi[1,2] | Dae Sung Yoon[3] | Chang-Nam Son[1]

[1]Division of Rheumatology, Department of Internal Medicine, Keimyung University School of Medicine, Daegu, Korea

[2]Department of Emergency Medical Technology, Gyeongbuk Provincial College, Gyeongsangbuk-do, Korea

[3]Department of Biomedical Engineering, Korea University College of Health Science, Seoul, Korea

Correspondence
Chang-Nam Son, MD, PhD, Department of Internal Medicine, Keimyung University School of Medicine, 1035 Dalgubeol-daero, Dalseo-gu, Daegu, 42601, Korea.
Email: cnson@kmu.ac.kr

Funding information
Ministry of Science, ICT and Future Planning, Grant/Award Number: NFR-2017R1C1B5017278 and NRF-2018M3C1B7020722; Rheumatology Research Foundation, Grant/Award Number: RRF-2019-03

Abstract

Aim: The incorporation of growth factors is an effective strategy to accelerate bone induction. Bone morphogenetic protein-2 (BMP-2) promotes osteoblast differentiation and induces bone formation. Alendronate (ALN) is an osteoclast deactivation drug. We investigated the effect of serial administration of recombinant human BMP-2 (rhBMP-2) and ALN on osteoblast differentiation.

Methods: The effect of serial administration of rhBMP-2 (0-150 ng/mL) and ALN (0-15 μmol/L) on the viability and differentiation of a clonal murine calvarial cell line, MC3T3-E1, was evaluated at various concentrations and for different periods. The Cell Counting Kit-8 assay was used to assess cell viability. The alkaline phosphatase activity was evaluated as an indicator of osteogenic differentiation. The expression levels of runt domain-containing transcription factor 2 (Runx2) and osteopontin (OPN) were analyzed by real-time polymerase chain reaction and western blotting. Statistical analyses were performed using Student's *t* test.

Results: The serial treatment with rhBMP-2 and ALN increased the expression of the differentiation-related factors Runx2 and OPN, as well as the differentiation ability of osteoblasts compared with individual or simultaneous treatment. The osteoblasts treated with rhBMP-2 followed by ALN showed the highest differentiation. The degree of differentiation in the group treated with rhBMP-2 for 7 days followed by ALN for 3 days was increased by 1.5 times compared with that of the group treated with rhBMP-2 alone ($P < .01$).

Conclusion: These findings indicate that the serial administration of rhBMP-2 and ALN may exert osteogenic effects on osteoblastic cells via the upregulation of Runx2 and OPN.

KEYWORDS

alendronate, bone morphogenetic protein-2, osteogenesis

1 | INTRODUCTION

Bone morphogenetic proteins (BMPs), belonging to the transforming growth factor β (TGF-β) superfamily, are inducers of osteoblast differentiation.[1] Over 20 subgroups of BMPs are known, among which, BMP-2 is the primary subgroup that has been used in several in vitro and in vivo studies.[2] BMP-2 is known to strongly induce osteogenesis and it plays an important role in the development and regeneration of bone and cartilage.[3] Based on animal experiments, Li et al.[4] reported an improvement in osteogenesis when BMP-2 and

© 2021 Asia Pacific League of Associations for Rheumatology and John Wiley & Sons Australia, Ltd.

BMP-7 were sequentially released compared with that when they were released separately. The combined treatment with insulin-like growth factor-1 (IGF-1), a growth-promoting cytokine that plays an important role in development, metabolism, and growth, and BMP-2 increased the differentiation of osteoblasts and expression of osteogenic factors.[5]

Bisphosphonates are potent inhibitors of bone resorption and are widely used in the treatment of bone diseases.[6] Alendronate (ALN), one of the most important bisphosphonates, is used to treat various skeletal disorders such as osteoporosis, tumor-related osteolysis, and Paget's disease.[7] The use of fibrin gel loaded with ALN in the treatment of rabbit calvarial defect has been reported to improve osteoanagenesis.[6] In addition, the combined use of ALN and curcumin, known to increase bone density, increased the expression of osteogenic factors, BMP-2, runt domain-containing transcription factor 2 (Runx2), and osteocalcin (OCN), in human mesenchymal stem cells and improved bone remodeling.[8]

Kim et al.[9] reported that the administration of recombinant human BMP-2 (rhBMP-2) and ALN to inorganic bovine bone (a xenograft) and their use for calvarial defects in rabbits increased osteogenesis in the group that was administered ALN at a lower concentration. In a study where rhBMP-2 and ALN were loaded on a collagen gel containing β-tricalcium phosphate and used for ulna deficit in rabbits, osteogenesis increased in the group that was administered ALN at a lower concentration.[10]

In humans, osteogenesis and osteoanagenesis involve various osteogenic factors that are released at different times.[4] The integration of osteogenic factors is a strategy to accelerate osteoinduction.[11,12]

In this study, we investigated the effect of serial administration of rhBMP-2 and ALN on osteoblast differentiation. The optimal concentration and treatment period of rhBMP-2 and ALN for osteoblast differentiation were evaluated. For this purpose, the viability and differentiation of osteoblasts treated with rhBMP-2, ALN, or their combination at different concentrations for different periods were compared.

2 | METHODS

2.1 | Cell culture and differentiation

MC3T3-E1 cells, which are clonal murine calvarial preosteoblasts, were purchased from the American Type Culture Collection (ATCC, Manassas, VA, USA). The growth medium used was α-minimum essential medium (without ascorbic acid; Gibco, Grand Island, NY, USA) supplemented with 10% fetal bovine serum (FBS, Gibco) and 1% penicillin/streptomycin. The cells were incubated at 37°C in a 5% CO_2 incubator and the medium was replaced every 2-3 days. To induce the differentiation of MC3T3-E1 cells into osteoblasts, 50 μg/mL ascorbic acid and 10 mmol/L β-glycerophosphate (Sigma, St. Louis, MO, USA) were added to the growth medium. We purchased rhBMP-2 from Sigma (St Louis, MO, USA). The osteoblasts were treated with rhBMP-2 at concentrations of 10-150 ng/mL for 1, 3, and 7 days, and with ALN (Sigma) at concentrations of 1-15 μmol/L for 1, 3, and 7 days.

2.2 | Cell viability assay

MC3T3-E1 cells (5×10^3 cells/well) were dispensed into a 96-well plate and cultured in the growth medium for 24 h. Thereafter, the growth medium was removed, and the cells were induced to differentiate for 1, 3, 7, and 10 days in the differentiation medium supplemented with rhBMP-2 (0-150 ng/mL) or ALN (0-15 μmol/L). Cell viability was evaluated using Cell Counting Kit-8 (Dojindo, Rockville, MD, USA). The absorbance of the sample was measured using a Victor 3 1420 multilabel counter (Perkin Elmer, Shelton, CT, USA).

2.3 | Alkaline phosphatase (ALP) assay

MC3T3-E1 cells (2×10^4 cells/well) were dispensed into a 24-well plate and cultured in growth medium for 24 h. Thereafter, the growth medium was removed, and the cells were induced to differentiate for 3, 7, and 10 days in the differentiation medium supplemented with rhBMP-2 (0-150 ng/mL) or ALN (0-15 μmol/L). The degree of cell differentiation was evaluated in terms of ALP activity using an ALP colorimetric assay kit (BioVision, Milpitas, CA, USA). The cells were lysed with the assay buffer of the ALP colorimetric assay kit according to the manufacturer's instructions. The absorbance of the sample was measured using a Victor 3 1420 multilabel counter (Perkin Elmer). To correct the measured values with respect to the protein concentration, the concentration of protein was determined using a bicinchoninic acid (BCA) protein assay kit (Thermo Fisher Scientific, Rockford, IL, USA).

2.4 | RNA extraction and real-time polymerase chain reaction (PCR)

RNA was extracted using TRI Reagent (MRC, Cincinnati, OH, USA) and was reverse transcribed to complementary DNA (cDNA) using the SuperScript Vilo cDNA Synthesis kit (Invitrogen, Burlington, ON, Canada). The synthesized cDNA was subjected to real-time PCR on the CFX96 Real-time PCR Detection System (Bio-Rad, Hercules, CA, USA) using FastStart Essential DNA Green Master (Roche, Mannheim, Germany). The steps in the real-time PCR were as follows: 40 cycles at 95°C for 10 seconds, 60°C for 10 seconds, and 72°C for 10 seconds. The sequences of the primers used were as follows: *β-actin*: 5′-tgttaccaactgggacgaca-3′, 5′-ggggtgttgaaggtctcaaa-3′; *RUNX2*: 5′-cccagccacctttacctaca-3′, 5′-agagatatggagtgctgctg-3′;

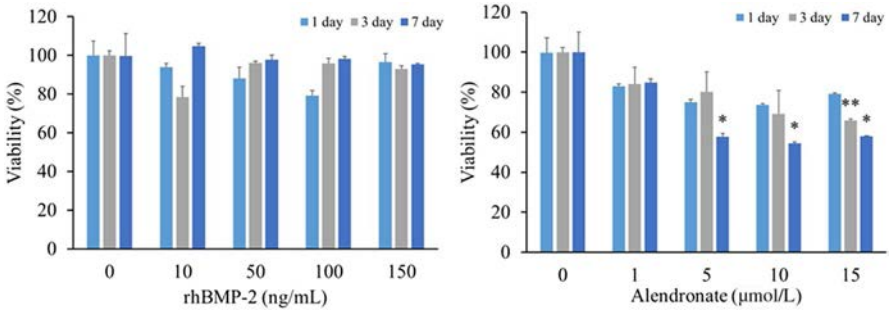

FIGURE 1 Viability of osteoblasts (MC3T3-E1) following treatment with different concentrations of recombinant human bone morphogenetic protein-2 (rhBMP-2) and alendronate for different periods. Error bars represent mean ±SD. **P* <.05 and ***P* <.01, compared with the control group

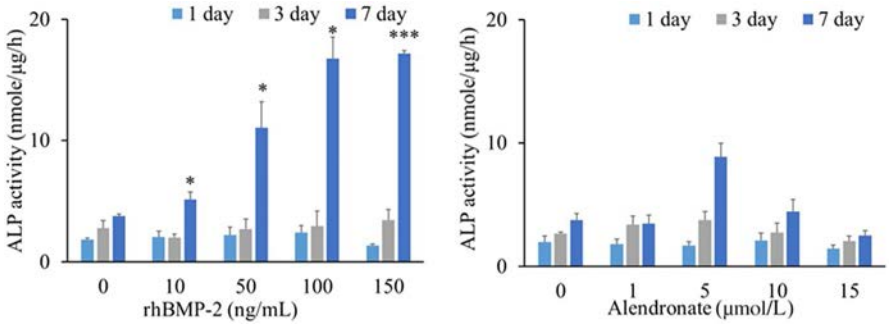

FIGURE 2 Alkaline phosphatase (ALP) activity in osteoblasts (MC3T3-E1) following treatment with different concentrations of recombinant human bone morphogenetic protein-2 (rhBMP-2) and alendronate for different periods. Error bars represent mean ±SD. **P* <.05 and ****P* <.001, compared with the control group

osteopontin (*OPN*): 5′-tgagaccgtcactgctagta-3′, 5′-aggtcctc atctgtggcatc-3′.

2.5 | Western blotting

MC3T3-E1 cells (1×10^5 cells/well) were dispensed into a six-well plate and cultured in the growth medium for 24 h. Thereafter, the growth medium was removed, and the cells were induced to differentiate for 3, 7, and 10 days in the differentiation medium supplemented with rhBMP-2 or ALN. The cells were then washed with phosphate-buffered saline and lysed in the lysis buffer (Thermo Fisher, Waltham, MA, USA) containing phosphatase and protease inhibitors (both from Roche, Basel, Switzerland) on ice for 15 minutes. The lysate was centrifuged at 16 000 *g* for 15 minutes at 4°C, and the supernatant containing the proteins was separated. The protein concentration in the supernatant was quantified using the BCA analysis. Twenty-five micrograms of protein samples were resolved by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE), and the proteins were transferred from the gel onto a nitrocellulose membrane (Amersham, Chicago, IL, USA). The membrane was blocked with 5% skimmed milk prepared in TBS-T solution (20 mmol/L Tris, 137 mmol/L NaCl, 0.05% Tween-20) for 1 h, and then sequentially incubated with primary and secondary antibodies. The primary antibodies used were anti-β-actin (1:5000; Sigma-Aldrich, St. Louis, MO, USA), anti-RUNX2 (1:1000; ab23981, Abcam), and anti-OPN (1:1,000; ab63856, Abcam). The secondary antibodies used were Peroxidase AffiniPure Donkey Anti-Mouse IgG (H + L) and Peroxidase-conjugated AffiniPure Donkey Anti-Rabbit IgG (H + L) (Jackson Immunoresearch, Baltimore, MD, USA). The protein expression was visualized using a chemiluminescent image analysis equipment (Fusion Solo 6S; Vilber Lourmat, Marne-La-Vallée, France).

2.6 | Statistical analysis

Data processing and statistical analyses were performed with SPSS 25.0 software (IBM, Armonk, NY, USA). The results obtained from the analysis are expressed as mean ±SD. To compare the differences between groups, viability was compared with the control group, and ALP activity and expression levels were compared with the control group and the group treated with 50 ng/mL rhBMP-2 for 10 days. Student's *t* test was employed to analyze statistical differences between groups. *P* values below .05 were considered statistically significant.

3 | RESULTS

3.1 | Effect of different concentrations of rhBMP-2 and ALN and treatment period on the viability of MC3T3-E1 cells

The osteoblasts were treated with rhBMP-2 at concentrations of 10-150 ng/mL for 1, 3, and 7 days, and the cell viability was assessed. The increase in the concentration of rhBMP-2 and treatment period did not affect the viability of osteoblasts (Figure 1). The osteoblasts were treated with ALN at concentrations of 1-15 μmol/L for 1, 3, and 7 days, and their viability was checked. With the increase in the

ALN concentration and treatment period, the viability of osteoblasts significantly decreased compared with that of the control group (Figure 1).

3.2 | Effects of the concentration of rhBMP-2 and ALN and treatment period on the degree of differentiation of MC3T3-E1 cells

The osteoblasts were treated with rhBMP-2 at concentrations of 10-150 ng/mL for 1, 3, and 7 days, and the degree of differentiation was checked. With the increase of rhBMP-2 concentration and treatment period, the degree of differentiation of osteoblasts significantly increased compared with that of the control group (Figure 2). The degree of differentiation of the osteoblasts treated with ALN at concentrations of 1-15 μmol/L for 1, 3, and 7 days was evaluated. It was highest in the group treated with 5 μmol/L ALN for 7 days, but the viability of osteoblasts was significantly lower (by 42%) than that of the control group (P =.016; Figures 1 and 2).

3.3 | Effect of the combination of rhBMP-2 and ALN on the viability of MC3T3-E1 cells

The treatment with 50 ng/mL rhBMP-2 for 7 days and 5 μmol/L ALN for 3 days had no effect on the viability of osteoblasts. Therefore, the viability of osteoblasts was compared between the control group (a) and the experimental groups treated with (b) 50 ng/mL rhBMP-2 for 10 days, (c) 5 μmol/L ALN for 10 days, (d) combination of 50 ng/mL rhBMP-2 and 5 μmol/L ALN for 10 days, (e) 50 ng/mL rhBMP-2 for 7 days followed by 5 μmol/L ALN for 3 days, and (f) 5 μmol/L ALN for 3 days followed by 50 ng/mL rhBMP-2 for 7 days (Figure 3). The viability of osteoblasts was not affected in the groups treated with rhBMP-2 alone (b), treated with rhBMP-2 first followed by ALN (e), and treated with ALN first followed by rhBMP-2 (f). However, the viability of osteoblasts significantly decreased in the groups treated with ALN alone (c, P =.025) and with a combination of rhBMP-2 and ALN (d, P =.015; Figure 3).

3.4 | Effect of the combination of rhBMP-2 and ALN on the degree of differentiation of MC3T3-E1 cells

The ALP activity was measured to compare the degree of differentiation of osteoblasts (Figure 4). The degree of differentiation in the group treated with rhBMP-2 followed by ALN was significantly increased by 1.5 times compared with that in the group treated with rhBMP-2 alone (P =.002). The degree of osteoblast differentiation in the group treated with ALN followed by rhBMP-2 was significantly increased by 1.3 times compared with that in the group treated with rhBMP-2 alone (P =.012). Among the experimental groups, the efficiency of differentiation was the highest in the group treated with rhBMP-2 followed by ALN.

3.5 | Effect of the combination of rhBMP-2 and ALN on the expression of *Runx2* and *OPN* messenger RNAs (mRNAs) in MC3T3-E1 cells

The expression levels of Runx2 and OPN, which are factors related to the differentiation of osteoblasts, were compared at the mRNA level (Figure 5). The expression of Runx2 mRNA was significantly increased by 3.1 times in the group treated with rhBMP-2 followed by ALN (P =.001) and by 3.5 times in the group treated with ALN followed by rhBMP-2 (P =.026) compared with that in the control group. The expression of OPN mRNA significantly increased by 1.7 times in the group treated with rhBMP-2 followed by ALN (P =.011) and decreased by about 28% in the group treated with ALN followed by rhBMP-2 compared with that in the control group.

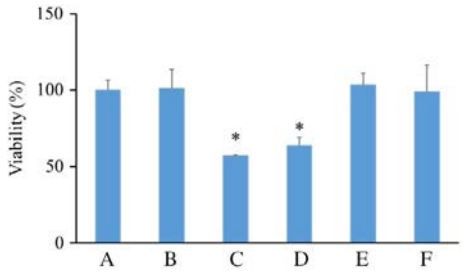

FIGURE 3 Viability of osteoblasts (MC3T3-E1) following treatment with recombinant human bone morphogenetic protein-2 (rhBMP-2) and alendronate. A, control; B, 50 ng/mL rhBMP-2 for 10 days; C, 5 μmol/L alendronate for 10 days; D, 50 ng/mL rhBMP-2 and 5 μmol/L alendronate for 10 days; E, 50 ng/mL rhBMP-2 for 7 days and 5 μmol/L alendronate for the next 3 days; F, 5 μmol/L alendronate for 3 days and 50 ng/mL rhBMP-2 for the next 7 days. Error bars represent mean ±SD. *P <.05 compared with the control group

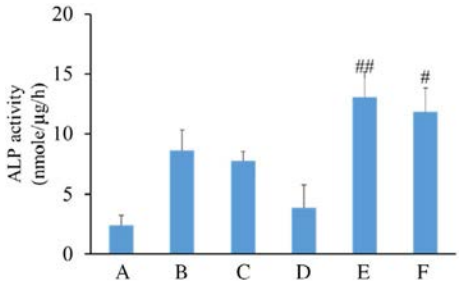

FIGURE 4 Alkaline phosphatase (ALP) activity in osteoblasts (MC3T3-E1) following treatment with recombinant human bone morphogenetic protein-2 (rhBMP-2) and alendronate. A, control; B, 50 ng/mL rhBMP-2 for 10 days; C, 5 μmol/L alendronate for 10 days; D, 50 ng/mL rhBMP-2 and 5 μmol/L alendronate for 10 days; E, 50 ng/mL rhBMP-2 for 7 days and 5 μmol/L alendronate for the next 3 days; F, 5 μmol/L alendronate for 3 days and 50 ng/mL rhBMP-2 for the next 7 days. Error bars represent mean ±SD. #P <.05 and ##P <.01, compared with group b

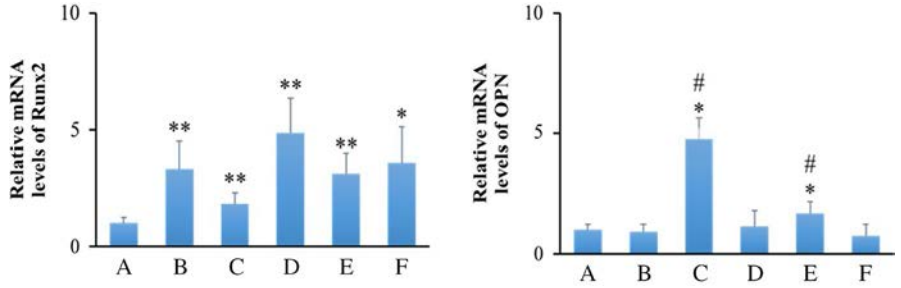

FIGURE 5 Levels of Runx2 and OPN mRNAs in osteoblasts (MC3T3-E1) following treatment with recombinant human bone morphogenetic protein-2 (rhBMP-2) and alendronate. A, control; B, 50 ng/mL rhBMP-2 for 10 days; C, 5 μmol/L alendronate for 10 days; D, 50 ng/mL rhBMP-2 and 5 μmol/L alendronate for 10 days; E, 50 ng/mL rhBMP-2 for 7 days and 5 μmol/L alendronate for the next 3 days; F, 5 μmol/L alendronate for 3 days and 50 ng/mL rhBMP-2 for the next 7 days. Error bars represent mean ±SD. **P* < 0. 05 and ***P* <.01, compared with the control group. #*P* <.05, compared with group b. Runx2, runt domain-containing transcription factor 2; OPN, osteopontin

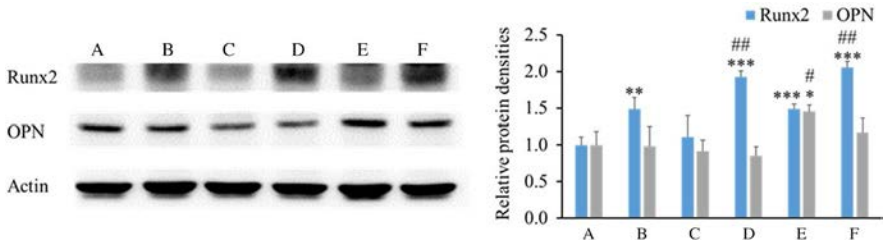

FIGURE 6 Protein levels in osteoblasts (MC3T3-E1) following treatment with recombinant human bone morphogenetic protein-2 (rhBMP-2) and alendronate. A, control; B, 50 ng/mL rhBMP-2 for 10 days; C, 5 μmol/L alendronate for 10 days; D, 50 ng/mL rhBMP-2 and 5 μmol/L alendronate for 10 days; E, 50 ng/mL rhBMP-2 for 7 days and 5 μmol/L alendronate for the next 3 days; F, 5 μmol/L alendronate for 3 days and 50 ng/mL rhBMP-2 for the next 7 days. Error bars represent mean ±SD. ***P* <.01 and ****P* <.001, compared with the control group. #*P* <.05 and ##*P* <.01, compared with group b. Runx2, runt domain-containing transcription factor 2; OPN, osteopontin

3.6 | Effect of the combination of rhBMP-2 and ALN on the expression of Runx2 and OPN in MC3T3-E1 cells

The expression of Runx2 and OPN was compared at the protein level (Figure 6). The expression of Runx2 increased by 1.5 times in the group treated with rhBMP-2 followed by ALN (*P* =.0006) and by 2.1 times in the group treated with ALN followed by rhBMP-2 (*P* =.00001) compared with that in the control group. The expression of Runx2 significantly increased by 1.4 times in the group treated with ALN followed by rhBMP-2 compared with that in the group treated with rhBMP-2 alone (*P* =.002). The expression of OPN significantly increased by 1.5 times in the group treated with rhBMP-2 followed by ALN (*P* =.046) and increased by 17%, without statistical significance, in the group treated with ALN followed by rhBMP-2 compared with that in the control group. The expression of OPN significantly increased by 1.5 times in the group treated with rhBMP-2 followed by ALN compared with that in the group treated with rhBMP-2 alone (*P* =.047).

4 | DISCUSSION

In this study, we investigated the optimal concentration and treatment period for the combination of rhBMP-2 and ALN to induce osteoblast differentiation. Compared with the control group, rhBMP-2 treatment for 1, 3, or 7 days at concentrations of 10-150 ng/mL did not affect the viability of osteoblasts. A similar pattern has been observed in human fetal osteoblast cells (hFOB 1.19) treated with rhBMP-2 at concentrations of 10-100 ng/mL for 3 days.[2] The same study reported that when hFOB 1.19 cells were treated with ALN at concentrations of 10-100 μmol/L for 3 days, their viability decreased with concentration beyond 50 μmol/L and treatment period.[2] In the present study, the viability of osteoblasts treated with ALN at concentrations of 1-15 μmol/L for 1, 3, and 7 days decreased with the increase in concentration and treatment period compared with that of the control group. These results indicate that even low ALN concentrations affect the viability of osteoblasts when the treatment is prolonged.

For comparison, the concentration and treatment period of rhBMP-2 were set to 50 ng/mL and 7 days, respectively, and those of ALN were set to 5 μmol/L and 3 days, respectively. Under these conditions, the viability of osteoblasts was not affected. The viability of osteoblasts was not affected in the groups treated with rhBMP-2 for 10 days, rhBMP-2 for 7 days followed by ALN for 3 days, and ALN for 3 days followed by rhBMP-2 for 7 days. However, the viability of osteoblasts decreased in the groups treated with ALN for 10 days and a combination of rhBMP-2 and ALN for 10 days. These results also indicate that when the treatment is prolonged, ALN affects the viability of osteoblasts.

The degree of differentiation of osteoblasts significantly increased in the groups treated with rhBMP-2 for 7 days followed by ALN for 3 days and ALN for 3 days followed by rhBMP-2 for 7 days ($P < .01$, $P < .05$). In particular, the efficiency of differentiation was the highest in the group treated with rhBMP-2 followed by ALN.

Runx2 belongs to the Runx transcription factor family and is one of the most important regulators involved in the proliferation and differentiation of osteoblasts.[13] It is a master gene for osteogenesis because it induces the expression of OPN, OCN, and osterix that are required for the differentiation of osteoblasts.[14] It has been reported that when osteoblasts were treated with a combination of IGF-1 and BMP-2, the expression of *Runx2*, *ALP*, and *OCN* mRNAs increased[6] and when treated with sinomenine, a plant-derived alkaloid, the differentiation of osteoblasts and the expression of Runx2 and OPN at the mRNA and protein levels was increased.[15]

It has been reported that increased BMP-2 expression in MC3T3-E1 cells increased the expression of downstream regulators Smad-1 and phosphorylated Smad-1, and this led to the increased expression of Runx2, ALP, collagen I, osteocalcin, and osteopontin.[16] When MC3T3-E1 cells were treated with ALN at low concentrations for 3 days, the ALP activity and mRNA expression of ALP, Col1, and OCN increased compared with that in the control group.[17]

In the present study, the mRNA and protein expression of Runx2 and OPN increased in the group treated with rhBMP-2 for 7 days followed by ALN for 3 days, in which the degree of osteoblast differentiation increased, compared with that in the control group. However, in the group treated with ALN for 3 days followed by rhBMP-2 for 7 days, the mRNA and protein expression of Runx2 increased but those of OPN did not significantly increase. These results suggest that treating osteoblasts with rhBMP-2 followed by ALN upregulates the expression of Runx2 and OPN, which are osteogenic factors that promote osteogenesis.

The bones in our body are maintained by a dynamic process in which osteogenesis, by osteoblasts, and bone resorption, by osteoclasts, occur constantly.[18] For the differentiation of osteoblasts and osteoclasts, the osteoblast–osteoclast coupling is indispensable.[19] Therefore, the experimental conditions used in this study should be applied in studies on osteoclasts and in vivo experiments to determine their effects.

5 | SUMMARY

In this study, the serial treatment with rhBMP-2 and ALN, rather than simultaneous treatment or treatment with each of these factors alone, promoted the differentiation of osteoblasts. In particular, the degree of differentiation of osteoblasts was found to be the highest in the group treated with rhBMP-2 followed by ALN. This can be attributed to the upregulation of osteogenic factors Runx2 and OPN. These findings can be expected to improve the effect of bone regeneration treatment by presenting the effect according to the concentration combination of bone morphogenetic factors and treatment period. The findings of this study can also be used as a basis to evaluate the effects of treatment with different combinations of different osteogenic factors and treatment periods.

ACKNOWLEDGMENTS

This work was supported by the National Research Foundation of Korea (NRF) Grant funded by the Korean Government (MSIP) (grant Nos. NRF-2018M3C1B7020722 and NFR-2017R1C1B5017278) and the research fund of Rheumatology Research Foundation (grant No. RRF-2019-03).

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Conceptualization: S-HK, DSY, and C-NS. Data curation: S-HK and H-JC. Formal analysis: all authors. Funding acquisition: DSY and C-NS. Investigation: S-HK, H-JC, and C-NS. Methodology: H-JC and C-NS. Project administration: C-NS. Resources: S-HK and C-NS. Software: H-JC. Supervision: C-NS. Validation: all authors. Visualization: S-HK, Hye-Jung Choi, and C-NS. Writing—original draft: all authors. Writing—review and editing: all authors. Approval of the final manuscript: all authors.

ORCID

Chang-Nam Son https://orcid.org/0000-0002-1722-2190

REFERENCES

1. Susperregui AR, Viñals F, Ho PW, Gillespie MT, Martin TJ, Ventura F. BMP-2 regulation of PTHrP and osteoclastogenic factors during osteoblast differentiation of C2C12 cells. *J Cell Physiol*. 2008;216:144-152.
2. Jeong S-Y, Hong J-U, Song JM, et al. Combined effect of recombinant human bone morphogenetic protein-2 and low level laser irradiation on bisphosphonate-treated osteoblasts. *J Korean Assoc Oral Maxillofac Surg*. 2018;44:259-268.
3. Nosho S, Tosa I, Ono M, et al. Distinct osteogenic potentials of BMP-2 and FGF-2 in extramedullary and medullary microenvironments. *Int J Mol Sci*. 2020;21:7967.
4. Li X, Yi W, Jin A, Duan Y, Min S. Effects of sequentially released BMP-2 and BMP-7 from PELA microcapsule-based scaffolds on the bone regeneration. *Am J Transl Res*. 2015;7:1417-1428.
5. Rico-Llanos GA, Becerra J, Visser R. Insulin-like growth factor-1 (IGF-1) enhances the osteogenic activity of bone morphogenetic protein-6 (BMP-6) in vitro and in vivo, and together have a stronger osteogenic effect than when IGF-1 is combined with BMP-2. *J Biomed Mater Res A*. 2017;105:1867-1875.
6. Kim BS, Shkembi F, Lee J. In vitro and in vivo evaluation of commercially available fibrin gel as a carrier of alendronate for bone tissue engineering. *Biomed Res Int*. 2017;2017:6434169.
7. He Y, Zhu T, Liu L, Shi X, Lin Z. Modifying collagen with alendronate sodium for bone regeneration applications. *RSC Adv*. 2018;8:16762-16772.
8. Dong J, Tao L, Abourehab MAS, Hussain Z. Design and development of novel hyaluronate-modified nanoparticles for combo-delivery of curcumin and alendronate: fabrication, characterization, and cellular and molecular evidences of enhanced bone regeneration. *Int J Biol Macromol*. 2018;116:1268-1281.

9. Kim H-C, Song J-M, Kim C-J, et al. Combined effect of bisphosphonate and recombinant human bone morphogenetic protein 2 on bone healing of rat calvarial defects. *Maxillofac Plast Reconstr Surg*. 2015;37:16.
10. Kitasato S, Tanaka T, Chazono M, et al. Local application of alendronate controls bone formation and beta-tricalcium phosphate resorption induced by recombinant human bone morphogenetic protein-2. *J Biomed Mater Res A*. 2020;108:528-536.
11. Ruaro B, Casabella A, Paolino S, et al. Dickkopf-1 (Dkk-1) serum levels in systemic sclerosis and rheumatoid arthritis patients: correlation with the Trabecular Bone Score (TBS). *Clin Rheumatol*. 2018;37:3057-3062.
12. Safari B, Aghanejad A, Roshangar L, Davaran S. Osteogenic effects of the bioactive small molecules and minerals in the scaffold-based bone tissue engineering. *Colloids Surf B Biointerfaces*. 2021;198:111462.
13. Chen H, Ji X, She F, Gao Y, Tang P. miR-628-3p regulates osteoblast differentiation by targeting RUNX2: Possible role in atrophic nonunion. *Int J Mol Med*. 2017;39:279-286.
14. Yin N, Zhu L, Ding L, et al. MiR-135-5p promotes osteoblast differentiation by targeting HIF1AN in MC3T3-E1 cells. *Cell Mol Biol Lett*. 2019;24:51.
15. Zhang B, Zhang H, Luo H, Yang C, Yuan Y. Sinomenine can promote the proliferation and differentiation of osteoblasts by regulating the Akt/Runx2 signaling pathway in MC3T3-E1 cells. *Pharmazie*. 2019;74:747-750.
16. Cho YE, Kwun IS. Zinc upregulates bone-specific transcription factor Runx2 expression via BMP-2 signaling and Smad-1 phosphorylation in osteoblasts. *J Nutr Health*. 2018;51:23-30.
17. Park MJ, Joo BS, Lee JE, Kim HJ, Moon SE, Moon HS. Alendronate enhances osteoblastic differentiation with increased expression of Id-1 and Id-2 in pre-osteoblast cell line, MC3T3-E1. *Korean J Obstet Gynecol*. 2010;53:274-281.
18. Datta HK, Ng WF, Walker JA, Tuck SP, Varanasi SS. The cell biology of bone metabolism. *J Clin Pathol*. 2008;61:577-587.
19. Chen X, Wang Z, Duan N, Zhu G, Schwarz EM, Xie C. Osteoblast-osteoclast interactions. *Connect Tissue Res*. 2018;59:99-107.

How to cite this article: Kim S-H, Choi H-J, Yoon DS, Son C-N. Serial administration of rhBMP-2 and alendronate enhances the differentiation of osteoblasts. *Int J Rheum Dis*. 2021;24:1266–1272. https://doi.org/10.1111/1756-185X.14189

Received: 28 May 2021 | Revised: 14 July 2021 | Accepted: 19 July 2021

DOI: 10.1111/1756-185X.14195

ORIGINAL ARTICLE

International Journal of Rheumatic Diseases

WILEY

Fibromyalgia in HIV-positive patients in Nigeria: A cross-sectional prospective study

Airenakho Emorinken[1] | Mercy Ofunami Dic-Ijiewere[1] | Cyril Oshomah Erameh[1] | Asuwemhe Johnson Ugheoke[1,2] | Folasade Ojuolape Agbebaku[1] | Oluwaseun Remi Agbadaola[1]

[1]Department of Internal Medicine, Irrua Specialist Teaching Hospital, Irrua, Nigeria

[2]Department of Medicine, Ambrose Alli University, Ekpoma, Nigeria

Correspondence
Airenakho Emorinken, Department of Internal Medicine, Irrua Specialist Teaching Hospital, Irrua, Edo State, Nigeria.
Email: emosairen@gmail.com

Abstract

Background: Fibromyalgia is a chronic pain syndrome of unknown etiology characterized by chronic widespread musculoskeletal pain and tenderness. It affects the quality of life of patients and has been associated with the human immunodeficiency virus (HIV). The study aimed to determine the prevalence of fibromyalgia in HIV-positive patients and assess the effect of fibromyalgia on their functional status.

Methodology: This was a cross-sectional study comprising 160 treatment-naive HIV-positive patients and 160 age- and sex-matched HIV-negative controls. The diagnosis of fibromyalgia was based on the 2011 modification of the 2010 American College of Rheumatology diagnostic criteria by assessing the widespread pain index and symptom severity score. The severity of fibromyalgia was assessed with the revised fibromyalgia impact questionnaire.

Results: The prevalence of fibromyalgia in HIV-positive individuals was found to be 10.6%, which was significantly higher compared with controls (3.1%; $P = .008$). There was no significant association between fibromyalgia and age, gender, or occupation. There was a significant relationship between CD4 count levels ($P < .001$), WHO clinical stage ($P < .001$), and fibromyalgia. A statistically significant higher score on the Revised FM Impact Questionnaire was found in HIV-positive individuals with fibromyalgia ($P < .001$).

Conclusion: The study found that HIV-positive patients had a significantly higher incidence of fibromyalgia than controls and this was related to active indices of HIV disease. Fibromyalgia had a greater clinical impact on HIV patients than in controls. As a result, fibromyalgia should be identified and treated in people living with HIV.

KEYWORDS

fibromyalgia, human immunodeficiency virus, musculoskeletal pain, Nigeria, treatment-naive

© 2021 Asia Pacific League of Associations for Rheumatology and John Wiley & Sons Australia, Ltd.

1 | INTRODUCTION

Fibromyalgia (FM) is a chronic pain condition with no known cause that is characterized by widespread musculoskeletal pain that lasts at least 3 months and soft-tissue tenderness.[1] It is associated with fatigue, cognitive dysfunction, mood disorders, sleep disturbance, morning stiffness, and varied somatic symptoms.[2,3]

Several epidemiological studies have examined the prevalence of FM in North America and Europe. The prevalence of FM has been estimated to be between 0.5% and 5% in the general population.[4] In the USA, Wolfe et al[5] estimated the prevalence of FM to be 2%. Dokwe et al[6] in Kenya reported its frequency to be 11% in patients with chronic musculoskeletal pain, and the overall frequency was 1%. Locally, Akintayo et al found a frequency of 17.3% in an audit of 660 patients seen in a rheumatology clinic over 20 months in north-central Nigeria.[7] The prevalence of FM is said to be related to age and sex. It affects mainly middle-aged women and the prevalence has been found to increase with age.[8]

The etiology of FM is unknown, but it has been postulated that its origin is multifactorial.[2,9] It has been suggested that chronic viral infections may trigger FM.[8,9] Patients with chronic infections such as Lyme disease, hepatitis C virus, and human immunodeficiency virus (HIV) infections are believed to have a higher prevalence of FM.[10-12] HIV infection has the greatest impact in sub-Saharan Africa, which is home to 70% of the world's HIV-infected individuals.[13] As of 2016, Nigeria has the second-highest burden of HIV in absolute numbers globally, with an estimated 3.2 million people living with HIV.[14] It has been shown that even with the advent of antiretroviral drugs, rheumatologic conditions and indeed FM remain relatively significant conditions.[15] Some of the antiretroviral drugs, like zidovudine, are known to cause musculoskeletal symptoms (myalgia, joint pain) as side effects of long-term use.[15]

In a study of 140 HIV-infected patients investigated for rheumatologic conditions in the USA, Simms et al found a 41% prevalence in people with musculoskeletal pain and an 11% prevalence overall in the study group. The mean age of the patients was 37 years. Fibromyalgia was found to be more prevalent in women and was linked to a longer period of HIV infection. There was no association with any highly active antiretroviral therapy (HAART) -specific regimen and no evidence of an increased frequency of FM in patients receiving zidovudine-based therapy.[16] Buskila et al found the prevalence of FM in HIV patients to be 29%, but found no correlation with age, HIV disease duration, stage of HIV disease, and zidovudine treatment.[11] Malombe et al found a 17.9% prevalence of FM in HIV-positive individuals in Kenya, after investigating 380 HIV-positive patients with musculoskeletal pain.[17] Fibromyalgia was independently associated with the female gender and unemployment. However, FM was not associated with levels of CD4 count and the use of HAART.[17] Umar et al, in a study done in Zaria, Nigeria to assess the frequency of rheumatologic conditions in HIV-positive individuals, found that FM existed in 0.5% of those evaluated.[18]

Patients with FM usually have impaired physical function and reduced quality of life. About 50% have difficulties with routine daily activities.[19] The FM impact questionnaire (FIQ), the Brief Pain Inventory-Short Form, the Hospital Anxiety and Depression scale, and the Medical Outcome Study Sleep Scale have been used to assess the burden of this disease.[20] The Revised FM Impact Questionnaire (FIQR) is used to assess the current health status of people with FM.[21] This study aimed to determine the prevalence of FM among treatment-naive HIV-positive adults and assess the impact of FM on the functional status of the participants using the FIQR.

2 | MATERIALS AND METHODS

2.1 | Study setting and population

The study was a comparative cross-sectional descriptive prospective study conducted at the HIV clinic of Irrua Specialist Teaching Hospital (ISTH) over 1 year from June 2016 to May 2017. The hospital is a tertiary health facility situated along the Benin-Abuja highway in Irrua, the headquarters of Esan Central, Local Government Area in the Central Senatorial District of Edo State, south-south, Nigeria. Participants in the study were ambulatory treatment-naive HIV-seropositive individuals aged 18 years or older who consented. Individuals with traumatic musculoskeletal disorders, rheumatic and connective tissue diseases, psychological disorders, hypothyroidism, chronic viral infections like hepatitis C virus; pregnant women; and patients on medications used to treat FM, like tricyclic antidepressants, gabapentin, and pregabalin, were excluded from the study.

2.2 | Sample size determination

The required sample size was obtained using Fisher's statistical formula ($n = Z^2pq/d^2$) for estimating the minimum sample size in descriptive health studies.[22] The sample size was calculated using a confidence interval (Z) of 1.96, which corresponds to a 95% confidence level, a tolerable sampling error (d) of 0.05, and a prevalence (p) of 17.9%[17] obtained in a previous study done in Kenya on FM in HIV-positive individuals. $q = 1–p$, which is the proportion of the sample population not covered by this study, and n is the minimum sample size. Using the formula $nf = n/1 + n/N$ for a target population of less than 10 000, the sample size was adjusted accordingly, where N is the estimation of population size. Giving an attrition risk of 5%, the sample size obtained was 157. However, this was rounded up to 160. As a result, 160 HIV-positive treatment-naive individuals and 160 age- and sex-matched HIV-negative controls were recruited. The participants were recruited consecutively among patients attending the HIV clinic through simple random sampling. Control individuals were drawn from general and medical outpatient clinics.

2.3 | Data collection and clinical assessment

A study proforma administered by an interviewer was used to collect sociodemographic, and clinical data. The HIV status, latest WHO clinical stage, and a recent CD4 count (within 3 months) were based on documentation in the HIV-positive participants' case folders. Blood samples for CD4 T-lymphocyte count were obtained and determined by flow cytometry (Partec, Münster, Germany) for individuals without a recent CD4 count. The widespread pain index (WPI) and symptom severity score (SSS), derived from the 2011 modification of the 2010 American College of Rheumatology preliminary diagnostic criteria for FM were also assessed.[23] The HIV screening test was done for controls according to the recommendations of the national guidelines using the serial testing algorithm with two different rapid screening tests; the Determine™ kit by Inverness Medical (Stockport, UK) and Uni-Gold™ by Trinity Biotech (Bray, Ireland), after counseling.[24]

The diagnosis of FM was based on the 2011 modification of the 2010 ACR preliminary diagnostic criteria.[23] For the diagnosis of FM, the following conditions were met: WPI at least 7 and SSS at least 5 or WPI between 3 and 6 and SSS at least 9; symptoms would have been present at a similar level for at least 3 months and the patient should not have a disorder that would otherwise explain the pain.

The FIQR was used to measure the severity of FM and its impact on the functional status/quality of life of the study participants. The FIQR has three domains. Each question was rated on a scale of 0 to 10. The first domain had nine questions whereby the patients were asked about the level of difficulty in performing certain daily activities. The second domain had two questions that assessed the overall impact of the patient's symptoms. The third domain had 10 questions that assessed specific symptoms and their severity on a scale of 0 to 10. The scores for each domain were added up and a normalization factor was applied—dividing the first domain by 3, the second domain by 1, and the third domain by 2. The total score, between 0 and 100, was the sum of the three normalized domain scores. Categorization of the scores into mild, moderate, and severe was done whereby 0-39 was mild, 40-59 was moderate, and a score of 60 or more was rated as severe. Higher scores were considered an increased disease impact, which meant a low functional level.

2.4 | Ethical considerations

The study was approved by the ISTH health research ethics committee with protocol number ISTH/HREC/2016/JUNE/040. The study was conducted following the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Informed consent was obtained from all study participants. Participants were at liberty to withdraw from the study at any stage without prejudice to their management. All data were fully anonymized.

2.5 | Statistical analysis

The data obtained were analyzed using the commercially available SPSS statistics® 2012 version 21.0 for Windows (IBM, Armonk, NY, USA). Continuous variables were presented as means and standard deviations, and categorical variables as frequencies and percentages. Student *t* test was used to compare the means between variables and the χ^2 test or the Fisher exact test was used to test for associations. Tests were considered statistically significant at a *P* value less than .05.

3 | RESULTS

The study enrolled 320 participants, including 160 HIV-positive treatment-naive patients and 160 HIV-negative controls. The mean ages of the HIV-positive participants and controls were correctly matched (44.34 ± 10.96 vs 44.51 ± 11.54 years). In both groups, women accounted for more than half of the participants. The majority of the participants in both groups were married. The occupational status and level of education of the two groups were similar, but there was a significant difference between the groups ($P < 0.001$). The sociodemographic characteristics of the study participants are shown in Table 1.

The average duration of HIV disease was 2.26 ± 1.51 months. The mean CD4 count levels was 442 ± 292.17 cells/μL with 28 patients (17.5%) having a CD4 count level less than 200 cells/μL. Ninety patients (56.3%) were in WHO clinical Stage 1. Table 2 represents the clinical staging of HIV and CD4 count levels of study participants.

Figure 1A, B shows the prevalence of FM in HIV-positive participants and controls (10.6% vs 3.1%), respectively. The difference in prevalence was statistically significant ($P = .008$).

The mean age of HIV patients with FM was 45.06 ± 5.57 years, and the majority (52.9%) were in the 40-49 age group. Thirteen (76.5%) of the FM patients in the HIV-positive group were female, and 4 (23.5%) were male, resulting in a female to male ratio of 3.5:1. The difference, however, was not statistically significant. ($P = 0.468$). Patients who were married accounted for 76.5% of all FM cases. There was no correlation between FM and gender, marital status, or occupational status. The mean CD4 count was 301.00 ± 92.32 cells/μL in HIV patients with FM, compared with 459.14 ± 303.23 cells/μL in those without FM. The majority of HIV patients with FM were in HIV WHO clinical Stages 2 and 3, whereas those without FM were in WHO clinical Stage 1. A significant association was observed between FM and the WHO clinical stages ($P < .001$), as well as the CD4 count levels ($P < .001$). The sociodemographic and clinical characteristics of HIV-positive participants with and without FM are shown in Table 3.

All HIV-positive adults and controls with FM reported experiencing pain and sleep disturbances in the preceding 7 days. Other frequently reported symptoms included fatigue, joint stiffness, depression, and memory loss in 94.1% of cases. This is similar to

TABLE 1 Socio-demographic characteristics of the study participants and controls[a]

Variables	HIV patients (N = 160) n (%)	Controls (N = 160) n (%)	*P* value
Sex			
Male	50 (31.3)	77 (48.1)	.002*
Female	110 (68.8)	83 (51.9)	
Age range (years)			
18-29	13 (8.1)	19 (11.9)	.313
30-39	51 (31.9)	35 (21.9)	
40-49	44 (27.5)	46 (28.8)	
50-59	39 (24.4)	46 (28.8)	
>60	13 (8.1)	14 (8.8)	
Mean ± SD	44.34 ± 10.96	44.51 ± 11.54	
Marital status			
Single	29 (18.1)	23 (14.4)	.211
Married	113 (70.6)	125 (78.1)	
Divorced	1 (0.6)	0 (0.0)	
Widowed	6 (3.8)	8 (5.0)	
Separated	11 (6.9)	4 (2.5)	
Occupational status			
Unemployed	7 (4.4)	13 (8.1)	<.001*
Civil servant	35 (21.9)	54 (33.8)	
Student	4 (2.5)	15 (9.4)	
Trader/Business	53 (33.1)	18 (11.3)	
Farmers	31 (19.4)	31 (19.4)	
Drivers/Transporters	5 (3.1)	0 (0.0)	
Others (artisans)	25 (15.6)	29 (18.1)	
Highest level of education			
None	8 (5.0)	4 (2.5)	<.001*
Primary	52 (32.5)	13 (8.1)	
Secondary	58 (36.3)	63 (39.4)	
Tertiary	42 (26.3)	80 (50.08)	

Abbreviations: HIV, human immunodeficiency virus; SD, standard deviation.

*Statistically significant *P* value.

[a]Values are given as number (percentage) unless stated otherwise.

the controls, in which all patients with FM reported pain, joint stiffness, sleep disturbances, and depression. This is represented in Figure 2.

In HIV-positive adults with FM, the mean FIQR score was 54.77 ± 7.84, compared with 36.00 ± 4.62 in HIV-negative controls with FM. The HIV-positive group with FM also had significantly higher subtotals for all three domains (activity, impact, and symptoms) compared with the control group. This is shown in Table 4. To assess severity, the FIQR scores were rated as mild, moderate, and severe for scores of 0-39, 40-59, and more than 60 respectively. The majority of HIV-positive participants with FM (70.6%) had moderate disease, compared with the control group with mild disease. The difference was statistically significant ($P < .003$). Figure 3 shows the severity of FIQR scores of HIV-positive participants and controls with FM.

4 | DISCUSSION

Musculoskeletal symptoms have long been recognized as a common complication of HIV infection, and previous findings suggest an increasing frequency of FM in HIV patients. This study aims to determine the prevalence of FM among HIV-positive, treatment-naive adults seeking care at ISTH, Irrua, Edo State, Nigeria.

The study's participants were on average 44 years old, with a female majority. Malombe et al[17] and Dotan et al[25] also reported a female-dominated population of participants in their studies. Several studies evaluating rheumatic disease in HIV found similar results.[18,26,27] The predominance of females among HIV-positive participants reflects the 2018 national HIV statistics.[28] Biologic factors, such as the larger female genital mucosal area, as well as sociocultural and economic risks, all increase female vulnerability to HIV

TABLE 2 Clinical staging of HIV and CD4 count levels of study participants[a]

Variable	HIV patients N = 160 n (%)
WHO Clinical stage	
1	90 (56.3)
2	33 (20.6)
3	29 (18.1)
4	8 (5.0)
Current CD4 count (cells/μL)	
<200	28 (17.5)
200-349	41 (25.6)
350-499	34 (21.3)
≥500	57 (35.6)

Abbreviations: CD, Cluster of Differentiation; HIV, human immunodeficiency virus; WHO, World Health Organization.
[a]Values are given as number (percentage) unless stated otherwise.

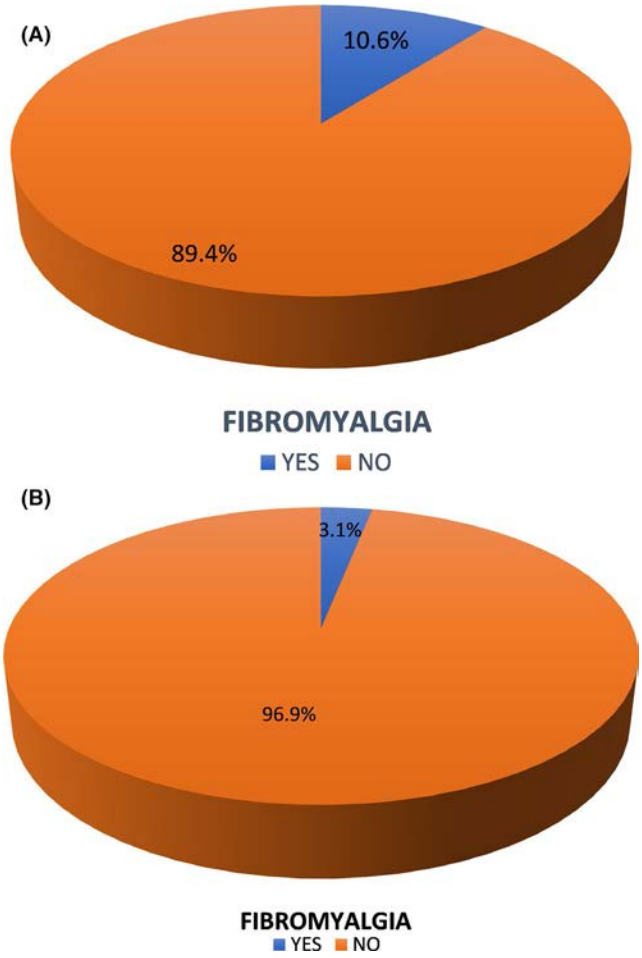

FIGURE 1 A, Prevalence of fibromyalgia in HIV-positive participants. B, Prevalence of fibromyalgia in HIV-negative controls

acquisition.[29] The gender disparity observed in this study is consistent with the trend of low male participation in HIV care.[30]

In this study, FM was shown to be prevalent in 10.6% of HIV-positive participants, which was much greater than the 3.1% seen in HIV-negative controls. This indicates that the illness exists in these patients, as well as suggesting a link between HIV and FM. In the past, a wide range of FM prevalence rates in HIV-positive individuals has been recorded, most likely reflecting a variety of factors such as geographic location, changing treatment patterns over time, and the evolution of diagnostic criteria.[31,32]

Despite the varying prevalence in the literature, our frequency of 10.6% is comparable to the 7.3% and 14.1% reported by Chiowchanwisawakit et al[31] and Dotan et al,[25] respectively. It is lower than the prevalence of 17% reported by Marquez et al[15] and the 17.9% reported by Malombe et al[17] in Kenya. However, our findings are much lower than those of Simms et al[16] in Boston City Hospital in the USA, who found a prevalence of 41% among HIV patients with musculoskeletal pain, and of Buskila et al,[11] who reported a prevalence of 29%. Population differences could explain these findings, especially as the Simms et al study participants were largely male Caucasians. The study by Simms et al. also included patients who were at risk for HIV acquisition due to intravenous drug use (IVDU).[16] This is assumed to have influenced their findings because IVDU, addiction, and substance misuse have been considered to be risk factors for rheumatologic diseases.[33,34] However, there was no record of an IVDU history in our study population. Previous investigations included individuals on HAART; however, this study included only treatment-naive patients. This may explain the study's relatively lower prevalence rate. Zidovudine has been associated with muscle pain and weakness in people who take it, but other studies have revealed no higher risk of FM in people receiving zidovudine-based therapy.[11,17,25] Another reason for our lower prevalence rate could be the exclusion of factors such as pregnancy and other rheumatic diseases that were not excluded in other studies. Overall prevalence of 0.5%-5% in the general population has been documented.[4] This is similar to the 3.1% prevalence in our control group.

The majority (76.5%) of FM patients were females in this study. This, however, was not statistically significant. This is consistent with the findings of other studies on FM, which indicate a female predominance.[16,17,25] Women are more likely to have rheumatologic diseases. Although the exact cause of this is unknown, it is hypothesized that sex hormones, particularly estrogen, may contribute to pain perception.[35] However, in the Boston study by Simms et al[16] and the Thai study by Chiowchanwisawakit et al[31], there were more male participants. This may be explained by the fact that the Simms et al sample cohort included a high proportion of patients who used IVDU as a risk factor for HIV acquisition.[16] Gender disparities may also be influenced by population differences.

The average age of FM patients was 45.06 years. This is equivalent to the mean ages of 42.2 and 40 years in the studies conducted by Malombe et al in Kenya[17] and Dotan et al in southern Israel,[25] respectively. The prevalence of FM rises with age, peaking at 60-70 years old.[5] The prevalence increased from 30-39 years old to

TABLE 3 Comparison of the sociodemographic and clinical variables between HIV-positive participants with and without fibromyalgia[a]

Variables	FM present (N = 17) n (%)	FM absent (N = 143) n (%)	*P* value
Sex			
Male	4 (23.5)	46 (32.2)	.468
Female	13 (76.5)	97 (67.8)	
Age range (years)			
18-29	0 (0.0)	13 (9.1)	.146
30-39	4 (23.5)	47 (32.9)	
40-49	9 (52.9)	35 (24.5)	
50-59	4 (23.5)	35 (24.5)	
Mean ± SD	45.06 ± 5.57	44.25 ± 11.44	
Marital status			
Single	1 (5.9)	38 (19.6)	.103
Married	13 (76.5)	100 (69.9)	
Divorced	1 (5.9)	0 (0.0)	
Widowed	1 (5.9)	5 (3.5)	
Separated	1 (5.9)	10 (7.0)	
Occupational status			
Unemployed	2 (11.8)	5 (3.5)	.398
Civil servant	4 (23.5)	31 (21.7)	
Student	0 (0.0)	4 (2.8)	
Trader/Business	6 (35.3)	47 (32.9)	
Farmers	1 (5.9)	30 (21.0)	
Drivers/Transporters	1 (5.9)	4 (2.8)	
Others(artisans)	3 (17.6)	22 (15.4)	
Highest level of education			
None	1 (5.9)	7 (4.9)	.250
Primary	2 (11.8)	50 (35.0)	
Secondary	9 (52.9)	49 (34.3)	
Tertiary	5 (29.4)	37 (25.9)	
CD4 count, (cells/μL)			
<200	2 (11.8)	26 (18.2)	<.001*
200-349	10 (58.8)	31 (21.7)	
350-499	5 (29.4)	29 (20.3)	
>500	0 (0.0)	57 (39.9)	
Mean ± SD	301.00 ± 92.32	459.14 ± 303.23	
WHO clinical stage			
Stage 1	2 (11.8)	88 (61.5)	<.001*
Stage 2	7 (41.2)	26 (18.2)	
Stage 3	8 (47.1)	21 (14.7)	
Stage 4	0 (0.0)	8 (5.6)	

Abbreviations: CD, Cluster of differentiation; FM, fibromyalgia; WHO, World Health Organization.

*Statistically significant *P* value

[a]Values are given as number (percentage) unless stated otherwise.

40-49 years old in this study. This study's younger age group may reflect the patients who were enrolled. It is unknown whether FM or other rheumatologic issues manifest earlier in HIV-positive individuals.

Most of the participants were employed in some capacity. However, there was no correlation between their occupation and FM. This is in contrast to a study conducted in Kenya, which found that the unemployed had a higher risk of FM.[17] In southern Israel,

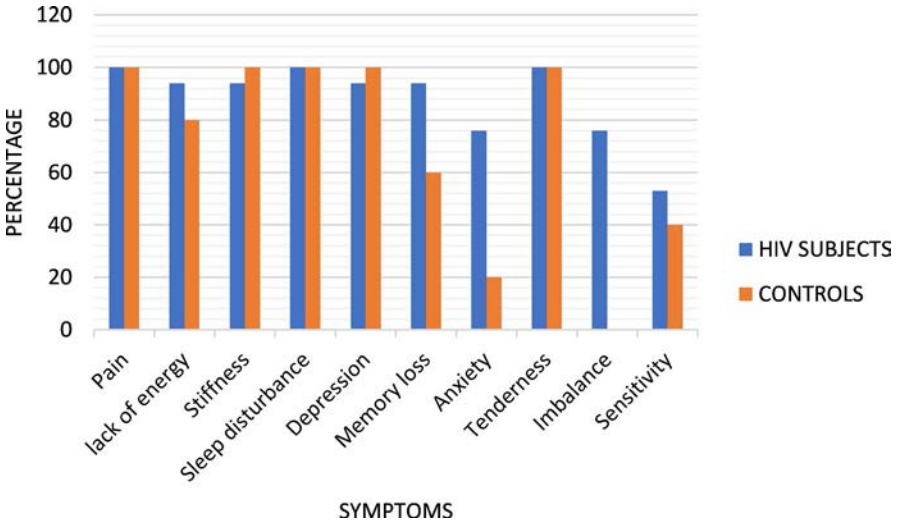

FIGURE 2 Frequency of fibromyalgia-related symptoms in HIV-positive participants and controls with fibromyalgia

TABLE 4 FIQR domain scores in HIV-positive participants and controls with fibromyalgia

FIQR domain	HIV patients with FM (N = 17) Mean ± SD	Controls with FM (N = 5) Mean ± SD	*t* test	*P* value
Function	19.64 ± 3.41	13.28 ± 1.95	3.94	<.001*
Impact	12.47 ± 1.70	9.52 ± 0.67	3.74	<.001*
Symptom	22.68 ± 5.10	13.20 ± 2.84	3.94	<.001*
Total	54.77 ± 7.84	36.00 ± 4.62	5.05	<.001*

Abbreviations: FIQR, Revised Fibromyalgia Impact Questionnaire; FM, fibromyalgia; HIV, human immunodeficiency virus; SD, standard deviation.

*Statistically significant *P*-value.

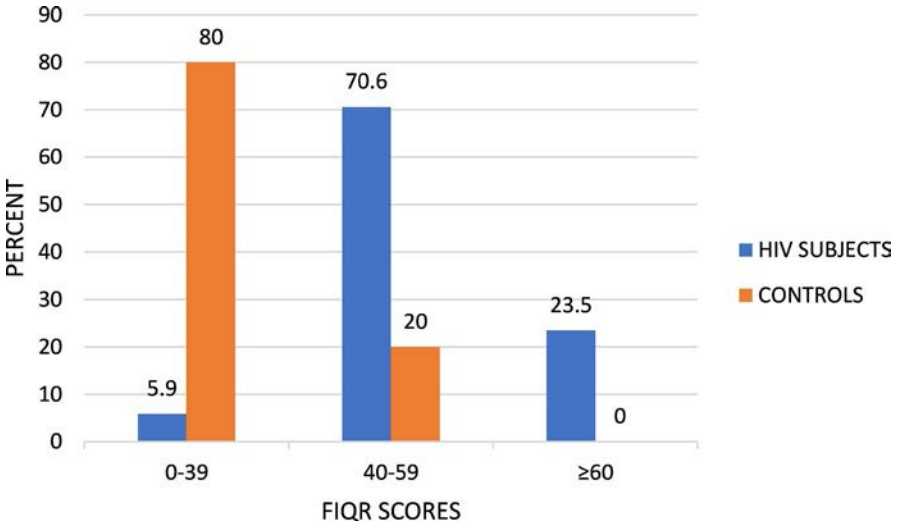

FIGURE 3 Severity of FIQR scores in HIV-positive participants and controls with fibromyalgia

however, Doltan et al observed no link between gender, family status, religion, occupation, or education with the development of FM.[25] Negative life events have been identified as stressors that may enhance the likelihood of developing FM. Occurrences such as being jobless, divorced, or widowed did not demonstrate an increased association with FM. However, it is known that the chronicity and severity of FM symptoms may prevent patients from working or force them to retire early.

The relevance of CD4 count in the development of musculoskeletal diseases in HIV-positive patients has received mixed reviews. Rheumatic diseases can occur at any stage of HIV infection, but they are most common in the late stages.[36] There was no evidence of FM in patients with WHO HIV Stage 4 infection in this study. This may have been influenced by the small number of participants recruited at this stage of HIV disease. The role of the FM criterion used cannot be ruled out, because it requires the exclusion of other clinical conditions

that may be responsible for symptoms. This is because the majority of patients in WHO HIV Stage 4 will have co-morbid conditions that could confound the results. However, this study found a significant relationship between levels of CD4 counts, HIV WHO clinical staging, and FM. This supports the findings of several studies in different parts of the world. Zhang et al identified CD4 lymphocyte depletion as an independent risk factor for the development of rheumatic disorders among HIV-positive patients in China,[37] while Rosemffet et al reported that more severely immunocompromised patients were more likely to have musculoskeletal symptoms.[38] In Enugu, Southeast Nigeria, Okwara et al observed that CD4 count was predictive of HIV-associated arthritis.[39] Umar et al in Zaria also reported an association between levels of CD4 counts, WHO clinical staging of HIV, and rheumatic diseases.[18] In contrast, reports from Dotan et al,[25] Buskila et al,[11] and Malombe et al[17] did not find an association between CD4 count levels, WHO clinical staging of HIV, and FM. Kaddu et al also found no association between CD4 count levels and rheumatic diseases in HIV patients in Malugo.[27] It is worth noting that several of the studies looked at rheumatic disorders in general, with individuals on HAART. Our study focused on FM as an entity and study participants were treatment-naive. However, there is a need for large cohort studies to determine the relationship between CD4 count, WHO clinical staging, and FM, as well as other rheumatic diseases.

The HIV patients with FM in this study had a more severe disease than the controls, as evidenced by higher FIQR scores. When compared with HIV-negative controls with mild illness, more HIV patients with FM had a moderate disease. This was comparable with the findings of Malombe et al[17] in Kenya. This meant that HIV-positive FM patients had a higher overall impact and symptom score and faced greater challenges in terms of being able to perform particular activities. Co-morbidities and other opportunistic infections may contribute to the increased severity and poor quality of life that HIV-positive people experience.

This study is unique in that it is the first in Nigeria to look at the prevalence of FM among HIV-positive people and, in particular, treatment-naive individuals. Because the study only included a relatively small number of HIV-positive participants and was performed in a single center, the results may not be generalizable. Furthermore, as a result of the study's cross-sectional design, we were unable to investigate FM's long-term effects. As a result, a more robust study with a larger sample size may be needed to validate these findings.

5 | CONCLUSION

Similar to previous reports, FM was more prevalent in HIV-positive participants than in HIV-negative controls. The study also noted that indices of active HIV disease like the CD4 count levels correlated with the development of FM. Patients with this condition should be evaluated for any accompanying symptoms and treated accordingly. Large prospective cohort studies will provide high-quality evidence on whether HIV is linked to FM. We suggest that screening for FM and for general musculoskeletal conditions should be an integral part of HIV care.

CONFLICT OF INTERESTS

The authors declare that they have no competing interests.

AUTHORS CONTRIBUTIONS

AE, MOD, and COE conceived and designed the study. All authors contributed to the acquisition of data. Analysis and interpretation of data were performed by AE, AJE, FOA, and ORA. The first draft of the manuscript was written by AE and all authors critically revised it for important intellectual content. All authors read and approved the final manuscript and agreed to be held accountable for all aspects of the work.

ORCID

Airenakho Emorinken https://orcid.org/0000-0002-3306-572X

REFERENCES

1. Häuser W, Fitzcharles MA. Facts and myths pertaining to fibromyalgia. *Dialogues Clin Neurosci*. 2018;20:53-62.
2. Simms RW. Fibromyalgia syndrome: current concepts in pathophysiology, clinical features, and management. *Arthritis Care Res*. 1996;9(4):315-328.
3. Mease P. Fibromyalgia syndrome: review of clinical presentation, pathogenesis, outcome measures, and treatment. *J Rheumatol Suppl*. 2005;75:6-21.
4. White KP, Harth M. Classification, epidemiology, and natural history of fibromyalgia. *Curr Pain Headache Rep*. 2001;5(4):320-329.
5. Wolfe F, Ross K, Anderson J, Russell IJ, Hebert L. The prevalence and characteristics of fibromyalgia in the general population. *Arthritis Rheum*. 1995;38(1):19-28.
6. Dokwe MS, Oyoo GO, Amayo EO. Prevalence of fibromyalgia at the medical out patient clinic. *East Afr Med J*. 2011;88(5):155-162.
7. Akintayo RO, Adelowo OO, Ahmed BA, Olafimihan KO, Olatunde-Olalere OA. Fibromyalgia in a rheumatology clinic in north-central Nigeria: an audit of the characteristics of the syndrome and the sensitivities of 4 sets of American College of Rheumatology criteria. *Int J Rheum Dis*. 2020;23(7):970-976.
8. Neumann L, Buskila D. Epidemiology of fibromyalgia. *Curr Pain Headache Rep*. 2003;7(5):362-368.
9. Buskila D, Atzeni F, Sarzi-Puttini P. Etiology of fibromyalgia: the possible role of infection and vaccination. *Autoimmun Rev*. 2008;8(1):41-43.
10. Dinerman H. Lyme disease associated with fibromyalgia. *Ann Intern Med*. 1992;117(4):281.
11. Buskila D, Gladman DD, Langevitz P, Urowitz S, Smythe HA. Fibromyalgia in human immunodeficiency virus infection. *J Rheumatol*. 1990;17(9):1202-1206.
12. Rivera J, de Diego A, Trinchet M, Monforte AG. Fibromyalgia-associated hepatitis C virus infection. *Br J Rheumatol*. 1997;36(9):981-985.
13. Kharsany ABM, Karim QA. HIV infection and AIDS in sub-Saharan Africa: current status, challenges and opportunities.. *Open AIDS J*. 2016;10(1):34-48.
14. WHO. Nigeria HIV country profile. 2016. https://www.WHO..int/hiv/data/Country_profile_Nigeria.pdf?ua=1. Cited May 28, 2021.
15. Marquez J, Restrepo CS, Candia L, Berman A, Espinoza LR. Human immunodeficiency virus-associated rheumatic disorders in the HAART era. *J Rheumatol*. 2004;31(4):741-746.

16. Simms RW, Zerbini CA, Ferrante N, Anthony J, Felson DT, Craven DE. Fibromyalgia syndrome in patients infected with human immunodeficiency virus. The Boston City Hospital Clinical AIDS Team. *Am J Med*. 1992;92(4):368-374.
17. Malombe MM, Oyoo GO, Maritim MC, Kwasa J. Prevalence of fibromyalgia in ambulatory HIV positive patients with musculoskeletal pain at Comprehensive Care Clinic. Kenyatta National Hospital. *Afr J Rheumatol*. 2013;1(2):70-75.
18. Umar A, Adelowo O, Garko S. Effect of CD4 T-lymphocyte count and human immunodeficiency virus (HIV) infection stage on the prevalence and pattern of rheumatologic disease in HIV-infected patients in Zaria. North-Western Nigeria. *Sub-Saharan Afr J Med*. 2018;5:45-51.
19. Berger A, Dukes E, Martin S, Edelsberg J, Oster G. Characteristics and healthcare costs of patients with fibromyalgia syndrome. *Int J Clin Pract*. 2007;61(9):1498-1508.
20. Perrot S, Schaefer C, Knight T, Hufstader M, Chandran AB, Zlateva G. Societal and individual burden of illness among fibromyalgia patients in France: Association between disease severity and OMERACT core domains. *BMC Musculoskelet Disord*. 2012;13(22):1-13.
21. Bennett RM, Friend R, Jones KD, Ward R, Han BK, Ross RL. The Revised Fibromyalgia Impact Questionnaire (FIQR): validation and psychometric properties. *Arthritis Res Ther*. 2009;11(4):R120.
22. Araoye MO. Sample size determination. In: *Research Methodology with Statistics for Health and Social Sciences*. Nathadex Publishers; 2004:56-57.
23. Wolfe F, Clauw DJ, Fitzcharles MA, et al. Fibromyalgia criteria and severity scales for clinical and epidemiological studies: a modification of the ACR preliminary diagnostic criteria for fibromyalgia. *J Rheumatol*. 2011;38(6):1113-1122.
24. Federal Ministry of Health. National Guidelines for HIV Counselling and Testing. 2011.
25. Dotan I, Riesenberg K, Toledano R, et al. Prevalence and characteristics of fibromyalgia among HIV-positive patients in southern Israel. *Clin Exp Rheumatol*. 2016;34(2 Suppl 96):S34-S39.
26. Prenam H, Kodjo K, Abass MT, et al. Rheumatic diseases in HIV-positive patients in Kara (Togo). *J AIDS Clin Res*. 2018;9(1):9-11.
27. Kaddu-Mukasa M, Ssekasanvu E, Ddumba E, Thomas D, Katabira ET. Rheumatic manifestations among HIV positive adults attending the Infectious Disease Clinic at Mulago Hospital. *Afr Health Sci*. 2011;11:24-29.
28. Federal Ministry of Health. Nigeria HIV/AIDS Indicator and Impact Survey (NAIIS) - Fact Sheet. 2019. https://naca.gov.ng/wp-content/uploads/2019/03/NAIIS-PA-NATIONAL-FACTSHEET-FINAL.pdf. Cited May 28, 2021
29. Ramjee G, Daniels B. Women and HIV in Sub-Saharan Africa. *AIDS Res Ther*. 2013;10(1):1-9.
30. Skovdal M, Campbell C, Madanhire C, Mupambireyi Z, Nyamukapa C, Gregson S. Masculinity as a barrier to men's use of HIV services in Zimbabwe. *Global Health*. 2011;7(1):13.
31. Chiowchanwisawakit P, Koolvisoot A, Ratanasuwan W, Suwanagool S. Prevalence of rheumatic disease in HIV infected Thai patients. *J Med Assoc Thai*. 2005;88(12):1775-1781.
32. Zeng QY, Chen R, Darmawan J, et al. Rheumatic diseases in China. *Arthritis Res Ther*. 2008;10(1):R17.
33. Lohr KM. Rheumatic manifestations of diseases associated with substance abuse. *Semin Arthritis Rheum*. 1987;17(2):90-111.
34. Monteagudo I, Rivera J, Lopez-Longo J, Cosin J, Garcia-Monforte A, Carreno L. AIDS and rheumatic manifestations in patients addicted to drugs. An analysis of 106 cases. *J Rheumatol*. 1991;18(7):1038-1041.
35. Susan H, Picavet J. Musculoskeletal pain complaints from a sex and gender perspective. *Dutch J Physiother*. 2008;118:109-112.
36. Hess EV, Brown AD. New perspectives from China on HIV rheumatic manifestations. *J Rheumatol*. 2007;34(8):1643-1644.
37. Zhang X, Li H, Li T, Zhang F, Han Y. Distinctive rheumatic manifestations in 98 patients with human immunodeficiency virus infection in China. *J Rheumatol*. 2007;34:1760-1764.
38. Rosemffet MG, Padulo LA, Stockhamer D, et al. Human immunodeficiency virus infection: search for musculoskeletal manifestations and mimicking of rheumatologic disorders. *J Clin Rheumatol*. 1996;2(3):125-128.
39. Okwara C, Ozoh G, Nwatu B. Clinical and laboratory predictors of articular disorders among HIV-infected patients seen at Teaching Hospital Southeast Nigeria. *Ann Med Health Sci Res*. 2015;5:447.

How to cite this article: Emorinken A, Dic-Ijiewere MO, Erameh CO, Ugheoke AJ, Agbebaku FO, Agbadaola OR. Fibromyalgia in HIV-positive patients in Nigeria: A cross-sectional prospective study. *Int J Rheum Dis*. 2021;24:1273–1281. https://doi.org/10.1111/1756-185X.14195

Received: 14 March 2021 | Revised: 13 July 2021 | Accepted: 23 July 2021

DOI: 10.1111/1756-185X.14203

ORIGINAL ARTICLE

International Journal of Rheumatic Diseases

WILEY

Handling missing data in a rheumatoid arthritis registry using random forest approach

Ahmad Alsaber[1] | Adeeba Al-Herz[2] | Jiazhu Pan[1] | Ahmad T. AL-Sultan[3] | Divya Mishra[4] | KRRD Group[2]

[1]Department of Mathematics and Statistics, University of Strathclyde, Glasgow, UK

[2]Department of Rheumatology, Al-Amiri Hospital, Kuwait City, Kuwait

[3]Department of Community Medicine and Behavioral Sciences, Kuwait University, Kuwait City, Kuwait

[4]Department of Plant Pathology, Kansas State University, Kansas, MN, USA

Correspondence
Ahmad Alsaber, Department of Mathematics and Statistics, University of Strathclyde, Glasgow, G1 1XH, UK.
Email: a.alsaber@strath.ac.uk

Funding information
This is an investigator study from the KRRD registry. The KRRD registry is supported by unrestricted grants from Pfizer

Abstract

Missing data in clinical epidemiological research violate the intention-to-treat principle, reduce the power of statistical analysis, and can introduce bias if the cause of missing data is related to a patient's response to treatment. Multiple imputation provides a solution to predict the values of missing data. The main objective of this study is to estimate and impute missing values in patient records. The data from the Kuwait Registry for Rheumatic Diseases was used to deal with missing values among patient records. A number of methods were implemented to deal with missing data; however, choosing the best imputation method was judged by the lowest root mean square error (RMSE). Among 1735 rheumatoid arthritis patients, we found missing values vary from 5% to 65.5% of the total observations. The results show that sequential random forest method can estimate these missing values with a high level of accuracy. The RMSE varied between 2.5 and 5.0. missForest had the lowest imputation error for both continuous and categorical variables under each missing data rate (10%, 20%, and 30%) and had the smallest prediction error difference when the models used the imputed laboratory values.

KEYWORDS

imputation techniques, *kNN*, *KRRD*, missing values, random forest, rheumatoid

1 | INTRODUCTION

In any clinical research, missing values or experimental values remain a problem in correctly analyzing results and in obtaining inaccurate outcomes. These missing values often lead to misinterpretation and biased results, which could ultimately affect the overall conclusion of an investigation.[1-4] The application of statistical analyses in experiments with missing values poses serious problems, as the missing values are often automatically ignored by the statistical algorithms. The results obtained by the investigator in such experiments may be insignificant or even meaningless.[5-7] Missing data are a common problem for all kinds of research data, especially in clinical trials. It always becomes problematic when sample collection was not performed in random order or were obtained using an improper methodology.[8] Certain factors are responsible for missing values in the data of a study: (a) the data are not captured due to some unknown reason, such as error in recording the data from an electronic detector/data recorder or manual recording by technical medical staff;

Abbreviations: kNN, k-nearest neighbors; KRRD, Kuwait Registry for Rheumatic Diseases; RMSE, root mean square error.

Ahmad Alsaber and Jiazhu Pan contributed equally to this study.

© 2021 Asia Pacific League of Associations for Rheumatology and John Wiley & Sons Australia, Ltd.

(b) data are missing due to a known reason, such as critical medical conditions; or (c) data are not recorded as they are unrelated to the patient's clinical medical condition.[6] However, the biased and misleading information obtained when values are missing can be managed by the application of imputation methods.

1.1 | Missing imputation - Rubin's approach

Imputation involves the substitution of missing values with known variables. This type of approach is widely used, as it produces complete data. However, the decision regarding the imputed value cannot be unbiased (eg, multiple imputation for missing data makes it possible for the researcher to obtain approximately unbiased estimates of all the parameters from the random error; the researcher cannot achieve this result from deterministic imputation, which the multiple imputation for missing data can do), as it could lead to an overestimation of confidence in the outcome. To overcome this problem, Rubin suggested the theory of multiple imputation, in which missing values are imputed using the appropriate model a few times (generally 3-5 times) and a standard method is applied for the analysis.[4,9,10,11] The imputation method provides more accurate results, but problems with the application of imputation include: (a) maximum use of the available data to reduce the error for univariate data and preserve covariance in multivariate data sets; and (b) reporting the variance estimates of uncertainty caused due to the imputed value.[11] Several parametric and non-parametric techniques have been employed to deal with missing values. Parametric methods depend on the assumed method, whereas non-parametric methods require a high number of observations.[12]

1.2 | Categorization of missing values

Rubin categorized the missing value problem into 3 groups: missing completely at random (MCAR), missing at random (MAR), and not missing at random/missing not at random (NMAR/MNAR).[10,12,13] The MAR method is generally used in clinical epidemiological research.[14,15] It is critical to determine the category of the data, in order to choose a statistical strategy.[16,17]

1.2.1 | MAR

Data are MAR if the missingness depends on the observed characteristics, not the unobserved characteristics, meaning that the relationships observed in the data can be used to predict the occurrence of missing values.

1.2.2 | MCAR

As the randomness of MAR is conditional on observed characteristics, which distinguishes it from the completely at random type of MCAR, dropping or omitting those cases with missing values in the analysis may lead to biased results.[15]

1.2.3 | MNAR

Data are considered MNAR if their missingness depends on characteristics that are not observed and cannot be fully explained by the observed characteristics. Systematic differences between missing and non-missing data exist for data that are MNAR. In some circumstances, randomness in the missing data mechanism may be ignored without affecting the inference.[10] Both MCAR and MAR can be considered ignorable, in the sense that a proper method (eg, multiple imputation) may recover the missing information without modeling. In contrast, the MNAR mechanism requires a method that considers the missing data mechanism to make inferences about the complete (and partially unobserved) data; in other words, the model for the missing data mechanism cannot be ignored.[18]

1.3 | Methods used for imputing missing values

To treat and estimate the missing values,[19] a non-parametric random forest (RF) model is proposed, which is an extended version of classification and regression trees (CARTs) and involves a supervised learning group method. The method used to build the trees involves replacement sampling of the main data set. The CARTs are created using the training data bootstrap samples and tree induction using random feature selection.[20,21] The performance of a tree is evaluated on the remaining data, which are contained in an out-of-bag sample.

1.3.1 | Missing imputation using RF

The best RF is determined based on the out-of-bag error, which is an unprejudiced gauge of the true prediction error.[22] RF has the following advantages: (a) it is applicable even when the number of variables is greater than the number of samples; (b) it is not prone to multicollinearity; (c) it is suitable for non-linear trends; (d) it does not suffer from the overfitting problem with an increase in the number of trees; and (e) it can tolerate outliers and missing values.[23]

1.3.2 | Missing imputation using sequential RF (missForest)

Another algorithm based on RF, called sequential random forest (missForest), has recently been developed for missing data imputation.[24] This algorithm can impute missing values on any kind of data and its goal is the prediction of every single missing value, instead of drawing random values from a distribution. This algorithm can handle multivariate data sets concurrently comprising categorical

and continuous variables.[25] The key advantages of missForest over other imputation methods include: (a) having no requirement for the tuning of parameters; (b) it does not depend on assumptions pertaining to the distribution of data sets; (c) it allows for assessment of imputation quality without setting test data or laborious cross-validations using out-of-bag imputation error estimates; and (d) it provides above-par imputation results, even for high-dimensional data sets (ie, when the number of variables is greater than the number of observations).[24]

The missForest approach is based on a decision tree that is supervised by a machine learning algorithm that can be used for both classification and regression problems. A decision tree is simply a series of sequential decisions made to reach a specific result. It initially imputes all missing data using the mean/mode, then for each variable with missing values, missForest fits a RF on the observed part and then predicts the missing part (sequential movement). This process of training and predicting repeats is an iterative process until a stopping criterion is met, or a maximum number of user-specified iterations is reached. The reason for the multiple iterations is that, from iteration 2 onward, the random forests performing the imputation will be trained on better quality data that itself has been predictively imputed. In other words, the method treats the variable of the missing value as a predictor and borrows information from other variables by the resampling-based CARTs to grow a RF for the final prediction. The method is repeated until the imputed values reach convergence.[26,27]

In general, missForest and k-nearest neighbors (kNN) are considered as machine learning algorithms because they do not explicitly require the users to define how the prediction is taking place, whereas multiple imputation and seasonal decomposition require model specifications by the users.

In the present investigation, we consider 4 data mining techniques to predict the missing values in the Kuwait Registry for Rheumatic Diseases (KRRD): predictive mean matching (PMM), kNN, RF, and sequential RF (missForest). The main objective of this study was to handle missing data in the KRRD, where the amount of missing data varied between 1% and 65.5% (Table 1). Our secondary objectives were to choose the best missing data mechanism (MAR, MCAR, or MNAR) when assuming 3 different rates of missingness (10%, 20%, and 30%), as well as to compare the selected imputation methods (PMM, RF, kNN, and missForest) for each missing data mechanism under each rate of missingness. To select the best method for imputing missing data in KRRD, the root mean square error (RMSE) was used to evaluate the best imputation method which minimized the difference between the imputed data points and the original data points (that were subsequently set to missing).

2 | METHODS

2.1 | Data Source: KRRD

All rheumatoid arthritis (RA) patients in this study were officially registered in the KRRD. The KRRD is a national registry listing adult patients with rheumatic diseases. Patients who fulfilled the American College of Rheumatology criteria for RA[28] registered from January 2012 through March 2020 were included in the study. The RA information data were collected from the rheumatology departments of 4 major government hospitals in Kuwait, based on patient visits. The selected hospitals are mainly distributed in different governorates covering the ethnic diversity of the Kuwaiti population. The KRRD, from which this study originated,

TABLE 1 Study variables with abbreviations and frequencies

Variable name	Abbreviation	Measures	Type of variable	Missing rate	Variable role
Rheumatoid arthritis disease duration		Baseline	Scale	12.4%	Independent
Smoking		Baseline	Categorical	26.0%	Independent
Rheumatoid factor	RF	Baseline	Categorical	8.3%	Independent
Antinuclear antibodies	ANA	Baseline	Categorical	21.4%	Independent
Anti-cyclic citrullinated peptide	ACPA	Baseline	Categorical	21.0%	Independent
Sicca symptoms	SICCA	Baseline	Categorical	19.8%	Independent
Rheumatoid nodules	Nodules	Baseline	Categorical	18.5%	Independent
Family history of rheumatic disease	FH	Baseline	Categorical	28.4%	Independent
Treatment class	TC	Repeated	Categorical	13.7%	Independent
Steroid therapy	Steroid	Baseline	Categorical	6.6%	Independent
Joint pain		Repeated	Categorical	3.8%	Independent
Disease Activity Score of 28 joint	DAS28	Repeated	Scale	1.0%	Target (outcome)
Erythrocyte sedimentation rate	ESR	Repeated	Scale	5.1%	Independent
C-reactive protein	CRP	Repeated	Scale	2.2%	Independent
Health Assessment Questionnaire					
Disability index	HAQ	Repeated	Scale	65.5%	Independent

was approved by the Ethics Committees of the Faculty of Medicine at Kuwait University and the Ministry of Health. Additionally, informed consent was obtained from all represented patients enrolled in the registry.[29]

Using the data obtained from KRRD, we conducted an in-depth comparative analysis of the different imputation methods. Missing data were entered into each data set, assuming a general missing data pattern and 3 mechanisms of missing data: MCAR, MAR, and NMAR. Under the MCAR assumption, missing values were randomly applied to each data set. Under the MAR assumption, the probability of information being missing depended on class attribute.

Under the NMAR assumption, the largest or smallest values of X_s were removed. The objective of the study was to derive a comparison of 4 different imputation methods for NMAR, MAR, and MCAR, concerning missing data. We simulated the rates of missing data by varying the value proportions by 10%, 20% and 30%.

2.2 | Calculating RA indices

RA disease activity scores are measured using 2 different indices: Disease Activity Score of 28 joints (DAS28) and Clinical Disease Activity Index (CDAI). The DAS28 is the sum of 4 outcome parameters: tender joint count of 28 joints (TJC28); swollen joint count of 28 joints (SJC28); erythrocyte sedimentation rate (ESR: in mm/h) (C-reactive protein [CRP] may be used as an alternative to ESR in the calculation); and patient global health assessment (GH: from 0 = best to 100 = worst) Equation (1).

$$DAS-28 = 0.56 \times \sqrt{TJC28} + 0.28 \times \sqrt{SJC28} + 0.70 \times \ln(ESROrCRP) + 0.14 \times GH, \quad (1)$$

The second index is the CDAI. The CDAI considers the following items: TJC28 (0-28); SJC28 (0-28); the patient global health assessment (PaGH: from 0 = best to 10 = worst); and the care provider global health assessment (PrGH: from 0 = best to 10 = worst) Equation (1). In this study, we used the first index (DAS28) as a target variable.

2.3 | Multiple Imputation (MI) process using Rubin's Rules

For our data sets, we used Rubin's rules[10] for handling missing data. The MI process was conducted separately for each variable in the data set (Figure 1). The first step in MI is to create values (imputes or m_i), with 5 iterations for each m_i (imputed: set 1 to set 5, Figure 1) to be substituted for the missing data. To create the imputed values, we need to identify a model (eg, a linear regression) that allows us to create imputes based on other variables in the data set (predictor variables). As we needed to perform this multiple times to produce multiple-imputed data sets, we identified a set of regression lines that were similar to each other.

2.4 | Number of needed imputations

An important aspect of previous technical treatments of MI is that the discussion of selecting the number of imputations that are required for acceptable statistical inference (eg, [30-32]). For example, Schafer and Olsen[32] recommend that in several applications, simply 3-5 imputations are enough to get sufficient results. Many are surprised by the claim that only 3-5 imputations may be needed. Rubin[30] shows that the efficiency of an estimate based on m imputations is approximately

$$\left(1+\frac{\gamma}{m}\right)^{-1}, \quad (2)$$

where γ is the fraction of missing information for the quantity being estimated gains rapidly diminish after the first few imputations. In most situations there's merely very little advantage to generate and analyzing over a few imputed datasets. In theory, the more imputation, the better performance in estimating missing values, but it takes a lot of time, which is a barrier for this research. It is convenient to set m = 5 during the stage of model building and raising the amount in the evaluation stage if it is needed.[33] So, in this study, the MI methods are performed with m = 5 imputed data sets which can be considered as satisfactory.[30]

2.5 | MI using RF method

Assume that $\mathbf{X} = (\mathbf{X_1}, \mathbf{X_2}, \ldots, \mathbf{X_p})$ is an n × p-dimensional data matrix. We propose using the RF technique to impute missing observations. The RF algorithm has a built-in routine to handle the values that are missing by weighing the frequencies of values with the proximity of a RF after the training of the mean data set is initially imputed.[34] This approach needs a response variable that is complete and useful for forest training. Instead, we directly estimate the values of all the missing values using a RF that is trained from the observed data set, where X is the matrix of the complete data. $\boldsymbol{X}_s$ contains all missing values at entries $i_{mis}^{(s)} \subseteq \{1, \ldots, n\}$. The data set can be separated into 4 parts:

1. $\mathbf{y}_{obs}^{(s)}$: the observed values of $\mathbf{X}_s$;
2. $\mathbf{y}_{mis}^{(s)}$: the missing values of $\mathbf{X}_s$;
3. $\mathbf{x}_{obs}^{(s)}$: the observations $\mathbf{i}_{obs}^{(s)} = \frac{\{1,\ldots,n\}}{\mathbf{i}_{mis}^{(s)}}$, which belong in the other variables $\mathbf{X}_s$;
4. $\mathbf{x}_{mis}^{(s)}$:the observations $\mathbf{i}_{mis}^{(s)}$ that belong in the other variables $\mathbf{X}_s$.

Note that and are not completely observed, as the index corresponds to the observed values of the variable $\mathbf{X}_s$.

According to Stekhoven and Bühlmann,[24] the process starts with an initial guess for missing values in $\mathbf{X}$ using a mean imputation approach or any other imputation method depending on the data. Then, we sort the predictors $\mathbf{X}_s$, s = 1,..., p, in ascending or descending order, $\mathbf{X}_s$, s = 1,..., p, according to the number of missing values. Then, for each variable $\mathbf{X}_s$ the missing values are imputed by RF (ie, the first

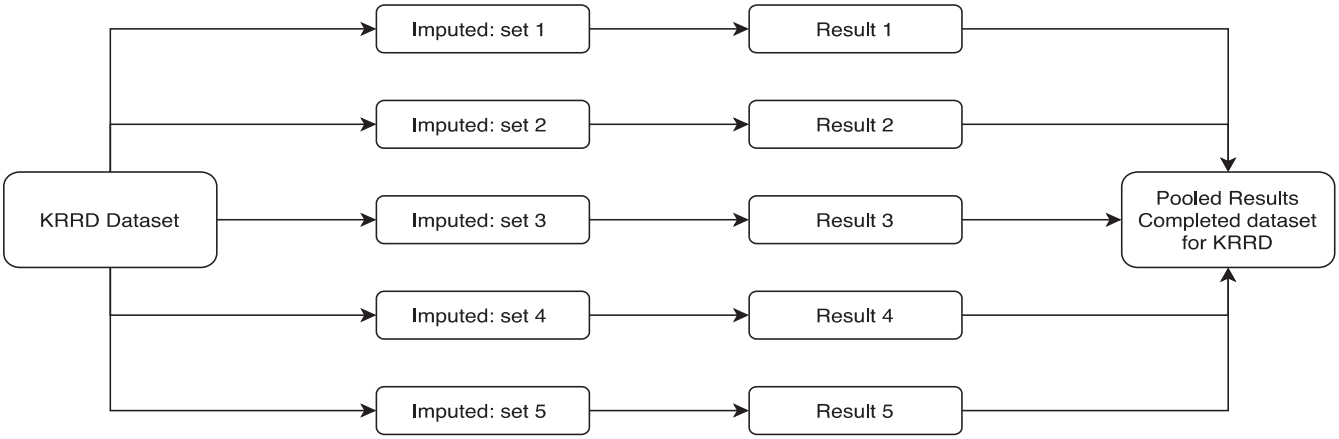

FIGURE 1 The steps of implementing multiple imputations using Rubin's rules to estimate missing values for the Kuwait Registry for Rheumatic Diseases (KRRD)

fitting) with response $\mathbf{y}_{obs}^{(s)}$ and predictors $\mathbf{x}_{obs}^{(s)}$. Next, the missing values $\mathbf{y}_{mis}^{(s)}$ are estimated by adopting the trained RF to $\mathbf{x}_{mis}^{(s)}$. The imputation approach should be repeated until a stopping criterion is reached. Pseudo Algorithm 1 shows a representation of the missForest method (Algorithm 1). The stopping criterion (γ) is met when the difference between the last imputed data matrix and the previous one increases for the first time with respect to both variable types. Here, the difference for the set of continuous variables **N** is defined as

$$\Delta_N = \frac{\sum_{j\in N}\left(X_{new}^{imp} - X_{old}^{imp}\right)^2}{\sum_{j\in N}\left(X_{new}^{imp}\right)^2}, \tag{3}$$

and that for the set of categorical variables **F** is defined as

$$\Delta_F = \frac{\sum_{j\in F}\sum_{i=1}^{n} I_{X_{new}^{imp}\neq X_{old}^{imp}}}{\#NA}, \tag{4}$$

where **X** is an n × p matrix, setting the stopping criterion (γ) and initial guesses for missing values; **k**← is the vector of sorted indices of columns in **X** with respect to increasing the amount of missing values; and $\mathbf{X}_{old}^{imp}$ stores the previously imputed matrix. We fit a RF $\mathbf{y}_{obs}^{(s)} \sim \mathbf{x}_{obs}^{(s)}$; predict $\mathbf{y}_{mis}^{(s)}$ using $\mathbf{x}_{mis}^{(s)}$; use $\mathbf{X}_{new}^{imp}$ to update the imputed matrix using the predicted $\mathbf{y}_{mis}^{(s)}$; and update γ using the imputed matrix $\mathbf{X}^{imp}$, where **NA** is the number of missing values in the categorical variables.

After imputing the missing values, the performance of different methods was assessed using the normalized root mean squared error (NRMSE) for the continuous variables, defined by:

$$NRMSE = \sqrt{\frac{mean\left(\left(X^{true} - X^{imp}\right)^2\right)}{\mathrm{var}\left(X^{true}\right)}}, \tag{5}$$

Algorithm 1: Impute missing values RF.[24]

Require: **X** is an n × p matrix. Set up the stopping criterion (γ)

1: set up initial guess for missing values;

2: **k** is the vector of sorted indices of columns in X wrt increasing the amount of missing values;

3: **while** not γ **do**.

4: $\mathbf{X}_{new}^{imp}$ stores the previously imputed matrix;

5: **for** s in **k do**.

6: fit a RF: $\mathbf{y}_{obs}^{(s)} \sim \mathbf{x}_{obs}^{(s)}$;

7: predict $\mathbf{y}_{mis}^{(s)}$ using $\mathbf{x}_{mis}^{(s)}$;

8: $\mathbf{X}_{new}^{imp}$ updates the imputed matrix using predicted $\mathbf{y}_{mis}^{(s)}$;

9: **end for**

10: updated γ

11: **end while**

12: return the imputed matrix $\mathbf{X}^{imp}$

where $\mathbf{X}^{true}$ and $\mathbf{X}^{imp}$ are the complete data matrix and the imputed data matrix, respectively. In this study, all predictors were classified as continuous observations. The mean and variance are used as a short notation for the empirical mean and variance computed over the missing values only, respectively. When an RF fits to the part that is observed on a variable, we reach the out-of-bag (OOB) estimate of the error for the variable. When the stopping criterion (γ) is met, we average it over the variable set of that type to obtain an approximation of the actual errors of imputation. We assessed the estimation performance by comparing the absolute difference between the OOB imputation error estimate in all simulation runs and the true imputation error.

2.6 | Evaluation criteria

To determine the best imputation method, 3 model performance tests were considered: RMSE, mean absolute error (MAE), and correlation coefficient (*R*), which are respectively calculated as follows:

$$RMSE = \sqrt{\frac{1}{n}\sum_{i=1}^{n}\left(y_i - \hat{y}_i\right)^2}, \tag{6}$$

$$MAE = \frac{1}{n}\sum_{i=1}^{n}\left|y_i - \hat{y}_i\right|, \tag{7}$$

TABLE 2 Baseline patient characteristics from the Kuwait Registry for Rheumatic Diseases (2012 to 2020)

	N = 1735	N
Gender, female	1090 (62.8%)	1735
Age, y	54.0 (12.6)	1719
RA disease duration, y	9.19 (6.76)	1520
Nationality		
Kuwaiti	839 (48.4%)	1735
Non-Kuwaiti	896 (51.6%)	
Main hospital		
Amiri	708 (40.8%)	1735
Farwaniya	663 (38.2%)	
Jahra	83 (4.78%)	
Mubarak	280 (16.1%)	
Sabah	1 (0.06%)	
Smoking, yes	133 (10.4%)	1284
Rheumatoid factor positive	1227 (77.1%)	1591
Sicca symptoms, yes	260 (18.7%)	1391
Antinuclear antibody positive	388 (28.4%)	1364
Anti-citrullinated peptide antibody positive	903 (65.9%)	1370
Family history positive	229 (18.4%)	1243
Treatment class, biologics	488 (32.6%)	1498
Comorbidity, yes	926 (53.4%)	1735
Current steroid, yes	366 (22.6%)	1620
Joint pain, yes	982 (58.8%)	1670

where y_i and $\hat{y}_i$ are the i^{th} observations for the reconstructed and comparison data sets, respectively. The error is measured based on the difference between the estimated and observed values. For RMSE and MAE, the smaller the value obtained, the more accurate the estimation method.

3 | RESULTS

The performance of 3 imputation mechanisms (MCAR, MAR, and MNAR) was analyzed using sub-data sets from KRRD patients using 3 different missingness rates (10%, 20%, and 30%). A total of 1735 patients (62.8% men and 37.2% women) from 2012-2020 were included in this study (Table 2). The baseline investigated patient characteristics included factors such as smoking, rheumatoid factor, sicca, antinuclear antibodies (ANA), anti-citrullinated peptide antibody (ACPA), family history, treatment class, comorbidity, steroid and joint pain.

The average duration of RA disease was 9.19 ± 6.76 (SD) years. Most of the data were recorded at Amiri and Farwaniya hospitals (79%). A majority of the patients were non-smokers (89.6%), 77.1% were rheumatoid factor-positive, 65.9% of RA patients were ACPA-positive, and 58.8% had joint pain. The results showed that RA patients had positive sicca (18.7%), positive ANA (28.4%), positive family history (18.4%), and positive steroid use (22.6%). Table 3 provides a descriptive analysis of RA lab tests for ESR, CRP, Health Assessment Questionnaire (HAQ), and DAS28, which were calculated 5 different times from 5 different data sets after implementing missing values methods (original data set compared with imputed data sets using PMM, RF, kNN, and missForest).

The mean and SD values of ESR, CRP, HAQ, and DAS28 were 27.5729 ± 22.2706, 5.9904 ± 4.9334, 0.9517 ± 0.6649, and 2.6756 ± 1.2902, respectively, for the original data, and those for the imputed data sets values ranged between 27.0639 and 27.1245, 6.4323 and 6.4456, 0.9042 and 0.9062, and 2.6759 and 2.6767, respectively. The skewness and kurtosis values were mostly positive: 1.2248, 1.0182, 0.8120, and 0.5963 for skewness and 1.6256, 0.3932, −0.0311, and 0.2599 for kurtosis in the case of imputed data sets that ranged between 1.2551 and 1.2675, 0.8085 and 0.8135, 1.1352 and 1.1430, and 0.5961 and 0.6005 for skewness, respectively, and 1.7394 and 1.7854, 0.1395 and 0.1493, 2.1178 and 2.1560, and 0.2664 and 0.2798 for kurtosis, respectively. The data showed that the original data set and the imputed data sets had very close values with small differences for all RA lab tests (ESR, CRP, HAQ, and DAS28).

3.1 | Predicting the influence of RA factors on DAS28 using the original data set

Here we are trying to estimate a regression model that explains the effect from the independent variables (Table 1) toward the outcome variable (DAS28). We used the original KRRD dataset. As we mentioned before, the original dataset contains missing values in all variables (Table 1).

The missing values rate in the original data set vary from 2% to 66%. Table 4 shows the estimated parameters predicting DAS28 using a multiple linear model. Only 6 variables were found to be significant risk factors that influenced DAS28 ($R^2_{DAS28} = 0.773$). The results showed that ESR, CRP, HAQ, disease duration, and current steroid use were risk factors predicting DAS28, with β = 0.034, 0.020, 0.129, 1.489, 0.247, 1.095, respectively (95% CIs: 0.032-0.036, 0.012-0.029, 0.075-0.183, 1.415-1.562, 0.138-0.356, and 0.963-1.228, respectively). Other factors (RF, ANA, ACPA, sicca, nodules, smoking, family history and joint pain) were not found to be risk factors influencing DAS28 (Table 4).

Because of the existing of missing values, smoking, joint pain and sicca were not found to be a significant risk factor for DAS28. However, many scholars showed that those variables (smoking, joint pain and sicca) can be risk factors toward DAS28.[35,3637]

3.2 | Predicting the influence of RA factors on DAS28 from the PMM-imputed data sets

Using the imputation process to predict all missing values in the KRRD data set using the 3 different missing imputation mechanisms

TABLE 3 Mean and SD for ESR, CRP, HAQ, and DAS28 from the original data set and the imputed data sets (IM)

Data set	Variable	n	Minimum	Maximum	Mean	SE	SD	Skewness	Kurtosis
Original data	ESR	10 703	0.0000	134.0000	27.5729	0.2153	22.2706	1.2248	1.6256
	CRP	8769	0.0000	21.0000	5.9904	0.0527	4.9334	1.0182	0.3932
	HAQ	4004	0.0125	3.0000	0.9517	0.0105	0.6649	0.8120	−0.0311
	DAS28	11 213	0.0000	9.7050	2.6756	0.0122	1.2902	0.5963	0.2599
IM_1 = PMM	ESR	11 282	0.0000	134.0000	27.0701	0.2066	21.9426	1.2589	1.7503
	CRP	11 282	0.0000	21.0000	6.4456	0.0441	4.6873	0.8108	0.1489
	HAQ	11 282	0.0125	3.0000	0.9053	0.0044	0.4647	1.1356	2.1236
	DAS28	11 282	0.0000	9.7050	2.6761	0.0121	1.2883	0.6005	0.2798
IM_2 = RF	ESR	11 282	0.0000	134.0000	27.0639	0.2068	21.9637	1.2675	1.7854
	CRP	11 282	0.0000	21.0000	6.4426	0.0442	4.6961	0.8135	0.1493
	HAQ	11 282	0.0125	3.0000	0.9042	0.0044	0.4657	1.1352	2.1178
	DAS28	11 282	0.0000	9.7050	2.6763	0.0121	1.2878	0.5992	0.2717
	CRP	11 282	0.0000	21.0000	6.4323	0.0441	4.6865	0.8085	0.1395
	HAQ	11 282	0.0125	3.0000	0.9061	0.0044	0.4658	1.1430	2.1560
	DAS28	11 282	0.0000	9.7050	2.6767	0.0121	1.2876	0.5974	0.2689
IM_4 = missForest	ESR	11 282	0.0000	134.0000	27.0939	0.2064	21.9236	1.2551	1.7394
	CRP	11 282	0.0000	21.0000	6.4396	0.0440	4.6772	0.8088	0.1444
	HAQ	11 282	0.0125	3.0000	0.9062	0.0044	0.4628	1.1375	2.1519
	DAS28	11 282	0.0000	9.7050	2.6759	0.0121	1.2861	0.5961	0.2664

Abbrevations: CRP, C-reactive protein; DAS28, Disease Activity Score of 28 joints; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; missForest, sequential random forest; PMM, predictive mean matching; RF, random forest.

(MAR, MCAR, and MNAR), we constructed a quality data set after fixing all missing values using PMM. Table 5 shows the estimated parameters when predicting DAS28 using multiple linear models and the PMM-imputed data sets.

The regression results showed the same significant risk factors, this time adding rheumatoid factor to predict DAS28 (R^2_{DAS28} = 0.727); in addition, smoking was found to be a very strong risk factor when we used the imputed data sets, but was not when we used the original data set to predict the influence on DAS28.

The regression model that used the original data set did not indicate that rheumatoid factor has a significant influence on DAS28 but, if we used the PMM-imputed data set, the regression model indicated that rheumatoid factor had a significant influence when predicting DAS28.

Due to the effect of bias induced by the missing values, the rheumatoid factor results were not significant when using the original data set; however, after we imputed all the missing data in the KRRD data set, the regression results became more sufficient and reliable.

3.3 | Predicting the influence of RA factors on DAS28 from the imputed data sets using kNN

The kNN-based imputation of missing data restored the leftover values in the KRRD data set and better standard data were obtained. As shown in Table 6, various parameters were used to establish DAS28 prediction using the kNN-imputed data sets.

The regression results were calculated based on similar factors as those of the original data set with further incorporation of rheumatoid factor and sicca and further prediction of DAS28 (R^2_{DAS28} = 0.727).

Similar to the PMM-based analysis, the kNN imputation revealed that rheumatoid factor can significantly influence the prediction of DAS28, which was not significant in the original data set due to bias. The disease duration factor had a negative value in both PMM and kNN, whereas it was positive in the original data set.

3.4 | Predicting the influence of RA factors on DAS28 from the RF-imputed data sets

The results of RF imputation, in terms of removing bias in the KRRD data set, were similar to those of PMM-based imputation. Table 5 shows that the factors that significantly affected the DAS28 parameter at $P < .01$ were similar between PMM- and RF-based imputation, with their values being very close. The adjusted R^2_{DAS28} value of 0.728 was obtained after imputation.

3.5 | Predicting the influence of RA factors on DAS28 from the missForest-imputed data sets

One of the best methods for imputation reported in the literature and evident from the analysis was missForest. Apart from all the

TABLE 4 Multiple regression coefficients with 95% confidence intervals (in parentheses) for predicting DAS28 using the original data set including the missing values

	DAS28
	Data set = Original
Erythrocyte sedimentation rate	0.034*** (0.032, 0.036)
C-reactive protein	0.020*** (0.012, 0.029)
Health Assessment Questionnaire	0.129*** (0.075, 0.183)
Rheumatoid factor	0.021 (−0.064, 0.106)
Antinuclear antibody	−0.062 (−0.139, 0.014)
Anti-citrullinated peptide antibody	0.008 (−0.066, 0.082)
Sicca symptoms	0.083 (−0.011, 0.178)
Nodules	−0.519 (−1.122, 0.083)
Smoking	0.184 (−0.019, 0.350)
Family history	−0.087 (−0.174, 0.001)
Joint pain	0.273 (−0.015, 0.530)
Disease duration	1.489*** (1.415, 1.562)
Current steroid	0.247*** (0.138, 0.356)
Constant	1.095*** (0.963, 1.228)
R^2	0.773
Adjusted R^2	0.769

Note: *P <.1;** P <.05;*** P <.01.
DAS28, Disease Activity Score of 28 joints.

factors listed in the original data set and compared to the imputation by PMM, kNN, and RF, the missForest-based imputation analysis produced better results, as evidenced by MAR, MCAR, and MNAR missing value mechanisms (Table 7 and Table 5).

The adjusted R^2_{DAS28} value was 0.731. The data set was the most refined and its quality was the most improved after applying the missForest imputation method.

We hypothesized that the missing data could be imputed using the different imputation strategies; therefore, the MCAR, MAR, and MNAR mechanisms were simulated for missing values in the 3 different missingness proportions of 10%, 20%, and 30%. To avoid bias in the comparison, we used 4 MI methods: PMM, kNN, RF, and missForest (Table 7).

The KRRD data set was simulated with these imputation methods; the best method was selected according to the RMSE score. As shown in Table 7, the RMSE value ranged between 2.518 to 6.066 for MAR, 2.555 to 5.590 for MCAR, and 3.631 to 8.004 for MNAR. The MAR had the lowest RMSE, compared to the other missing data methods.

Similar investigations have been previously performed and our data were in agreement with those in earlier reports.[38,39]

In the MAR, MCAR, and MNAR mechanisms, missForest was the best method of imputation, having the lowest RMSE values for all of the parameters and at all 3 percentages of simulated missing data (MAR: 2.518, 3.013, and 3.032; MCAR: 3.168, 2.555, and 2.871; and MNAR: 4.962, 4.180, and 3.631 for 10%, 20%, and 30%, respectively) which agrees with other authors.[38,40,41]

This was followed by kNN, which performed better than the other 2 imputation methods (RF and PMM), in terms of RMSE values, at every percentage of missingness (MAR: 4.107, 4.884, and 4.184; MCAR: 3.820, 3.560, and 3.734; and MNAR: 6.236, 5.507, and 5.062 for 10%, 20%, and 30%, respectively); see Table 7. Similar results have been reported that strongly support the better imputation of kNN, compared with RF and PMM.[42] RF and PMM were the worst-performing MI methods; of the 2, using RF had a slight advantage over PMM but PMM had better imputation in a few of the cases, such as MAR 30% or MNAR 10% and 30%, where RF had a larger RMSE value than PMM. Table 5 and Table 6 represent the multiple regression coefficients with 95% CIs for the prediction of DAS28 using the imputed data sets (PMM, RF, kNN, and missForest). The table demonstrates the effect of patient demographics on RA disease activity, where DAS28 was the response variable.

The score for DAS28 is also reported, where R^2_{DAS28} = 0.727 for PMM method, and R^2_{DAS28} = 0.728 for RF method. Regarding kNN and missForest, R^2_{DAS28} = 0.728 for the kNN method, and R^2_{DAS28} = 0.731 for the missForest method. The results depict the positive effect of various factors, such as ESR, CRP, HAQ, rheumatoid factor, sicca, smoking, joint pain, and current steroid use, with β = .031, .015, .202-.204, .050-.061, .057-.065, .131-.140, .674-.677, and .118-.129, respectively, on RA disease activity, whereas family history and disease duration—with β = .029 to −.021, and 0.007, respectively—had negative effects under all 4 imputation methods (Table 5 and Table 6).

Additionally, nodules and constant showed diverse effects per imputation method. The nodules had positive values for PMM and missForest, with β = .016 and .004, respectively, and negative values for RF and kNN, with β = .011 and .002, respectively. Constant had negative values for PMM, kNN, and missForest, with β = .032, .017, and .037, respectively, and a positive value for RF, with β = .002 (Table 5 and Table 6).

4 | DISCUSSION

The obtained RA patient data recorded in the KRRD registry were utilized to quantify the RA DAS. All the information was acquired from 1735 patients from public healthcare facilities with permission from the relevant ethics committees. The baseline variables under investigation for every patient included smoking, gender, disease duration, age, nationality, sicca, rheumatoid factor, ACPA, ANA, family history, treatment class (biologics, conventional disease-modifying antirheumatic drugs), current steroids, comorbidity, DAS28 group, and joint pain.

Systematic errors that existed between the anticipated and noted values were due to the missing values which led to outcome bias. However, to get the accurate missing values,[43] it is significant to eliminate the bias and apply the optimal approach to guarantee reliability and quality of data analysis. The uncompleted data sets contradicted significantly with the complete data file.[44] The emergence

TABLE 5 Multiple regression coefficients with 95% confidence intervals (in parentheses) to predict DAS28 from other predictors from PMM- and RF-imputed data sets

	DAS28	
	Imputed data set	
	PMM	RF
Erythrocyte sedimentation rate	0.031*** (0.030, 0.031)	0.031*** (0.030, 0.031)
C-reactive protein	0.015*** (0.012, 0.017)	0.015*** (0.012, 0.017)
Health Assessment Questionnaire	0.202*** (0.178, 0.226)	0.202*** (0.178, 0.225)
Rheumatoid factor	0.061*** (0.035, 0.087)	0.050*** (0.024, 0.076)
Antinuclear antibody	0.005 (−0.020, 0.031)	0.003 (−0.023, 0.028)
Anti-citrullinated peptide antibody	0.003 (−0.020, 0.026)	0.008 (−0.016, 0.031)
Sicca symptoms	0.064*** (0.034, 0.094)	0.060*** (0.031, 0.090)
Nodules	0.016 (−0.044, 0.077)	−0.011 (−0.071, 0.049)
Smoking	0.131*** (0.086, 0.177)	0.140*** (0.095, 0.186)
Family history	−0.029 (−0.059, 0.001)	−0.022 (−0.052, 0.008)
Joint pain	0.674*** (0.662, 0.686)	0.676*** (0.664, 0.688)
Disease duration	−0.007*** (−0.009, −0.006)	−0.007*** (−0.009, −0.005)
Current steroid	0.128*** (0.093, 0.162)	0.118*** (0.084, 0.153)
Constant	−0.032 (−0.146, 0.083)	0.002 (−0.112, 0.117)
Observations	11,282	11,282
R^2	0.727	0.728
Adjusted R^2	0.727	0.728

Note: *P <.1;** P <.05;*** P <.01.

Abbrevations: DAS28, Disease Activity Score of 28 joints; PMM, predictive mean matching; RF, random forest.

of imputation algorithms has been attributed to their substantial global use.

Imputation methods overcome the existing prejudice in missing values. However, their values may potentially lead to bias in the result. Therefore, they should be used vigilantly. The research utilized numerous variables to define the RA DAS. The application of many factors resulted in data with missing characteristics in various patients, leading to bias results. The focal point was to identify the suitable imputation approach to complete the missing features in the RA data set.

The variation of the missing data ranged from 2% to 66%. At this point, 4 imputation approaches were assessed, the kNN, PMM, missForest, and RF through 3 diverse missing approaches, MAR, MNAR, and MCAR, with the KRRD RA infection data set. Performance evaluations of the imputation methods were done utilizing RMSE values, with the minimum RMSE value showing the best imputation technique.

MI are computationally comprehensive and require estimations. To get enough needed results, several algorithms should be run frequently, where running time increases with more missing data. In our case scenario, MI generated variable approximates almost similar to known approximates to the traditional missing data techniques. MI provided mean and SE closely similar to the noted values, outperforming the single imputation methods or deletion.

The findings, in this case, are similar to the findings obtained when using a hypothetical data set to differentiate missing data approaches. Putting traditional methods into consideration in all the conducted research, the regression imputation generated the approximate mean, and deletion generated the approximate SD when contrasted to the finalized data sets. The current research was dominant since the variable estimates attained by each missing data approach could be contrasted to the already known variables of an absolute data set acquired from the clinical setting. The result reveals that is possible to apply missing data methods like MI in the current context.[45]

However, despite the effectiveness of the MI method in undertaking the missing data, it is significant to note that the associated problem with missing data cannot be enhanced by any missing data approach. MI and numerous missing data techniques are useful for MAR or MCAR despite their unreliability when data is MNAR. Determination of whether data is MAR or MNAR is often difficult as there is no reliable technique to do so. But, in some clinical or environmental studies,[4,14,46,47] either MAR or MCAR are preferable rather than the MNAR mechanism.

In general, our results show that MI using MAR mechanism had the lowest RMSE among the other missingness mechanisms (MCAR or MNAR). Compared with complete case analysis, its effectiveness is due to MI's use of information in incomplete cases, while complete case analysis is only valid in the case of MAR or MCAR data.[48]

TABLE 6 Multiple regression coefficients with 95% confidence intervals (in parentheses) to predict DAS28 from other predictors from kNN- and missForest-imputed data sets

	DAS28	
	Imputed data set	
	kNN	missForest
Erythrocyte sedimentation rate	0.031*** (0.030, 0.031)	0.031*** (0.030, 0.031)
C-reactive protein	0.015*** (0.013, 0.018)	0.015*** (0.012, 0.017)
Health Assessment Questionnaire	0.203*** (0.180, 0.227)	0.204*** (0.180, 0.227)
Rheumatoid factor	0.058*** (0.032, 0.084)	0.056*** (0.030, 0.082)
Antinuclear antibody	0.001 (−0.025, 0.026)	0.008 (−0.018, 0.033)
Anti-citrullinated peptide antibody	0.004 (−0.019, 0.027)	0.004 (−0.020, 0.027)
Sicca symptoms	0.065*** (0.035, 0.094)	0.057*** (0.027, 0.087)
Nodules	−0.002 (−0.062, 0.058)	0.004 (−0.056, 0.063)
Smoking	0.132*** (0.087, 0.177)	0.139*** (0.093, 0.184)
Family history	−0.024 (−0.054, 0.006)	−0.021 (−0.051, 0.010)
Joint pain	0.674*** (0.662, 0.686)	0.677*** (0.666, 0.689)
Disease duration	−0.007*** (−0.009, −0.005)	−0.007*** (−0.009, −0.005)
Current steroid	0.125*** (0.091, 0.159)	0.129*** (0.094, 0.163)
Constant	−0.017 (−0.131, 0.098)	−0.037 (−0.151, 0.077)
Observations	11,282	11,282
R^2	0.728	0.731
Adjusted R^2	0.728	0.731

Abbrevations: DAS28, Disease Activity Score of 28 joints; kNN, k-nearest neighbors; missForest, sequential random forest.

In well-designed studies, such as clinical trials, MAR mechanism is more common than MCAR, because in most cases, observable data explain most of the deficiencies.[49]

MI technique sometimes is not the better method even when MCAR or MAR is missing. Concerning the sample size, it is important to note that a small sample size may minimize the accuracy of MI.[50] Additionally, the utilization of MI in longitudinal designs with layered data may present challenges that may need the use of MI algorithms or other approaches other than MI.[51-53] Another challenge is that statistical packages vary with their ease of usability in respect to the merging variables and test statistics. The provision of numerous missing data methods indicates the benefits of using MI in the clinical surrounding. Additionally, it also indicates the significance of having a comprehensive understanding of the type and the effect of the missing data despite active handling of the data. It is also important to consider factors that may potentially facilitate missing data before the beginning of the research.[53] That way, researchers can measure these factors influencing data missingness and do extensive analysis.

Finally, the variety of data and the negative effects of missing data, and the correlated restraints that come with using traditional approaches to handle the missingness of data are not considered important. The findings show that techniques like MI perform better than the traditional approaches as they facilitate the reintroduction of the difference that would occur upon attaining missing scores. As a result, this reduces bias produced by missing data and enhances the ability to realize meaningful influences. MI and other techniques are fast and elementary to use and their long-term merits are valuable, given the time taken to learn the techniques and when applied within the clinical research setting. From the results, missForest is regarded as the most productive imputation technique with the least RMSE values at 95% credence, reproduced employing 10%, 20%, and 30% missing data. Thereafter, kNN was conducted. The RF and PMM were identified as the least performing imputation techniques. Due to the availability of large data from registered RA patients used, the research and its outcomes are considered robust. Additionally, the imputation method considered and missingness procedures (implemented at 10% to 30% utilizing MAR, MNAR, and MCAR) ameliorated data reliability with notable *P* values attained. Also, to check the robustness of the results for the imputation methods, particularly when missingness rate is high, we have repeated the new missing imputation using missForest, RF, kNN and PMM for missingness rate = 30% only and m = 25. We found that this is very computationally intensive and the results showed differences in the RMSE scores (m = 25 is better than m = 5). However, the preferences between imputation methods based on RMSE scores are similar without any change in ranking order. So, the main results for m = 25 have the same conclusion for m = 5, which means that missForest is a highly accurate method of imputation for missing data

TABLE 7 Comparison between imputation methods after we simulated 10%, 20%, and 30% missing data in the Kuwait Registry for Rheumatic Diseases data set

Method	MAR			MCAR			MNAR		
Missingness rate	10%	20%	30%	10%	20%	30%	10%	20%	30%
Predictive mean matching	5.349	6.066	4.944	5.590	4.590	5.135	6.950	7.471	6.516
Random forest	4.618	5.233	5.234	4.837	4.204	4.539	8.004	7.212	6.737
Classification and regression trees (kNN)	4.107	4.884	4.184	3.820	3.560	3.734	6.236	5.507	5.062
missForest	2.518	3.013	3.032	3.168	2.555	2.871	4.962	4.180	3.631

The root mean square error (RMSE) is used to highlight and select the best missing imputation method with the lowest RMSE score.
Abbrevations: kNN, k-nearest neighbors; MAR, missing at random; MCAR, missing completely at random; missForest, sequential random forest; MNAR, missing not at random.

in KRRD and outperforms other common imputation techniques in terms of imputation error and maintenance of predictive ability with imputed values in clinical predictive models. This approach can be used in registries to improve the accuracy of data, including the ones for RA patients.

5 | CONCLUSION

missForest is a highly accurate method of imputation for missing data in KRRD and outperforms other common imputation techniques in terms of imputation error and maintenance of predictive ability with imputed values in clinical predictive models. This approach can be used in registries to improve the accuracy of data, including the ones for RA patients.

ACKNOWLEDGEMENTS

The authors would like to thank the KRRD group for their help to provide all the necessary information and data. Also, the authors would like to thank all of those who have contributed to data collection and data processing for the registry. Without them, this study would not have been possible.

CONFLICT OF INTEREST

Authors have declared that no competing interests exist.

ORCID

Ahmad Alsaber https://orcid.org/0000-0001-9478-0404

REFERENCES

1. Sartori N, Salvan A, Thomaseth K. Multiple imputation of missing values in a cancer mortality analysis with estimated exposure dose. *Computational Statistics & Data Analysis*. 2005;49(3):937-953. http://dx.doi.org/10.1016/j.csda.2004.06.013
2. Branden KV, Verboven S. Robust data imputation. *Comput Biol Chem*. 2009;33(1):7-13.
3. Frisell T. SP0187 why missing data is a problem, and what you shouldn't do to solve it. BMJ Publishing Group Ltd. 2016.
4. Alsaber AR, Pan J, Al-Hurban A. Handling complex missing data using random forest approach for an air quality monitor-ing dataset: a case study of Kuwait environmental data (2012 to 2018). *Intern J Environ Res Public Health*. 2021;18(3):1333.
5. Mondelo D. *Imputation Strategies for Missing Data in Environment Time Serial for an Unlucky Situation*. Springer; 2006.
6. Kang H. The prevention and handling of the missing data. *Korean J Anesthesiol*. 2013;64(5):402.
7. Stavseth MR, Clausen T, Røislien J. How handling missing data may impact conclusions: a comparison of six different imputation methods for categorical questionnaire data. *SAGE Open Med*. 2019;7:2050312118822912.
8. Junninen H, Niska H, Tuppurainen K, Ruuskanen J, Kolehmainen M. Methods for imputation of missing values in air quality data sets. *Atmos Environ*. 2004;38(18):2895-2907.
9. Higgins JP, White IR, Wood AM. Imputation methods for missing outcome data in meta-analysis of clinical trials. *Clin Trials*. 2008;5(3):225-239.
10. Little RJ, Rubin DB. *Statistical analysis with missing data*, vol. 793. John Wiley & Sons; 2019.
11. Rubin DB. *Statistical analysis with missing data*. Wiley; 1987.

12. Di Zio M, Guarnera U, Luzi O. Imputation through finite Gaussian mixture models. *Comput Stat Data Anal*. 2007;51(11):5305-5316.
13. Thijs H, Molenberghs G, Michiels B, Verbeke G, Curran D. Strategies to fit pattern-mixture models. *Biostatistics*. 2002;3(2):245-265.
14. Pedersen AB, Mikkelsen EM, Cronin-Fenton D, et al. Missing data and multiple imputation in clinical epidemiological research. *Clin Epidemiol*. 2017;9:157.
15. Van der Heijden GJ, Donders ART, Stijnen T, Moons KG. Imputation of missing values is superior to complete case analysis and the missing-indicator method in multivariable diagnostic research: a clinical example. *J Clin Epidemiol*. 2006;59(10):1102-1109.
16. Fielding S, Fayers PM, McDonald A, et al. Simple imputation methods were inadequate for missing not at random (MNAR) quality of life data. *Health Qual Life Outcomes*. 2008;6(1):57.
17. Moons KG, Donders RA, Stijnen T, Harrell FE Jr. Using the outcome for imputation of missing predictor values was preferred. *J Clin Epidemiol*. 2006;59(10):1092-1101.
18. Zhang N. Methodolgical progress note: handling missing data in clinical research. *J Hosp Med*. 2019;14:E1.
19. Breiman L. Random forests. *Mach Learn*. 2001;45(1):5-32.
20. Svetnik V, Liaw A, Tong C, Culberson JC, Sheridan RP, Feuston BP. Random forest: a classification and regression tool for compound classification and QSAR modeling. *J Chem Inf Comput Sci*. 2003;43(6):1947-1958.
21. Bagheri H, Tapak L, Karami M, Amiri B, Cherghi Z. Epidemiological features of human brucellosis in iran (2011–2018) and prediction of brucellosis with data-mining models. *J Res Health Sci*. 2019;19(4):e00462.
22. Amini P, Maroufizadeh S, Hamidi O, Samani RO, Sepidarkish M. Factors associated with macrosomia among singleton live-birth: A comparison between logistic regression, random forest and artificial neural network methods. Epidemiology, Biostatistics and Public. *Health*. 2016;13(4);10.
23. Fan S, Kind T, Cajka T, et al. Systematic error removal using random forest for normalizing large-scale untargeted lipidomics data. *Anal Chem*. 2019;91(5):3590-3596.
24. Stekhoven DJ, Bühlmann P. MissForest—non-parametric missing value imputation for mixed-type data. *Bioinformatics*. 2012;28(1):112-118.
25. Shah AD, Bartlett JW, Carpenter J, Nicholas O, Hemingway H. Comparison of random forest and parametric imputation models for imputing missing data using MICE: a CALIBER study. *Am J Epidemiol*. 2014;179(6):764-774.
26. Liao SG, Lin Y, Kang DD, et al. Missing value imputation in high-dimensional phenomic data: imputable or not, and how? *BMC Bioinformatics*. 2014;15(1):1-12.
27. Stekhoven DJ. missForest: Nonparametric missing value imputation using random forest. Astrophysics Source Code. *Library*. 2015;15:5.
28. Aletaha D, Neogi T, Silman AJ, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum*. 2010;62(9):2569-2581.
29. Al-Herz A, Al-Awadhi A, Saleh K, et al. A comparison of rheumatoid arthritis patients in Kuwait with other populations: results from the KRRD registry. *J Adv Med Medical Res*. 2016;14:1-11.
30. Rubin DB. *Multiple imputation for survey nonresponse*. Wiley; 1987.
31. Schafer JL. *Analysis of incomplete multivariate data*. CRC Press; 1997.
32. Schafer JL, Olsen MK. Multiple imputation for multivariate missing-data problems: A data analyst's perspective. *Multi-variate Behav Res*. 1998;33(4):545-571.
33. Van Buuren S. *Flexible imputation of missing data*. Chapman and Hall/CRC. 2018.
34. Cutler A, Cutler DR, Stevens JR. Random forests. *Ensemble Machine Learning Springer*. 2012;157-175.
35. Martínez G, Feist E, Martiatu M, Garay H, Torres B. Autoantibodies against a novel citrullinated fibrinogen peptide related to smoking status, disease activity and therapeutic response to methotrexate in cuban patients with early rheumatoid arthritis. *Rheumatol Int*. 2020;40:1873-1881.
36. Choe JY, Bae J, Lee H, Bae SC, Kim SK. Relation of rheumatoid factor and anti-cyclic citrullinated peptide antibody with disease activity in rheumatoid arthritis: cross-sectional study. *Rheumatol Int*. 2013;33(9):2373-2379.
37. Ma JD, Chen CT, Lin JZ, et al. Muscle Wasting aggravates rheumatoid arthritis in elderly patients as a mediator. *Scand J Rheumatol*. 2020;50:280.
38. Valdiviezo HC, Van Aelst S. Tree-based prediction on incomplete data using imputation or surrogate decisions. *Information Sci*. 2015;311:163-181.
39. Junger W, De Leon AP. Imputation of missing data in time series for air pollutants. *Atmos Environ*. 2015;102:96-104.
40. Kokla M, Virtanen J, Kolehmainen M, Paananen J, Hanhineva K. Random forest-based imputation outperforms other methods for imputing LC-MS metabolomics data: a comparative study. *BMC Bioinformatics*. 2019;20(1):1-11.
41. Tang F, Ishwaran H. Random forest missing data algorithms. *Statist Analy Data Mining*. 2017;10(6):363-377.
42. Zakaria NA, Noor NM. Imputation methods for filling missing data in urban air pollution data formalaysia. *Urbanism Arhitectura Constructii*. 2018;9(2):159.
43. Alsaber A, Pan J, Al-Herz A, et al. Influence of ambient air pollution on rheumatoid arthritis disease activity score Index. *Intern J Environ Res Public Health*. 2020;17(2):416.
44. Forbes D, Hawthorne G, Elliott P, et al. A concise measure of anger in combat-related posttraumatic stress disorder. *J Traumatic Stress*. 2004;17(3):249-256.
45. Baraldi AN, Enders CK. An introduction to modern missing data analyses. *J Sch Psychol*. 2010;48(1):5-37.
46. Tsiampalis T, Panagiotakos DB. Missing-data analysis: socio-demographic, clinical and lifestyle determinants of low response rate on self-reported psychological and nutrition related multi-item instruments in the context of the ATTICA epidemiological study. *BMC Med Res Methodol*. 2020;20:1-13.
47. Mishra S, Khare D. On comparative performance of multiple imputation methods for moderate to large proportions of missing data in clinical trials: a simulation study. *J Med Stat Inform*. 2014;2(1):9.
48. Little RJ. Regression with missing X's: a review. *J Am Statis Assoc*. 1992;87(420):1227-1237.
49. Verbeke G. Linear mixed models for longitudinal data. In: *Linear mixed models in practice Springer*; 1997:63-153.
50. McKnight PE, McKnight KM, Sidani S, Figueredo AJ. *Missing data: A gentle introduction*. Guilford Press; 2007.
51. Enders CK. Applied missing data analysis. Guilford press. 2010.
52. Enders CK. Analyzing longitudinal data with missing values. *Rehabil Psychol*. 2011;56(4):267.
53. Missing GJW. *data: Analysis and design*. Springer Science & Business Media; 2012.

How to cite this article: Alsaber A, Al-Herz A, Pan J, AL-Sultan AT, Mishra D; KRRD Group. Handling missing data in a rheumatoid arthritis registry using random forest approach. *Int J Rheum Dis*. 2021;24:1282–1293. https://doi.org/10.1111/1756-185X.14203

Received: 17 April 2021 | Revised: 29 July 2021 | Accepted: 10 August 2021

DOI: 10.1111/1756-185X.14207

ORIGINAL ARTICLE

International Journal of Rheumatic Diseases

WILEY

Assessing methotrexate intolerance and its prevalence in rheumatoid arthritis: Development and validation of the MISA questionnaire

Deeksha Vijaykumar[1] | Varun Dhir[1] | Siddharth Jain[1] | Venkatesh Pai[2] | Jaswinder Kaur[1] | Godasi SRSNK Naidu[1] | Aman Sharma[1] | Shefali Khanna Sharma[1] | Sanjay Jain[1]

[1]Department of Internal Medicine (Rheumatology Division), Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India

[2]Division of Rheumatology, Department of General Medicine, All India Institute of Medical Sciences, Rishikesh, India

Correspondence
Varun Dhir, Department of Internal Medicine (Rheumatology Unit), 4th Floor, Nehru Hospital, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh 160012, India.
Email: varundhir@gmail.com

Funding information
This study did not receive specific funding.

Abstract

Objective: Methotrexate (MTX) intolerance refers to unpleasant symptoms that accompany use of MTX. Although a validated questionnaire on MTX intolerance exists for children with juvenile idiopathic arthritis, it is lacking for adult rheumatoid arthritis (RA) patients.

Methods: A 10-item questionnaire called Methotrexate Intolerance and Severity assessment in Adults (MISA) was developed to assess MTX intolerance. On receiver operating characteristic analysis, its predictive ability was compared to Methotrexate Intolerance Severity Score (MISS), a validated questionnaire for children. Subsequently, prevalence and associations of intolerance were assessed in 414 RA patients. After 1 year, discontinuation of MTX was compared between patients with and without MTX intolerance.

Results: MISA score had a good predictive ability (area under the curve [AUC] of 0.904), with sensitivity and specificity of 91.4% and 84.3% (cut-off ≥1) to correctly classify MTX intolerance and was better than MISS score (AUC of 0.823). Among 414 RA patients, 159 (38.4%) had MTX intolerance, with common symptoms being nausea, lethargy, irritability and loss of appetite. On multivariable analysis, age (odds ratio 0.972) and body mass index (odds ratio 1.061) were significant predictors of MTX intolerance. At 1 year, a higher proportion of patients with intolerance than without intolerance had discontinued MTX (odds ratio 2.4, $P = 0.02$). To classify severity of intolerance, another score, MISA-cross-product, was developed and validated, with an AUC of 0.899.

Conclusions: The newly developed MISA questionnaire and score had good predictive ability to diagnose MTX intolerance. Intolerance to MTX was common, being found in one-third of RA patients. Patients with intolerance were twice more likely to discontinue MTX at 1 year.

Deeksha V and Varun Dhir contributed equally to the study

© 2021 Asia Pacific League of Associations for Rheumatology and John Wiley & Sons Australia, Ltd.

KEYWORDS
adverse effects, fatigue, methotrexate, nausea, surveys and questionnaires, vomiting

1 | INTRODUCTION

In 1972, Rex Hoffmeister first published his experience on the successful use of methotrexate (MTX) in rheumatoid arthritis (RA).[1] Since then MTX has come a long way, and is considered as the gold standard treatment for RA.[2] However, Hoffmeister noticed that patients had "minor but sometimes troublesome toxicity" with MTX.[3] These unpleasant symptoms, like nausea, vomiting, stomachache, dizziness, headache, flu-like symptoms and so on, are best expressed by the term "MTX intolerance". They were found to be a common cause of MTX discontinuation in early long-term studies.[4,5]

Initially these were ascribed to folate deficiency, and folic acid was proven to reduce them.[6] However, despite common use of folic acid,[7] MTX intolerance is still reported in 30%-60% of patients. [8,9] This may be one of the reasons why despite MTX being cheap and effective, its adherence is only 50% to 94% at 1 year and 25%-79% at 5 years [10]. To prevent escalating healthcare costs, optimizing MTX therapy is important. Thus, efforts are needed to improve patient tolerability; an important initial step will be to measure intolerance with MTX.

However, there is no validated score for MTX intolerance in adults with RA unlike the Methotrexate Intolerance Severity Score (MISS) which is validated for children with juvenile idiopathic arthritis.[11] Thus, this study was planned to develop and validate a new questionnaire (Methotrexate Intolerance and Severity assessment in Adults [MISA] questionnaire) and scores for measuring MTX intolerance and its severity in RA patients.

Key Messages

1. MISA is the first validated questionnaire for assessing MTX intolerance in RA and had sensitivity and specificity of 91.4% and 84.3% (cut-off ≥1), to detect MTX intolerance.
2. MTX intolerance was present in 38.4% of RA patients, with nausea, lethargy and irritability being the most common symptoms.
3. On follow up after 1 year, the odds ratio of discontinuing MTX was 2.4 (95% CI 1.1–5.3, $P = 0.02$) in those with intolerance as assessed by the MISA score.

2 | METHODS

2.1 | Design, study population and parameters collected

This was a cross-sectional study conducted in outpatient rheumatology clinics of 2 university hospitals. It was approved by both the Institutional Ethics Committees (PGIMER, INT/IEC/2019/001377 and AIIMS, Rishikesh, AIIMS/IEC/20/633), and written informed consent was taken from all patients.

2.2 | Development of a preliminary questionnaire

Two rheumatologists (VD, SN), a fellow (SidJ) and a medicine resident (DV) reviewed previous studies[4-6,12,13] and our own symptom lists used in prior studies with MTX.[14-16] Fourteen unpleasant symptoms were included in a preliminary questionnaire for MTX intolerance (Supplementary Figure S1). The first 8 questions needed to be answered as either no (scored as 0) or yes (rated as mild, moderate or severe; scored as 1, 2, 3) and patients needed to mention how long the symptom lasted per week (in days from 0.5 to 7). The next 6 questions needed to be answered only as no or yes (0 or 1).

In addition, the MISS questionnaire[11] was modified to make it suitable for use in adults, by replacing "My child" with "I", and removing the question on crying. Both MISA and MISS questionnaires were translated into Hindi (and back-translated) by 2 different teams.

2.3 | Patients

We included patients with RA who fulfilled the American College of Rheumatology / European League Against Rheumatism 2010 classification criteria and were taking MTX ≥6 months.[17] The study was conducted in 3 phases, the first phase consisting of 105 RA patients to refine and validate the questionnaire, a second phase, consisting of 414 RA patients, to determine the prevalence of MTX intolerance and its associations, and a third phase to assess discontinuation of MTX in those with intolerance.

2.4 | Phase 1: Refining and validating the questionnaire in RA patients

2.4.1 | Preliminary questionnaire administration

The preliminary questionnaire (and MISS) were administered to 105 patients at 1 center, followed by a brief standardized interview by a rheumatologist (VD) (Supplementary Figure S1). In the interview patients were asked 3 questions: "Do you have any unpleasant symptoms related to methotrexate?", "How much do these symptoms disturb you" and "For how long do they last?" Those patients

reporting any unpleasant symptoms that were related to MTX intake, were categorized as having MTX intolerance by the interviewer. If these symptoms of intolerance disturbed patients and disrupted their routine, and/or lasted for ≥2 days, patients were categorized as having severe intolerance. If these caused only slight (or not at all) disruption of routine, and lasted ≤1 day, patients were classified as having mild intolerance. Patients who were assessed to fall between these 2 categories were classified to have moderate intolerance.

2.4.2 | Refining the MISA questionnaire

Patients were divided into 2 groups (intolerant or not intolerant to MTX) based on the interview, and the average scores of individual questions were statistically compared. Questions in which scores were not significant (with *P* values >0.05) were removed and the refined questionnaire (10 questions) was called the MISA. Its score (MISA score) was calculated by adding the scores of the first 7 questions (0 to 3), to the last 3 questions (0 or 1) and ranged from 0 to 24 (Supplementary Figure S2). In addition, the MISS score was also calculated by adding the scores of its questions.

2.4.3 | Comparing scores to gold standard

Receiver operating characteristic (ROC) analysis (interview as gold standard) was used to compare MISA and MISS scores to correctly categorize patients as having MTX intolerance (see statistical methods). In addition, to assess the severity of MTX intolerance, a new score that gave weightage to duration of symptoms was developed and called the MISA cross-product score (MISA-CP) (Supplementary Figure S2).

2.5 | Phase 2: Prevalence and associations of intolerance in RA patients

The MISA questionnaire was administered to a total of 414 RA patients and details of their demographic, disease characteristics and disease activity (by Clinical disease activity index [17]) were noted. From this data, the prevalence of intolerance and factors associated with intolerance were determined.

2.6 | Phase 3: Follow up at 1-year for discontinuation of MTX

Patients were followed up after 1 year from their initial assessment (telephonic or clinic) to assess how many had discontinued MTX. We then calculated the odds ratios of discontinuation of MTX in those with and without intolerance as assessed by the MISA questionnaire.

2.7 | Statistical analysis

Mann-Whitney *U* test was used to compare scores of individual questions between tolerant and intolerant and Cronbach's alpha was calculated for internal consistency. We compared MISA and MISS scores by ROC analysis and area under the curve (AUC) values; cut-offs were selected that maximized the sum (of sensitivity and specificity). Characteristics were compared by *t* test or Mann-Whitney *U* test. All variables with *P* <0.15 were entered into a model using multivariable logistic regression. All tests were done on IBM SPSS Statistics, Version 25.0 (IBM Corp, Armonk, NY, USA).

3 | RESULTS

3.1 | Phase 1: Refining and validating the questionnaire in RA patients

There were 148 RA patients screened and 105 who were on MTX ≥6 months were included, with mean age of 51 (13.4) years and taking MTX at a dose of 18.8 ± 6 mg/wk (Supplementary Table S1). Thirty-five (33%) were found to be intolerant to MTX based on interview. After comparing scores of individual questions between intolerant and tolerant patients, 4 questions of the preliminary questionnaire did not have any significant difference in scores and were removed (Table 1). The revised questionnaire was called the MISA questionnaire and MISA score was used for all subsequent analyses. The Cronbach's alpha increased from .625 for the preliminary questionnaire to .641 for the MISA questionnaire. The MISA questionnaire fulfilled face validity as per the expert opinion of rheumatologists (VD, SN, AS, SS), and fulfilled content validity as it incorporated all usual unpleasant symptoms. It was feasible as it required less than 5 minutes to answer.

3.1.1 | MISA score for MTX intolerance

On ROC analysis, the MISA score had a higher AUC of 0.904 (95% CI 0.838-0.971) compared to MISS with an AUC of 0.823 (95% CI 0.728-0.919) for MTX intolerance (Figure 1). The optimal cut-off for MISA score was ≥1, having a sensitivity and specificity of 91.4% and 84.3% respectively (Table 2). There was reasonably good correlation between the MISA and MISS scores with Pearson's coefficient of correlation of .6 (*P* <0.001).

3.1.2 | MISA-CP score for severity of intolerance

On ROC analysis, MISA-CP had the highest AUC of 0.899 (95% CI 0.831-0.966) for discriminating moderate-severe intolerance. The AUC for MISS and MISA scores were 0.847 (95% CI 0.768-0.927)

TABLE 1 Comparison of the scores of various symptoms by the preliminary 14-item questionnaire between tolerant and intolerant patients (N = 105)

	Questions	Score in tolerant, mean (SD)	Score in intolerant, mean (SD)	*P* value
1	Nausea after MTX	0.01 (0.12)	0.74 (0.98)	<0.001
2	Vomiting after MTX	0 (0)	0.11 (0.40)	0.013
3	Stomach discomfort after MTX	0.06 (0.29)	0.40 (0.70)	<0.001
4	LOA after MTX	0.07 (0.31)	0.37 (0.55)	<0.001
5	Lethargy/listlessness after MTX	0.04 (0.27)	0.29 (0.67)	0.003
6	Dizziness/headache after MTX	0.06 (0.29)	0.17 (0.45)	**0.07**
7	Irritation after MTX	0.06 (0.29)	0.37 (0.60)	<0.001
8	Diarrhea after MTX	0.01 (0.12)	0.11 (0.32)	0.024
9	Nausea while thinking of MTX	0.01 (0.12)	0.14 (0.36)	0.008
10	Reduction of dose due to intolerance	0.06 (0.23)	0.14 (0.36)	**0.141**
11	Skipped dose due to intolerance	0.03 (0.17)	0.09 (0.28)	**0.197**
12	Use of anti-emetics or other for side effects	0 (0)	0.20 (0.41)	<0.001
13	Increased hair fall after MTX	0.16 (0.37)_	0.26 (0.44)	**0.221**
14	Oral sores after MTX	0.01 (0.12)	0.17 (0.38)	0.002

Note: Highlighted lines represent the questions in which scores were non-discriminative between tolerant and intolerant patients (*P* >0.05).
LOA, loss of appetite; MTX, methotrexate.

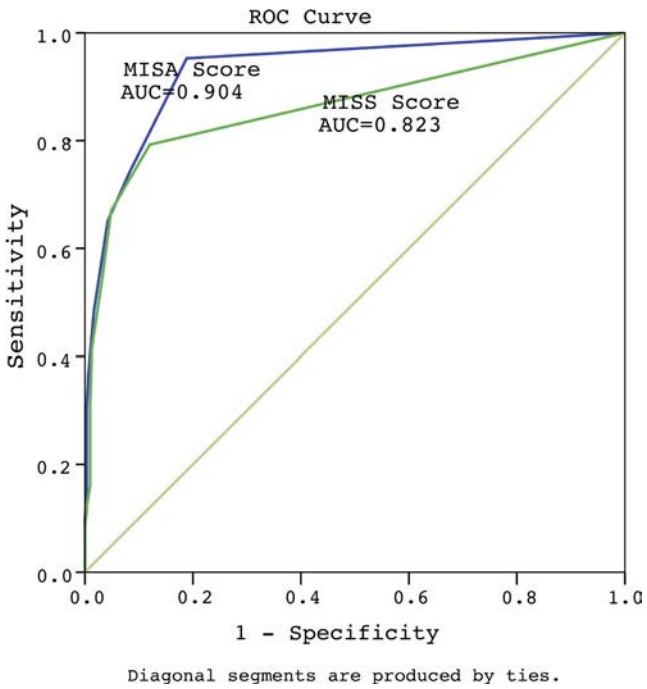

FIGURE 1 Figure showing the receiver operating characteristic (ROC) curve for Methotrexate Intolerance and Severity assessment in Adults (MISA) and Methotrexate Intolerance Severity Score (MISS) questionnaires for methotrexate intolerance. AUC, area under the curve

and 0.837 (95% CI 0.754-0.920) respectively (Figure 2). The optimal cut-off for MISA-CP was ≥4, with sensitivity and specificity of 93.5% and 77.3% respectively (Supplementary Table S2).

3.2 | Phase 2: Prevalence and associations of intolerance in RA patients

Among 414 RA patients, MTX intolerance was found in 159 (38.4%), with common symptoms being nausea, lethargy, irritability, and loss of appetite lasting for 1 to 1.5 days per week (Figure 3). On comparing MTX intolerant with tolerant patients (Table 3), intolerant patients were significantly younger and had higher use of anti-emetics. There was no significant difference in dose, route, or duration of MTX, or in use of other disease modifying antirheumatic drugs. On multivariable regression, on entering age, prednisolone use and body mass index (all variables with *P* ≤.15), only age and body mass index were significant in the final model (Table 3). Moderate-severe intolerance (MISA-CP ≥4) was present in 67 (16%).

3.3 | Phase 3: Follow up at 1 year for discontinuation of MTX

At 1 year, we could contact 229 patients, out of whom 5 had died. Among 224 patients, 31 (13.8%) had discontinued MTX. A significantly higher proportion of patients with intolerance than without intolerance had discontinued MTX (20, 9.3%, *P* =0.02, odds ratio 2.4, 95% CI 1.1–5.3).

4 | DISCUSSION

MTX intolerance refers to unpleasant symptoms experienced by patients on MTX. We developed and validated a new instrument and

TABLE 2 The sensitivity, specificity and sum of sensitivity and specificity at various cut-offs of the MISA score to detect methotrexate intolerance in rheumatoid arthritis patients (N = 105)

Cut-off for MISA score	Sensitivity	1-specificity	Specificity	Sum (sensitivity +specificity)
-1	1	1	0	1
1	0.914	0.157	0.843	1.757
2	0.6	0.071	0.929	1.529
3	0.486	0.029	0.971	1.457
4	0.4	0.014	0.986	1.386
5	0.257	0.014	0.986	1.243
6	0.171	0	1	1.171
7	0.029	0	1	1.029
10	0	0	1	1

Note: The shaded area shows the best cut-off which maximizes the sum of sensitivity +specificity.
MISA, Methotrexate Intolerance and Severity assessment in Adults.

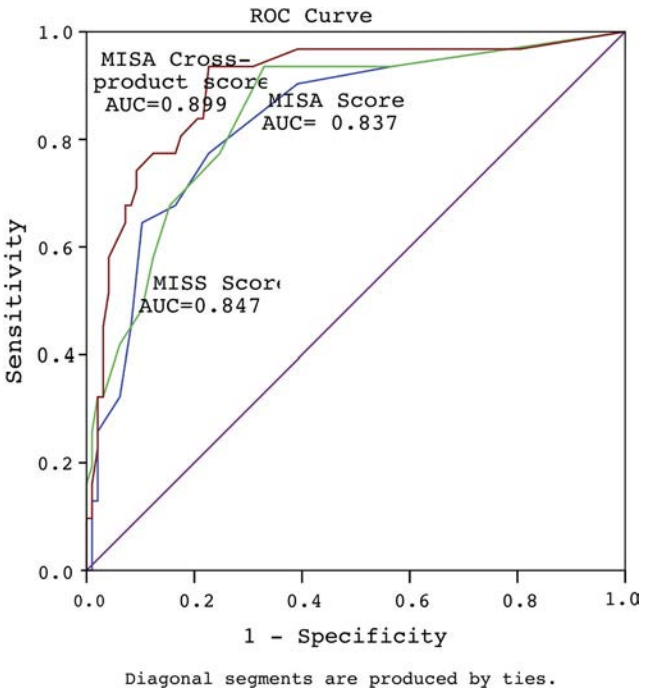

FIGURE 2 Figure showing the receiver operating characteristic (ROC) curve for Methotrexate Intolerance and Severity assessment in Adults (MISA)-cross-product, MISA and Methotrexate Intolerance Severity Score (MISS) questionnaires for moderate-to-severe methotrexate intolerance. AUC, area under the curve

score, the MISA questionnaire and MISA score, to assess MTX intolerance in RA patients. Using the MISA score, the prevalence of MTX intolerance was found in 38.4%, and moderate-severe intolerance in 16%.

Historically efforts tended to aggregate MTX intolerance, laboratory abnormalities and life-threatening issues into a single score like the toxicity score by Morgan[6] and drug toxicity index by Fries et al.[18] In the last 15 years, newer scores that focused only on intolerance (symptoms) have been developed; however, they were targeted and validated in children. An initial score (Gastrointestinal Symptom Score for Kids) focused only on gastrointestinal problems,[19] but the MISS was more comprehensive. Although it was developed for parents to fill for their children, it has been used in adults as well.[20] However, it gives great importance to anticipatory and associative symptoms which are less common in adults.[11,21] Considering these problems, we developed the MISA questionnaire that focused only on symptoms, was graded by their severity and also included duration of symptoms (Supplementary Table S3).

The MISA questionnaire is simple, consists of 10 questions, and takes only 5-10 minutes to answer. The MISA score was excellent at classifying intolerance in terms of the AUC. It was found to be better on ROC analysis than an existing questionnaire developed for use in children, namely the MISS. The differences between them is that MISA includes questions on symptoms like fatigue (flu-like symptoms), loss of appetite, bad taste, using drugs for intolerance, which were not present in MISS. Also, MISA has just 1 question on anticipatory symptoms, keeping with their less importance in adults, unlike MISS which asks regarding anticipatory or associative occurrence of every symptom.[21] At 1 year, discontinuations of MTX were found to be twice as common in the patients who were intolerant by the MISA score, thus validating its predictive ability for MTX discontinuation.

Another score that was developed and validated in this study was the MISA cross-product score for severity of intolerance. We suggest an algorithmic approach to MTX intolerance, first establishing intolerance and then its severity (Supplementary Figure S3). The development of scores for MTX intolerance will be helpful in evaluation of interventions for its alleviation, like mindfulness, yoga and meditation,[22] medications like prednisolone[23] or ondansetron, lifestyle measures like having coffee [24] and changing the route of MTX administration.[25]

We found MTX intolerance to occur in 38.4%, which was consistent with previous studies that have usually found symptoms of intolerance to range from 30% to 80%.[5,9,12,20,26-28] Similar to other studies, gastrointestinal complaints like nausea were the most common in our study. In our study, MTX intolerance was associated with a younger age which has also been shown by previous studies.[9,21,29] Previously, some studies in juvenile idiopathic

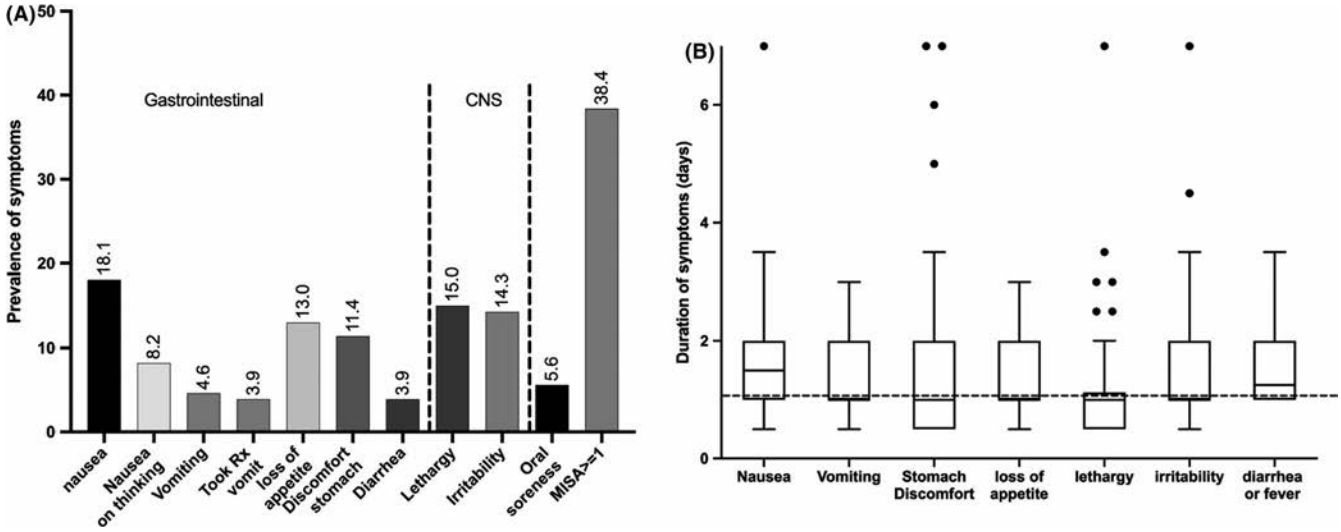

FIGURE 3 Bar diagram showing the prevalence of various symptoms of intolerance as per the Methotrexate Intolerance and Severity assessment in Adults questionnaire in 414 rheumatoid arthritis patients (A), and box-and-whiskers plot showing the duration of various unpleasant symptoms as per MISA questionnaire (B) (symbols above boxplots represent outliers). CNS, central nervous system

TABLE 3 Baseline characteristics of patients included in the prevalence study and comparison of variables between tolerant or intolerant by MISA score≥1 (N = 414)

Variable	All (n = 414)	Tolerant (n = 255)	Intolerant (n = 159)	*P* value tol. vs intol.	*P* value multivariable model
Females, n (%)	370 (89)	231 (91)	139 (87)	0.31	
Age, y, mean (SD)	50 (12.5)	51.2 (12.6)	48.2 (12.2)	0.016*	0.008**
Duration of RA, y, mean (SD)	10.0 (7.0)	10.8 (7.4)	9.6 (6.3)	0.168	
BMI, kg/m[a], mean (SD)	24.0 (4.9)	23.6 (4.9)	24.6 (4.7)	0.107	0.03*
RF positive[b], n (%)	300 (73)	191 (82)	109 (78)	0.29	
Anti-CCP[c] positive, n (%)	156 (76)	94 (76)	62 (78)	0.86	
CDAI, mean (±SD)	14.0 (11.8)	14 (12.1)	14.1 (11.4)	0.69	
Dose of MTX, mg/wk, mean (SD)	18.6 (5.6)	18.6 (5.5)	18.7 (5.8)	0.83	
Duration of MTX, y, mean (SD)	5.6 (4.3)	5.6 (3.9)	5.7 (4.8)	0.69	
Injectable MTX, n (%)	47 (11)	25 (10)	22 (14)	0.21	
Oral MTX, n (%)	367 (89)	230 (90)	137 (86)	0.26	
Use of FA, n (%)	395 (95)	241 (95)	154 (97)	0.27	
Dose of FA, mg/wk, median (IQR)	5 (5 – 10)	5 (5-10)	5 (5-10)	0.50	
Use of other DMARD, n (%)	272 (66)	160 (62)	112 (70)	0.11	
HCQ, n (%)	209 (51)	123 (48)	86 (54)	0.25	
Leflunomide, n (%)	112 (27)	64 (25)	48 (30)	0.22	
Sulfasalazine, n (%)	64 (16)	38 (15)	26 (16)	0.69	
Prednisolone, n (%)	156 (38)	87 (34)	69 (43)	0.058	0.21
Using anti-emetics, n (%)	12 (3)	1 (0.5)	11 (7)	<0.001	

Note: % are rounded off to the nearest whole number.

Abbreviations: BMI, body mass index; CCP, anti-citrullinated cyclical peptide assay; CDAI, Clinical disease activity index; DMARD, disease modifying antirheumatic drug; FA, folic acid; MTX, methotrexate; RA, rheumatoid arthritis; RF, rheumatoid factor.

[a]Available for 262 patients.

[b]Available for 372 patients.

[c]Available for 203 patients.

arthritis have found parenteral use to be associated with both higher and lower occurrence of intolerance.[11,30] However, we did not find any such association, perhaps due to a smaller proportion of patients on parenteral MTX in this study. Also like a majority of previous studies, this study also did not find any association of intolerance with MTX dose. This is possibly due to the cross-sectional design of this and other studies.

Limitations to this study was using an interview as the gold standard for assessing intolerance, which remains subjective. However, this is the best option considering that MTX intolerance refers to subjective symptoms felt by patients. We tried to eliminate any variability by having a standard set of questions administered by a single person who then rated the patients blinded to the results of their questionnaires. Although the Cronbach's alpha of the MISA questionnaire was better than the preliminary version, it was still low. However, we feel it is acceptable due to the diverse symptoms of intolerance which are lumped together but do not occur together.[31]

To conclude, the newly developed MISA questionnaire had good predictive ability to discern MTX intolerance and its severity and was predictive of MTX discontinuation at 1 year. MTX intolerance was common; present in more than one-third of RA patients which was mainly gastrointestinal.

ACKNOWLEDGEMENTS

The authors would like to thank Dr Ashok Pannu, Dr Aadhaar Dhooria, Dr Sakshi Mittal of PGIMER, Chandigarh for helping in translation of the questionnaires into Hindi and back-translation to English. Two other rheumatology fellows, Dr Adarsh MB and Dr Preksha Diwedi at PGIMER, Chandigarh offered useful criticisms of the questionnaire in its development. Two interns Dr Archita Gupta and Dr Arpit Goel helped to coordinate with patients in AIIMS, Rishikesh.

CONFLICTS OF INTEREST

None of the authors report any conflicts of interest with regard to this study.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr Varun Dhir had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study conception and design: Varun Dhir, Deeksha V, Siddharth Jain. Acquisition of data: Varun Dhir, Deeksha V, Shankar Naidu, Venkatesh S Pai, Aman Sharma, Shefali Sharma, Sanjay Jain. Analysis and interpretation of data: Varun Dhir, Deeksha V, Siddharth Jain.

DATA AVAILABILITY STATEMENT

The data set will be made available on request.

ORCID

Varun Dhir https://orcid.org/0000-0002-3626-0694
Siddharth Jain https://orcid.org/0000-0003-4065-5880
Venkatesh Pai https://orcid.org/0000-0002-5935-8627
Godasi SRSNK Naidu https://orcid.org/0000-0002-9727-044X
Aman Sharma https://orcid.org/0000-0003-0813-1243

REFERENCES

1. Hoffmeister RT. Methotrexate in rheumatoid arthritis. *Arthritis Rheum*. 1972;15(abstr):114.
2. Mian A, Ibrahim F, Scott DL. A systematic review of guidelines for managing rheumatoid arthritis. *BMC Rheumatol*. 2019;3:42. https://doi.org/10.1186/s41927-019-0090-7
3. Hoffmeister RT. Methotrexate therapy in rheumatoid arthritis: 15 years experience. *Am J Med*. 1983;75(6a):69-73. https://doi.org/10.1016/0002-9343(83)90477-1
4. Alarcon GS, Tracy IC, Blackburn WD Jr. Methotrexate in rheumatoid arthritis. Toxic effects as the major factor in limiting long-term treatment. *Arthritis Rheum*. 1989;32(6):671–676.
5. Kremer JM, Phelps CT. Long-term prospective study of the use of methotrexate in the treatment of rheumatoid arthritis. Update after a mean of 90 months. *Arthritis Rheum*. 1992;35(2):138–145. https://doi.org/10.1002/art.1780350203
6. Morgan SL, Baggott JE, Vaughn WH, et al. The effect of folic acid supplementation on the toxicity of low-dose methotrexate in patients with rheumatoid arthritis. *Arthritis Rheum*. 1990;33(1):9-18.
7. Pope JE, Hong P, Koehler BE. Prescribing trends in disease modifying antirheumatic drugs for rheumatoid arthritis: a survey of practicing Canadian rheumatologists. *J Rheumatol*. 2002;29(2):255-260.
8. Dhir V, Aggarwal A. Methotrexate-related minor adverse effects in rheumatoid arthritis: more than a nuisance. *J Clin Rheumatol*. 2012;18(1):44-46. https://doi.org/10.1097/RHU.0b013e31823ee540
9. Ćalasan MB, van den Bosch OF, Creemers MC, et al. Prevalence of methotrexate intolerance in rheumatoid arthritis and psoriatic arthritis. *Arthritis Res Ther*. 2013;15(6):R217. https://doi.org/10.1186/ar4413
10. Curtis JR, Bykerk VP, Aassi M, Schiff M. Adherence and Persistence with Methotrexate in Rheumatoid Arthritis: A Systematic Review. *J Rheumatol*. 2016;43(11):1997-2009. https://doi.org/10.3899/jrheum.151212
11. Bulatović M, Heijstek MW, Verkaaik M, et al. High prevalence of methotrexate intolerance in juvenile idiopathic arthritis: development and validation of a methotrexate intolerance severity score. *Arthritis Rheum*. 2011;63(7):2007-2013. https://doi.org/10.1002/art.30367
12. Weinblatt ME, Kaplan H, Germain BF, et al. Methotrexate in rheumatoid arthritis. a five-year prospective multicenter study. *Arthritis Rheum*. 1994;37(10):1492–1498. https://doi.org/10.1002/art.1780371013
13. Morgan SL, Baggott JE, Vaughn WH, et al. Supplementation with folic acid during methotrexate therapy for rheumatoid arthritis. A double-blind, placebo-controlled trial. *Ann Intern Med*. 1994;121(11):833–841.
14. Dhir V, Aggarwal A. Methotrexate-related minor adverse effects in rheumatoid arthritis: More than a nuisance. *J Clin Rheumatol*. 2012;18(1):44-46. https://doi.org/10.1097/RHU.0b013e31823ee540
15. Sandhu A, Dhir V, Ahmad S, Dhawan V, Kaur J, Bhatnagar A. Clinico-genetic model to predict methotrexate intolerance in rheumatoid arthritis. *Clin Rheumatol*. 2020;39(1):201-206. https://doi.org/10.1007/s10067-019-04770-4
16. Dhir V, Sandhu A, Kaur J, et al. Comparison of two different folic acid doses with methotrexate–a randomized controlled trial (FOLVARI Study). *Arthritis Res Ther*. 2015;17:156. https://doi.org/10.1186/s13075-015-0668-4
17. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European

League Against Rheumatism collaborative initiative. *Arthritis Rheum*. 2010;62(9):2569-2581. https://doi.org/10.1002/art.27584
18. Fries JF, Spitz PW, Williams CA, Bloch DA, Singh G, Hubert HB. A toxicity index for comparison of side effects among different drugs. *Arthritis Rheum*. 1990;33(1):121-130. https://doi.org/10.1002/art.1780330117
19. Brunner HI, Johnson AL, Barron AC, et al. Gastrointestinal symptoms and their association with health-related quality of life of children with juvenile rheumatoid arthritis: validation of a gastrointestinal symptom questionnaire. *J Clin Rheumatol*. 2005;11(4):194-204. https://doi.org/10.1097/01.rhu.0000173616.81928.44
20. Fatimah N, Salim B, Nasim A, Hussain K, Gul H, Niazi S. Frequency of methotrexate intolerance in rheumatoid arthritis patients using methotrexate intolerance severity score (MISS questionnaire). *Clin Rheumatol*. 2016;35(5):1341-1345. https://doi.org/10.1007/s10067-016-3243-8
21. Patil P, Parker RA, Rawcliffe C, et al. Methotrexate-induced nausea and vomiting in adolescent and young adult patients. *Clin Rheumatol*. 2014;33(3):403-407. https://doi.org/10.1007/s10067-013-2389-x
22. Redd WH, Montgomery GH, DuHamel KN. Behavioral intervention for cancer treatment side effects. *J Natl Cancer Inst*. 2001;93(11):810-823. https://doi.org/10.1093/jnci/93.11.810
23. Malysheva OA, Wahle M, Wagner U, et al. Low-dose prednisolone in rheumatoid arthritis: adverse effects of various disease modifying antirheumatic drugs. *J Rheumatol*. 2008;35(6):979-985.
24. Malaviya A, Baghel S, Verma S, Thakran R, Messi C. Use of coffee for alleviating methotrexate intolerance in rheumatic diseases. *Indian J Rheumatol*. 2019;14(1):79-80. https://doi.org/10.4103/injr.injr_144_18
25. Li D, Yang Z, Kang P, Xie X. Subcutaneous administration of methotrexate at high doses makes a better performance in the treatment of rheumatoid arthritis compared with oral administration of methotrexate: A systematic review and meta-analysis. *Semin Arthritis Rheum*. 2016;45(6):656-662. https://doi.org/10.1016/j.semarthrit.2015.11.004
26. Alarcón GS, Tracy IC, Strand GM, Singh K, Macaluso M. Survival and drug discontinuation analyses in a large cohort of methotrexate treated rheumatoid arthritis patients. *Ann Rheum Dis*. 1995;54(9):708-712. https://doi.org/10.1136/ard.54.9.708
27. Attar SM. Adverse effects of low dose methotrexate in rheumatoid arthritis patients. *A hospital-based study. Saudi Med J*. 2010;31(8):909-915.
28. Hoekstra M, van Ede AE, Haagsma CJ, et al. Factors associated with toxicity, final dose, and efficacy of methotrexate in patients with rheumatoid arthritis. *Ann Rheum Dis*. 2003;62(5):423-426. https://doi.org/10.1136/ard.62.5.423
29. Amaral J, Brito M, Kakehasi A. High frequency of methotrexate intolerance in longstanding rheumatoid arthritis: using the methotrexate intolerance severity score (MISS). *Adv Rheumatol*. 2020;60(1):43. https://doi.org/10.1186/s42358-020-00145-5
30. Falvey S, Shipman L, Ilowite N, Beukelman T. Methotrexate-induced nausea in the treatment of juvenile idiopathic arthritis. *Pediatr Rheumatol Online J*. 2017;15(1):52. https://doi.org/10.1186/s12969-017-0180-2
31. Tavakol M, Dennick R. Making sense of Cronbach's alpha. *Int J Med Educ*. 2011;2:53-55. https://doi.org/10.5116/ijme.4dfb.8dfd

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Vijaykumar D, Dhir V, Jain S, et al. Assessing methotrexate intolerance and its prevalence in rheumatoid arthritis: Development and validation of the MISA questionnaire. *Int J Rheum Dis*. 2021;24:1294–1301. https://doi.org/10.1111/1756-185X.14207

Received: 7 May 2021 | Revised: 9 July 2021 | Accepted: 14 August 2021

DOI: 10.1111/1756-185X.14209

ORIGINAL ARTICLE

International Journal of Rheumatic Diseases

WILEY

Infliximab therapy in parenchymal neuro-Behçet's disease: A single-center experience

Demet Yalcin Kehribar | Serkan Gunaydin | Metin Ozgen

Department of Rheumatology, Medical Faculty, Ondokuz Mayıs University, Samsun, Turkey

Correspondence
Serkan Gunaydin, Medical Faculty, Department of Rheumatology, Korfez Mahallesi, Ondokuz Mayis University, 55270, Atakum/Samsun, Turkey.
Email: drserkangunaydin@hotmail.com

Abstract

Background: Parenchymal neuro-Behçet's disease involvement is the most serious complication of Behçet's disease, and no sufficient data on its treatment exists. This study aims to investigate the efficacy and safety of infliximab treatment in neuro-Behçet's disease patients with parenchymal involvement.

Materials and Methods: Patients who were diagnosed with Behçet's disease with parenchymal neurological involvement and underwent infliximab treatment for at least 12 months were included in the study. Demographic, clinical, and radiological data of the patients were accessed through the electronic database of our hospital.

Results: This study comprises 19 patients who were diagnosed with neuro-Behçet's disease and used infliximab: 12 male and 7 female patients. The mean age of the patients was 36.5 ± 11.7 years, and the diagnostic age was 26.3 ± 10.8 years. The duration of treatment with infliximab was 32.3 months (minimum 11, max 79). In the 19 patients receiving infliximab treatment, 11 (58%) patients achieved remission (complete disappearance of neurological symptoms) and 7 (37%) patients achieved disease stability (no new neurological findings); steroid treatments were discontinued for these 18 patients. In addition, only 5 patients were concomitantly taking immunosuppressive drugs with the infliximab. Infliximab was discontinued after the development of a new parenchymal attack in the 9th month of infliximab treatment.

Conclusion: In conclusion, parenchymal neurological involvement in Behçet's disease is an important cause of disability, and no sufficient data exists in literature on its treatment. The results of our study suggest that infliximab treatment was effective and safe in neuro-Behçet's disease parenchymal involvement for preventing long-term neurological attacks and discontinuing corticosteroid treatment.

KEYWORDS

Behçet's disease, infliximab, parenchymal

1 | INTRODUCTION

Behçet's disease was first described by Turkish dermatologist Hulusi Behçet as the combination of oral ulcers, genital ulcers, and uveitis attacks.[1] It is the only vasculitis in the body that can hold vascular structure of any diameter, type, and localization.[2] The most common clinical manifestations are associated with involvement of the skin, mucous, eyes, joints, venous and arterial vessels, and central nervous system.[3] The mean onset age of Behçet's disease is the 3rd and 4th decades of life. Although it

© 2021 Asia Pacific League of Associations for Rheumatology and John Wiley & Sons Australia, Ltd.

equally occurs in both genders, it is more severe and progressive in young men.[4]

Etiopathogenesis is not fully known; however, in addition to genetic predisposition, environmental factors play important roles in the pathogenesis of the disease. The prevalence of Behçet's disease significantly varies based on geographical areas. It is more common in countries located on the Mediterranean Sea and the historical Silk Road, while it has low prevalence in America and European countries.[5] The highest prevalence has been reported in Turkey.[6]

The involvement of the central nervous system in Behçet's disease is called neuro-Behçet's disease and is reported with a frequency of 4%–10% in large Behçet's disease cohorts.[7,8] Neuro-Behçet's disease is one of the most serious complications of Behçet's disease, an important cause of morbidity and mortality, and its prevalence is 5.6% in women and 13% in men.[9] Neuro-Behçet's disease is classified into 2 types: parenchymal and non-parenchymal (vascular). Significant differences in clinical presentation, neuroimaging findings, and concomitant Behçet's disease complications are observed between these involvements.[10] Between 75% and 80% of neuro-Behçet's disease cases involve parenchymal involvement, which has a more severe clinical picture compared to vascular involvement.[11] An algorithmic approach has been suggested for the treatment of neuro-Behçet's disease based upon pathological, clinical, prognostic, and medico-economic issues.[12]

This study aims to investigate the efficacy and safety of infliximab treatment in patients with neuro-Behçet's disease with parenchymal involvement, which is a significant cause of morbidity and mortality in Behçet's disease.

2 | MATERIALS AND METHODS

Patients who presented to our rheumatology clinic between February 1, 2013 and May 31, 2019 and were diagnosed with Behçet's disease, based on 1990 international criteria for Behçet's disease[13] and new international study group Behçet's disease criteria,[14] were included in the study (in patients diagnosed before 2014, 1990 criteria was used). The data of all patients were retrospectively accessed using the electronic database of our hospital. In the established cohort, patients diagnosed with neuro-Behçet's disease were identified using International Consensus Recommendation criteria for neuro-Behçet's disease.[15]

Demographic data of patients diagnosed with Behçet's disease, oral ulcers, genital ulcers, skin findings, joint involvement, arterial and venous vascular involvement, and pathergy results were recorded. In addition, neurological symptoms and signs of patients diagnosed with neuro-Behçet's and their laboratory data, radiological images, treatment modalities, and course of disease were retrospectively evaluated.

Disease activity and neurological disability in parenchymal neuro-Behçet's disease involvement were evaluated using acute phase reactants, newly developed neurological symptoms and findings or progression of existing neurological findings, modified Rankin score,[16] and imaging methods. The disappearance of all neurological symptoms and not taking corticosteroid doses higher than 5 mg methylprednisolone daily or its equivalent were defined as remission. Acute phase values at normal limits, not taking corticosteroid doses higher than 5 mg methylprednisolone daily or its equivalent, no clinical and radiological progression in neurological findings, and the absence of new neurological involvement were considered as stable disease. The emergence of objective neurological symptoms that could not be explained by any other known disease or treatment was described as relapse.

Before starting anti-tumor necrosis factor (anti-TNF) treatment in our clinic, routine screening was performed for latent tuberculosis, hepatitis B and C, human immunodeficiency virus, and malignancies. These data of the patients were also recorded. Our treatment protocol for neuro-Behçet's disease involvement constituted following intravenous 1000 mg pulse methylprednisolone treatment for 3 days followed by oral methylprednisolone 1 mg/kg/d, and this treatment was gradually reduced and discontinued within 2-3 months. Infliximab treatment was administered at a dose of 5 mg/kg every 8 weeks following loading doses at weeks 0, 2, and 6. Patients achieving remission with infliximab treatment continued treatment as long as the treatment-related side effects did not develop and the patients did not request to discontinue the treatment. Leukopenia was defined as lower than 4000/mm^3. Elevated liver transaminases were defined as greater than 2 times the upper limit of normal for alanine aminotransferase and/or aspartate aminotransferase. Patients without cardiac complaints were not routinely evaluated by echocardiography.

2.1 | Statistical Analysis

Statistical Package for the Social Sciences (SPSS 22.0, Chicago, IL, USA) was used for statistical analyses. The results were expressed as mean ± SD or mean (minimum and maximum). The data from the initial and final control evaluations were compared using paired *t* test. Spearman Chi-squared test was used to evaluate categorical data. Data were considered statistically significant when the *P* value was lower than .05.

3 | RESULTS

The mean age of the patients was 36.5 ± 11.7 years, and the age at diagnosis of Behçet's disease was 26.3 ± 10.8 years. Out of the 19 patients who were diagnosed with neuro-Behçet's disease and who underwent infliximab treatment, 12 were male and 7 were female. Eleven of them had brainstem involvement, 3 patients had mixed presentations (both brainstem and hemispheric involvement), 3 had hemispheric involvement, 2 had meningoencephalitic involvement and none of them had spinal cord involvement. Headache (12 patients) was the most commonly observed symptom in the study.

Based on the examination of other clinical findings accompanying neuro-Behçet's disease, all patients had oral ulcers, 15 had genital ulcers, 12 had papulopustular skin lesions, 7 had erythema nodosum, 14 had ocular involvement, 4 had deep vein thrombosis, and 3 had arterial thrombosis.

Of the 19 participants, 11 patients had remission, 7 had stable disease, and 1 had relapse. In addition, in the 18 patients with remission and stable disease, no new attack occurred in terms of genital ulcers, papulopustular skin lesions, erythema nodosum, ocular involvement, deep vein thrombosis, or arterial thrombosis. Oral ulcers recurred in only 4 patients; although there was no scoring, significant improvement in the frequency of oral ulcer recurrence and rate of recovery was reported for these 4 patients. Corticosteroid treatment was discontinued for the 18 patients in the first 3 months of infliximab treatment, and no Behçet's disease clinically requiring steroid treatment developed (Table 1). Only 5 patients received concomitant immunosuppressive treatment (4 patients were on azathioprine 150 mg/d and 1 patient was on methotrexate 15 mg/wk). While the median Rankin score was 3 (1-6) before the infliximab treatment, it dropped to 1 (0-4) after the treatment (P <.001). A significant regression in erythrocyte sedimentation (44.8 ± 24.0 mm/h to 22.6 ± 17.0 mm/h, P <.001) and C-reactive protein (47.6 ± 35.6 mg/L to 7.2 ± 6.7 mg/L, P <.001) levels was observed with infliximab treatment.

The duration of follow-up with neuro-Behçet's disease diagnosis was 64.32 months (min 13, max 192), while the follow-up period under infliximab treatment was 32.3 months (min 11, max 79) (Table 1 and Table 2). In the 14th month of treatment in 1 patient, infliximab treatment was discontinued due to an allergic reaction, and the patient was switched to adalimumab treatment. This patient was on the 12th month of adalimumab treatment and was being monitored in remission. In addition, 1 patient was switched to tocilizumab treatment due to the development of acute neurological attacks in the 11th month of combination treatment with infliximab, methotrexate 15 mg/wk, colchicine 1.5 mg/d, and methylprednisolone 4 mg/d, and the patient was monitored in remission for 24 months with tocilizumab treatment. For 1 patient being followed in remission after 24 months of infliximab treatment and another patient after 39 months of infliximab treatment, infliximab treatment was discontinued as per their request, and treatment with azathioprine 150 mg/d and colchicine 1 mg/d was started; they are still being monitored in remission (24 months and 9 months, respectively).

In the follow-up of the 19 patients included in the study, no latent tuberculosis or hepatitis B or C reactivation or malignancy was observed in any patient. Except for an allergic reaction that occurred in 1 patient, no side effects were observed that required the discontinuation of infliximab treatment.

4 | DISCUSSION

In this retrospective study, the results of 19 patients who were diagnosed with Behçet's disease, had parenchymal neurological involvement, and underwent infliximab treatment were evaluated. Mean follow-up in our study was 32.3 months (min 11, max 79). Only 1 patient had a new neurological event under infliximab treatment. With infliximab treatment, remission was achieved in 11 patients and stable disease was observed in 7 patients in terms of neurological involvement. In addition, remission or pronounced clinical response was achieved in terms of other clinical manifestations of Behçet's disease. Corticosteroid treatment was discontinued in all 18 patients who had remission or stable disease with infliximab treatment; only 5 patients required concomitant immunosuppressive drugs.

Behçet's disease is a heterogeneous disease and therefore, is also called Behçet's syndrome. Neurological involvement in Behçet's disease is also divided into 2 groups: parenchymal and vascular. Neuro-Behçet's disease vascular involvement is often associated with the involvement of venous structures in other parts of the body, while parenchymal neuro-Behçet's disease is more often associated with ocular involvement.[17] In our study, we found that parenchymal involvement was accompanied by ocular involvement in 14 (74%) of the 19 patients, which is consistent with previous studies. This suggests that the treatment approaches for vascular neuro-Behçet's and parenchymal neuro-Behçet's involvement cannot be the same.

Neurological involvement is responsible for 25% of permanent sequela in Behçet's disease.[18] Since no controlled therapeutic trials in neuro-Behçet's disease with parenchymal involvement exist, treatments are prescribed based on clinical experience and expert opinion. In the acute stage, after high-dose intravenous methylprednisolone pulse therapy for 7-10 days, 1 mg/kg oral steroid treatment was administered, and the dose was gradually reduced in 3-6 months.[11] Immunosuppressive treatments are recommended as maintenance to prevent relapse after acute treatment.[19] High-dose and long-term use of corticosteroid treatment leads to a lot of side effects. In addition, pulse cyclophosphamide treatment, which is another option in neuro-Behçet's involvement, is a more toxic treatment modality compared to anti-TNF treatments.[11] The literature includes case reports on the effectiveness of anti-TNF treatments in parenchymal neuro-Behçet's involvement and observational studies involving a small number of patients.[20,21] In this respect, new data on the effectiveness and safety of anti-TNF treatments are needed in the involvement of parenchymal neuro-Behçet's.

Desbois et al.[20] published a multi-center study involving 17 parenchymal neuro-Behçet's disease patients with a follow-up period of 17 (3-163) months in 2016 and reported complete response in 6 (35%) patients and partial response in 10 (59%) patients with infliximab treatment. In their study, 4 patients received adalimumab treatment and 13 received infliximab treatment. Moreover, all patients continued to receive concomitant corticosteroids in addition to anti-TNF treatments, and 9 patients continued to receive concomitant immunosuppressive treatment (azathioprine, methotrexate, and mycophenolate mofetil). In our single-center study, which comprises 19 parenchymal neuro-Behçet's disease patients with an average follow-up period of 32 (11-79) months, all patients were treated with infliximab. Remission was achieved in 11 (58%) patients, disease stability was achieved in 7 (37%), and steroid treatments of all patients were discontinued. In addition,

TABLE 1 Clinical characteristics of the patients with parenchymal neuro-Behçet's disease

Gender / age	Age at diagnosis (y)	Duration of neuro-Behçet's (mo)	Previous treatment for neuro-Behçet's	Duration of infliximab treatment (mo)	Current treatment	Outcome
M/24	17	48	Cyclosporine Azathioprine Corticosteroid Colchicine	24	Azathioprine Colchicine	Remission
F/33	27	48	Cyclophosphamide Colchicine	44	Infliximab	Stable disease
M/33	32	13	Azathioprine Cyclosporine Colchicine	13	Infliximab	Remission
M/48	34	36	Azathioprine Corticosteroid Colchicine	24	Infliximab	Remission
M/25	16	72	Azathioprine Corticosteroid Colchicine	39	Azathioprine Colchicine	Stable disease
F/18	15	16	Azathioprine Corticosteroid Colchicine Cyclosporine	14	Infliximab	Remission
M/40	18	144	Pulse steroid Cyclophosphamide Azathioprine Cyclosporine	60	Infliximab	Stable Disease
M/24	18	72	Corticosteroid	41	Infliximab	Remission
M/36	21	48	Interferon Imuran	45	Infliximab	Remission
F/41	15 years	192	Cyclophosphamide Corticosteroid Azathioprine Colchicine	52	Infliximab Colchicine Azathioprine	Remission
M/48	18	180	Cyclosporine Corticosteroid Azathioprine	22	Infliximab Azathioprine	Stable disease
M/44	37	23	Cyclosporine Corticosteroid Azathioprine	23	Infliximab	Remission
M/48	41	27	Cyclosporine Corticosteroid Azathioprine Colchicine	25	Infliximab Azathioprine	Stable disease
F/40	29	72	Interferon Azathioprine Cyclosporine	21	Infliximab Azathioprine	Remission
M/67	56	96	Azathioprine Colchicine Corticosteroid	79	Infliximab	Stable disease
F/25	12	46	Azathioprine Corticosteroid Colchicine	38	Infliximab	Stable disease
M/36	23	30	Interferon Azathioprine Cyclosporine Colchicine	11	Tocilizumab Methotrexate Colchicine	Relapse

(Continues)

TABLE 1 (Continued)

Gender / age	Age at diagnosis (y)	Duration of neuro-Behçet's (mo)	Previous treatment for neuro-Behçet's	Duration of infliximab treatment (mo)	Current treatment	Outcome
F/35	24	27	Azathioprine Cyclosporine Colchicine	14	Adalimumab Methotrexate	Remission Allergic reaction
F/30	25	30	Azathioprine Cyclosporine Colchicine	24	Infliximab	Remission

TABLE 2 Summary of the study results

Gender, female/male	7/12
Age, y	36.0 (18-67)
Age at diagnosis, y	23.2 (12-56)
Duration of neuro-Behçet's, mo	48 (13-192)
Duration of infliximab treatment, mo	24 (11-79)
Concomitant treatment, yes/no	8/11
Outcome, remission/stable disease, n	11/7
Adverse reaction, n	1

only 5 patients were administered concomitant immunosuppressive drugs with infliximab treatment. These results show that infliximab treatment, which has low toxicity, eliminates the need for steroid treatment in neuro-Behçet's patients and reduces the need for immunosuppressive treatment.

In the study by Zeydan et al.[21] which was published in 2016 and investigated the effectiveness of infliximab treatment in 14 patients with parenchymal neuro-Behçet's involvement with an average follow-up period of 39 months (range: 16-105), no patient had relapse, and 4 patients had improved scores in the expanded disability status scale modified for neuro-Behçet's syndrome. In our study, only 1 patient had a new neurological attack under infliximab treatment, and significant improvement in modified Rankin[16] scores was observed, indicating neurological disability after infliximab treatment. Our study as well as the study by Zeydan et al.[21] show that infliximab treatment is effective and safe in preventing relapses in the long term.

In our study, there was found no difference between those who received infliximab treatment alone and those who received infliximab plus other synthetic disease-modifying antirheumatic drug treatment. In previous studies with small number of cases, it has been reported that combined treatments may be more effective.[22-23] However, these studies included only a small number of cases and their design was not aimed to compare combined treatments with the infliximab treatment alone. Different results have been reported also regarding the effect of infliximab treatment in patients with parenchymal neuro-Behçet's disease[20-23]. However, the initiation of treatments at different stages of the disease and the presence of neurological damage at the time of the initiation of the infliximab treatment can explain these different results.

This study has some limitations. First of all, the retrospective nature of this study is the most important limitation. In addition, obtaining reliable data on the effectiveness of treatment in a disease without new attacks is difficult, even in some patients who have intermittent attacks and do not receive treatment. Furthermore, prospective recording and data collection starting from the moment of diagnosis could have been better. However, in this rare disease, we think that achieving remission and/or stable disease in 95% of patients, discontinuation of corticosteroid therapies, and significant reduction in immunosuppressive use with infliximab treatment are important data.

As a result, in parenchymal neuro-Behçet's involvement, which is an important cause of disability in Behçet's disease and requires highly effective and less toxic treatments, infliximab treatment appears to be effective and safe in preventing neurological attacks in the long term and reducing or stopping corticosteroid doses.

ACKNOWLEDGEMENT

The authors would like to thank Enago (www.enago.com) for English language review.

CONFLICT OF INTEREST

The authors declare they have no competing financial interests.

AUTHOR CONTRIBUTIONS

Conceptualization: Metin Ozgen, Serkan Gunaydin, Demet Yalcin Kehribar. Data curation: Demet Yalcin Kehribar. Formal analysis: Metin Ozgen, Demet Yalcin Kehribar. Investigation: Demet Yalcin Kehribar. Methodology: Metin Ozgen, Demet Yalcin Kehribar. Validation: Metin Ozgen, Demet Yalcin Kehribar. Visualization: Demet Yalcin Kehribar. Roles/writing - original draft: Metin Ozgen, Serkan Gunaydin, Demet Yalcin Kehribar. Writing - review and editing: Metin Ozgen, Serkan Gunaydin, Demet Yalcin Kehribar.

ETHICAL APPROVAL

This study was approved by the local Ethics Committee (OMU/KAEK no:2020/526), and signed informed consent was obtained from the participants. The study was conducted ethically in accordance with the Declaration of Helsinki.

ORCID

Serkan Gunaydin https://orcid.org/0000-0002-1131-2531

REFERENCES

1. Yazici H. Behçet's syndrome: an update. *Curr Rheumatol Rep*. 2003;5(3):195-199.
2. Merashli M, Eid RE, Uthman I. A review of current management of vasculo-Behcet's. *Curr Opin Rheumatol*. 2018;30:50-56.
3. Zeidan MJ, Saadoun D, Garrido M, et al. Behçet's disease physiopathology: a contemporary review. *Auto Immun Highlights*. 2016;7(1):1-12. https://doi.org/10.1007/s13317-016-0074-1
4. Yazici H, Hamuryudan V, Hizli N, et al. The ten-year mortality in Behcet's syndrome. *Br J Rheumatol*. 1996;35:139-141.
5. Maldini C, Druce K, Basu N, et al. Exploring the variability in Behcet's disease prevalence: a meta-analytical approach. *Rheumatology (Oxford)*. 2018;57:185-195.
6. Yurdakul S, Günaydin I, Tüzün Y, et al. The prevalence of Behçet's syndrome in a rural area in northern Turkey. *J Rheumatol*. 1988;15(5):820-822.
7. Yan D, Liu JJ, Zhang Y, et al. The Clinical Features and Risk Factors of Parenchymal Neuro-Behcet's Disease. *Journal of Immunology Research*. 2019;2019:1–7. https://doi.org/10.1155/2019/7371458
8. Davatchi F, Shahram F, Chams-Davatchi C, et al. Behcet's disease in Iran: analysis of 6500 cases. *Int J Rheum Dis*. 2010;13(4):367-373.
9. Kural-Seyahi E, Fresko I, Seyahi N, et al. The long-term mortality and morbidity of Behçet syndrome: a 2-decade outcome survey of 387 patients followed at a dedicated center. *Medicine*. 2003;82(1):60-76.
10. Bolek EC, Sari A, Kilic L, et al. Clinical features and disease course of neurological involvement in Behcet's disease: HUVAC experience. *Mult Scler Relat Disord*. 2020;38(101512):1-7. https://doi.org/10.1016/j.msard.2019.101512
11. Uygunoğlu U, Siva A. Behçet's Syndrome and Nervous System Involvement. *Curr Neurol Neurosci ReBp*. 2018;18(7):35.
12. Haghighi AB, Safari A. Proposing an algorithm for treatment of different manifestations of neuro-Behcet's disease. *Clin Rheumatol*. 2010;29(6):683-686. https://doi.org/10.1007/s10067-010-1414-6
13. International Study Group for Behçet's Disease. Criteria for diagnosis of Behçet's disease. International Study Group for Behçet's Disease. *The Lancet*. 1990;335(8697):1078-1080.
14. Davatchi F, Assaad-Khalil S, Calamia Kt, et al. The International Criteria for Behçet's Disease (ICBD): a collaborative study of 27 countries on the sensitivity and specificity of the new criteria. *J Eur Acad Dermatol Venereol*. 2014;28(3):338–347. https://doi.org/10.1111/jdv.12107
15. Kalra S, Silman A, Akman-Demir G, et al. Diagnosis and management of neuro-Behcet's disease: international consensus recommendations. *J Neurol*. 2014;261:1662-1676.
16. Banks JL, Marotta CA. Outcomes validity and reliability of the modified Rankin scale: implications for stroke clinical trials: a literature review and synthesis. *Stroke*. 2007;38(3):1091-1096.
17. Bitik B, Tufan A, Sahin K, et al. The association between the parenchymal neurological involvement and posterior uveitis in Behçet's syndrome. *Clin Exp Rheumatol*. 2016;34(102):82-85.
18. Noel N, Bernard R, Wechsler B, et al. Long-term outcome of neuro-Behçet's disease: outcome of neuro-Behçet's disease. *Arthritis Rheumatol*. 2014;66:1306-1314.
19. Akman-Demir G, Saip S, Siva A. Behçet's Disease. *Curr Treat Options Neurol*. 2011;13(3):290-310.
20. Desbois AC, Addimanda O, Bertrand A, et al. Efficacy of Anti-TNFα in Severe and Refractory Neuro-Behcet Disease. *Medicine*. 2016;95(23):e3550. https://doi.org/10.1097/MD.0000000000003550
21. Zeydan B, Uygunoglu U, Saip S, et al. Infliximab is a plausible alternative for neurologic complications of Behçet disease. *Neurol – Neuroimmunol Neuroinflamm*. 2016;3(5):e258. https://doi.org/10.1212/NXI.0000000000000258
22. Arida A, Fragiadaki K, Giavri E, et al. Anti-TNF agents for Behçet's disease: analysis of published data on 369 patients. *Semin Arthritis Rheum*. 2011;41(1):61-70. https://doi.org/10.1016/j.semarthrit.2010.09.002
23. Haghighi AB, Safari A, Nazarinia MA, et al. Infliximab for patients with neuro-Behcet's disease: case series and literature review. *Clin Rheumatol*. 2011;30(7):1007-1012. https://doi.org/10.1007/s10067-011-1726-1

How to cite this article: Yalcin Kehribar D, Gunaydin S, Ozgen M. Infliximab therapy in parenchymal neuro-Behçet's disease: A single-center experience. *Int J Rheum Dis*. 2021;24:1302–1307. https://doi.org/10.1111/1756-185X.14209

Received: 25 May 2021 | Revised: 26 August 2021 | Accepted: 27 August 2021

DOI: 10.1111/1756-185X.14216

International Journal of Rheumatic Diseases

WILEY

ORIGINAL ARTICLE

The relationship of ocular parameters with clinical parameters and disease-related quality of life in patients with systemic sclerosis: A cross-sectional study

Serdar Kaymaz[1] | Yılmaz Halil[2] | Hüseyin Kaya[3] | Ugur Karasu[1] | Veli Cobankara[1]

[1]Department of Rheumatology, Faculty of Medicine, Pamukkale University, Denizli, Turkey

[2]Department of Gastroenterology, Faculty of Medicine, Pamukkale University, Denizli, Turkey

[3]Department of Ophthalmology, Faculty of Medicine, Pamukkale University, Denizli, Turkey

Correspondence
Serdar Kaymaz, Pamukkale University, Faculty of Medicine, Department of Rheumatology, 20070 Kinikli, Denizli, Turkey.
Email: dr.serdarkymaz@gmail.com

Funding information
There has been no significant financial support for this work that could have influenced its outcome.

Abstract

Objective: To evaluate choroidal thickness (CT), corneal parameters, and scleral thickness (ST) in patients with systemic sclerosis (SSc) and to determine their relationship with disease-related quality of life (QoL).

Methods: The study included 38 patients with SSc and 40 healthy controls. A detailed ocular examination was performed on all participants. Corneal parameters such as K1, K2, Km, corneal volume (CV), central corneal thickness (CCT), and ST at a distance of 1000, 2000, and 3000 μm from the scleral spur were measured. CT was measured at five points, including the subfoveal area and the temporal and nasal points at radii of 750.0 and 1500.0 μm. The scleroderma health assessment questionnaire (SHAQ) was administered to SSc patients to investigate the disease-related QoL.

Results: Individuals with SSc had thicker ST at all distances from the scleral spur (P=0.008, P=0.001, P=0.002, respectively). All corneal parameters were significantly lower in the SSc group than in the control group ($P < 0.05$). Moreover, SSc patients had significantly lower median CT at N750.0, N1500.0, T750.0, and T1500.0 points and thinner subfoveal CT than healthy controls ($P < 0.05$). There was a weak-moderate negative correlation between ST and the components of the SHAQ scale and SHAQ-global.

Conclusion: Despite not having ocular involvement, SSc patients had thicker ST but thinner CT and corneal parameters than healthy controls. This may indicate subclinical inflammation in patients with SSc. Only ST was affected by organ involvement and QoL among the ocular parameters.

KEYWORDS

choroidal thickness, corneal parameters, scleral thickness, systemic sclerosis

1 | INTRODUCTION

Systemic sclerosis (SSc) is a rare autoimmune connective tissue disease of unknown etiology. The incidence of SSc peaks between the ages of 30 and 60 years, with women having a higher incidence (6:1).[1] The clinical characteristics of SSc vary greatly in terms of internal organ involvement and the extent of skin involvement.[2] The major causes of morbidity and mortality of this disease include vasculopathy, dysregulation of lymphokine production, and increased fibrosis of the skin and internal organs (heart, lung, kidney, and gastrointestinal organs).[1,3-7]

© 2021 Asia Pacific League of Associations for Rheumatology and John Wiley & Sons Australia, Ltd

In the literature, there are many reported ocular manifestations of SSc, some of which are well-known, whereas others have been reported first in case reports. Among the described ocular findings are telangiectasia, eyelid skin changes, conjunctival changes, shallowing of the fornices, keratoconjunctivitis sicca, eye dryness, pinguecula, uveitis, and peripheral ulcerative keratitis.[8-14] The study of Zina and Faıq reported dry eye more commonly than eyelid skin thickening, keratoconjunctivitis sicca, and telangiectasia.[15] Kreps et al reported increased CT and more frequent dry eye than other ocular findings in patients with SSc.[16] However, a study reported that the CT of these patients was not different from that of healthy controls.[17]

The sclera is the outermost layer of the eye, consisting of dense fibrous connective tissue, which is responsible for protecting the eye from external injuries, maintaining its structure, and providing shape to the eye. The sclera is mainly composed of type 1 and type 3 collagen.[18] Its structure and biochemical properties are affected by factors such as age, refractive errors, and glaucoma.[19] SSc patients rarely have corneal involvement. However, rich collagen tissue and the rich vascular structure of the episclera and conjunctiva pose a risk for corneal involvement.[20] The stromal structure of the cornea is mainly composed of type 1 and type 5 collagen. Although sclera and corneal involvement have been reported in SSc patients, the number of studies on these anatomical structures is limited.[12,13] This study aimed to evaluate scleral thickness (ST), choroidal thickness (CT), and corneal parameters in patients with SSc, and to determine their relationship with clinical parameters and health-related quality of life (QoL). We hypothesized that these ocular parameters may be altered in the eyes of SSc patients as the result of collagen and vascular tissue involvement of the disease.

2 | MATERIALS AND METHODS

This study has a cross-sectional design. The study was conducted with the participation of patients with SSc and healthy participants between 1 February 2021 and 1 May 2021. The participants were informed about the content of the study. Their written informed consent was obtained. The study was designed in accordance with the principles of the Helsinki Declaration, and approval for the study was obtained from the local ethics committee (Approval number: 60116787-020/25922).

Two groups were created for the study: the SSc group comprising patients who were followed up by the Rheumatology Clinic and the control group comprising age- and gender-matched healthy individuals who presented to the Eye Clinic of the same hospital for a routine ophthalmological examination. SSc was diagnosed by a rheumatologist based on the diagnostic criteria of the American College of Rheumatology for SSc, defining two major subsets of the disease as diffuse or limited based on the diagnostic criteria proposed by LeRoy et al.[21,22]

A thorough physical examination was performed on all patients. Their hematological parameters including complete blood count, C-reactive protein, erythrocyte sedimentation rate, clinical chemistry (glucose, sodium, potassium, creatinine, uric acid, triglycerides, total cholesterol, aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transferase, total protein, and total bilirubin), and anti-nuclear antibodies were measured. An indirect immunofluorescence assay was performed to determine the presence of anti-nuclear antibodies.

A detailed ophthalmological examination including visual acuity testing, refractive error assessment, biomicroscopy, intraocular pressure measurement, fundus examination, ST, corneal parameters, and CT measurement was also performed on all participants. The study exclusion criteria were as follows: the presence of glaucoma, active ocular inflammation, any ocular active surface disease (eg, dry eye), corneal or lenticular opacity, refractive errors of more than ±2 diopters, a history of ocular trauma and surgery, failure of adaptation to any of the measurement techniques, and recent or current use of topical eye drops.

Based on the exclusion criteria, seven patients with SSc were excluded from the study for various reasons, such as overlap syndrome, diabetes mellitus, dry eye, and failure of adaptation to measurement techniques. The study flow diagram is presented in Figure 1.

2.1 | Measurement techniques

One eye of each participant was randomly selected and included in the analysis. A random number generator was used for randomization. The ST, CT, and corneal parameters of the participants were evaluated by an independent expert who was blinded to the information of the participants.

Scleroidal thickness was measured using Spectralis Anterior Segment Module Optical Coherence Tomography (AS-OCT) (Heidelberg Engineering GmbH, Heidelberg, Germany). The measurements were carried out with the eye at 45° nasal gaze fixated upon a fixation target. At least three measurements were made to achieve the optimal image quality. The image quality was then evaluated for feasibility for ST measurement. Patients with unsuitable images for measurement or non-cooperative patients were excluded from the study. All measurements were performed between 09:00AM and 11:00AM to rule out the possibility of diurnal variations. ST and the location of the scleral spur (SS) were manually marked. Because of the risk of imprecise measurement of ST at 4-5 mm and to exclude the margin of error that would be caused by single-level measurement, the measurement of ST was performed at distances of approximately 1000, 2000, and 3000 μm from SS. The deep episcleral vascular plexus visualized as a thin hyporeflective space above the solid scleral tissue was used to determine the outer limit of the sclera. ST was measured only at the temporal point. Figure 2 illustrates ST measured at the temporal point on the OCT image.

An Oculus Pentacam HR (Oculus, Wetzlar, Germany) was used to measure the corneal parameters of the participants. The Pentacam HR automatically measured the central corneal thickness (CCT) and corneal volume (CV). The measurements of corneal curvatures

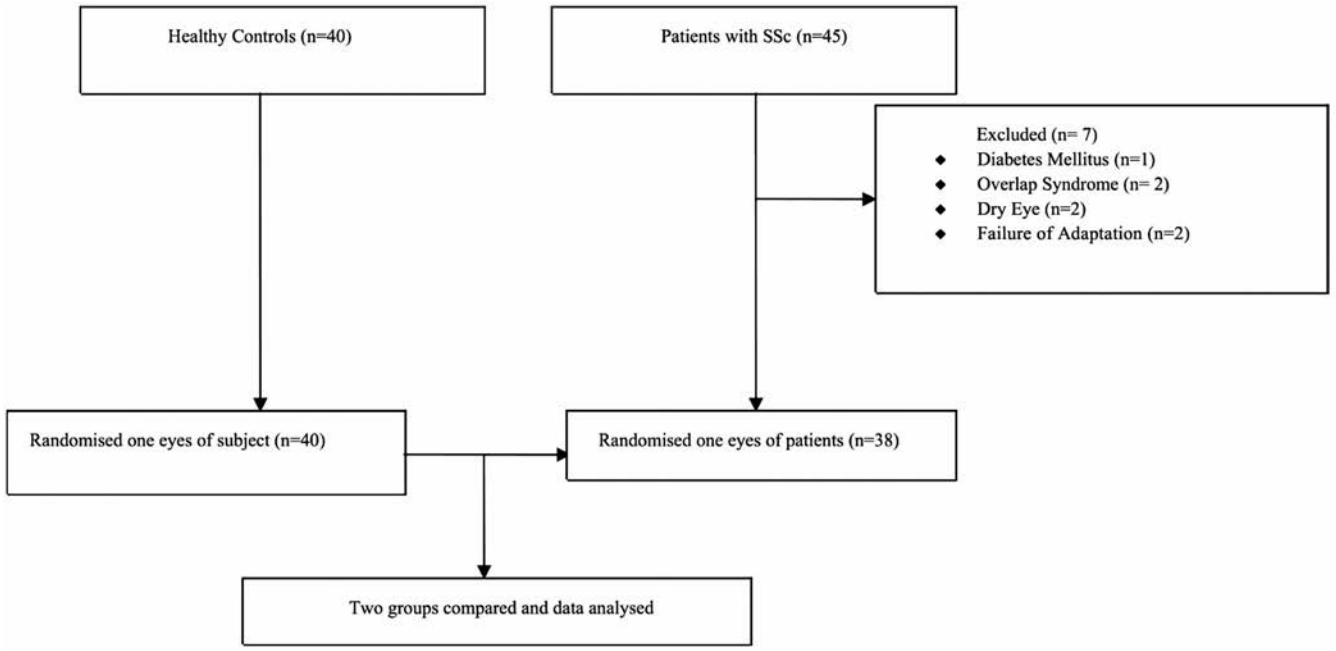

FIGURE 1 Flow chart of participants recruited in the study

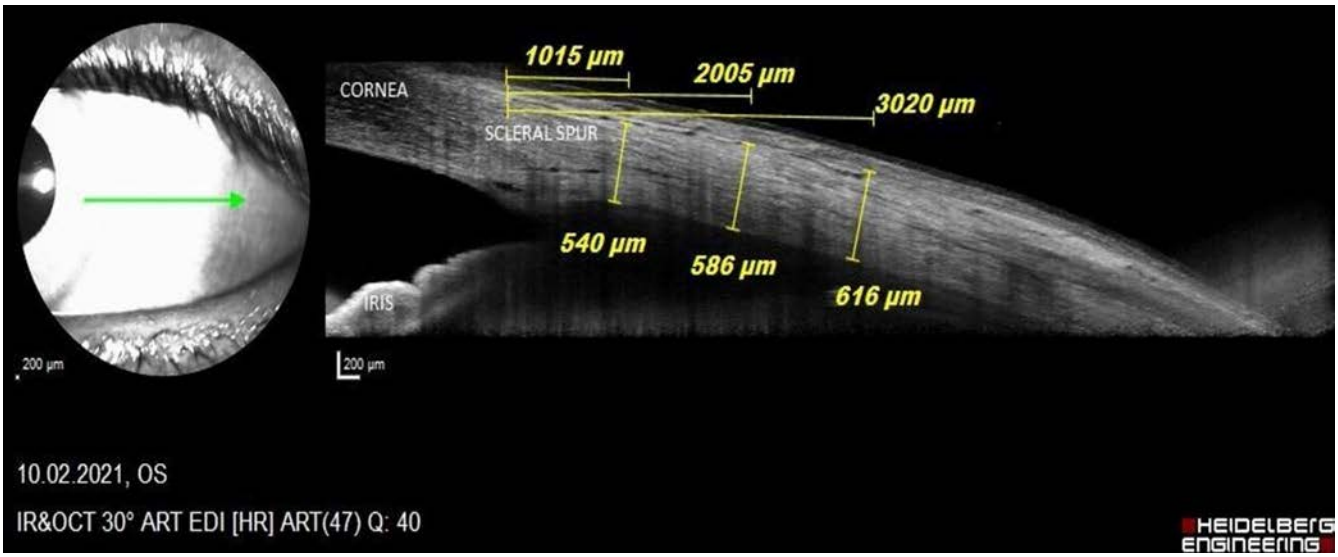

FIGURE 2 Illustration of the optical coherence tomography imaging performed on each participant. Scleral thickness was measured by anterior segment optical coherence tomography

including flat keratometry (K1), steep keratometry (K2), and mean keratometry (Km) were recorded from screen readings of the refractive power map of the Pentacam HR. The measurements were repeated several times to achieve one high-quality image for calculations of corneal density. The images from 90° to 270° were obtained for each participant.

The HD 5 Line Raster scan protocol was followed to acquire the image of the choroid. This protocol offers the ability to obtain high-quality images, consisting of 6.0 mm parallel lines with 1024 A-scans/B-scans, with an average of four B-scans per image. Inversion of the image causes pixellation and low resolution, so Cirrus software was used; in this way, the choroid could be brought into closer proximity to the zero-delay line. The thinnest point of the macula was selected on the image to avoid the effect of positioning on the measured foveal thickness. The image size was enlarged twice and centered on the fovea. The linear measurement tool of the Cirrus software was used for manual measurement of the subfoveal choroidal thickness (sfCT) through the outer part of the hyperreflective line that corresponds to the pigmented layer of retina attached to the inner surface of the sclera.[23] CT was also measured from the points 750 µm

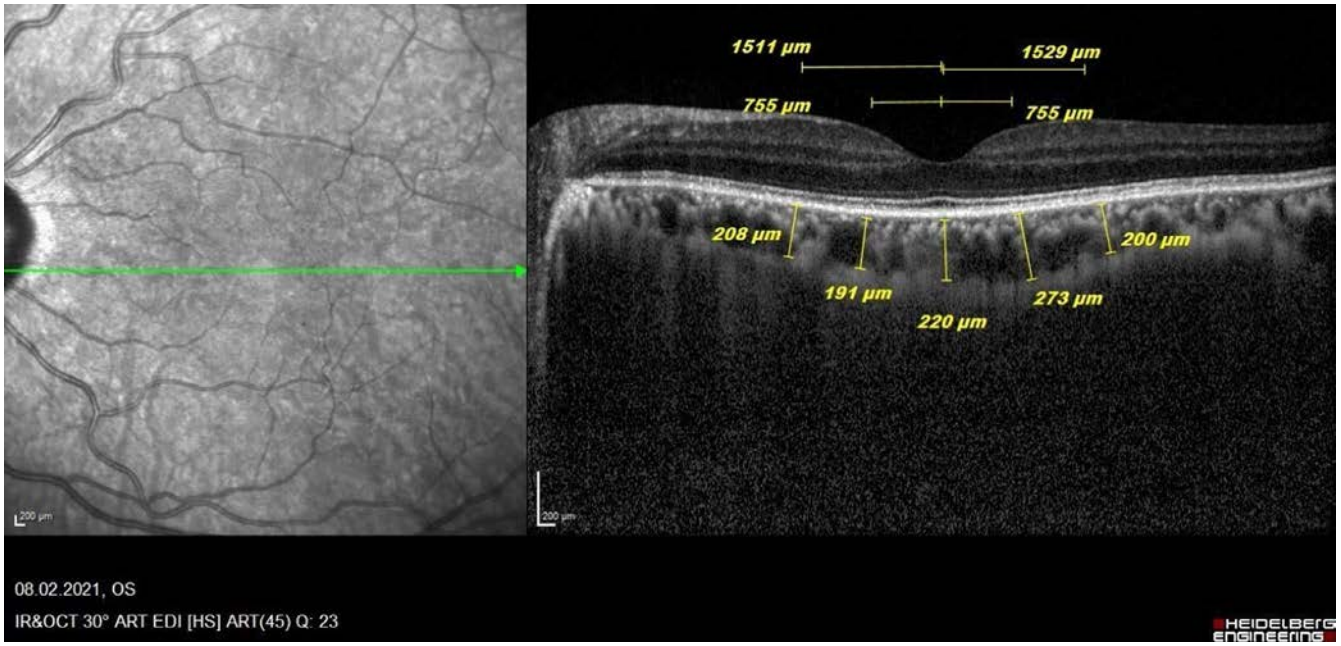

FIGURE 3 Enhanced-depth imaging optical coherence tomographic images of a healthy participant. Yellow lines show choroidal thickness measurements retrieved perpendicularly from the outer edge of the hyper-reflective retinal pigment epithelium. Measurements were made at five points: the subfoveal area and the temporal and nasal points at radii of 750 and 1500 pm

TABLE 1 Age-matched and disease duration-matched comparison of all ocular parameters

	Patients with SSc (n = 38)		Healthy controls (n = 40)		
	Mean (SD)	Range	A	Range	*P-value*
Age, years	48.3 (11.7)	27-68	42.9 (10.5)	20-60	0.074
Disease duration, years	11.4 (9.6)	1-40	–	–	–
Choroidal thickness, µm					
T750	208.3 (49.2)	111-312	420 (75.3)	244-586	<0.001*
T1500	218.7 (37)	135-303	440.9 (81.9)	301-577	<0.001*
SFCT	212 (36.3)	162-321	405 (73.1)	235-560	0.03*
N750	212.8 (38)	130-322	420 (73.9)	279-557	<0.001*
N1500	219 (42.5)	150-331	464.1 (74)	324-589	0.001*
Scleral thickness, µm					
ST1000	613.7 (90.6)	461-899	571.8 (49.2)	475-681	0.008*
ST2000	611.6 (82.8)	501-844	547.7 (57.2)	425-696	<0.001
ST3000	613.9 (82.6)	470-767	567 (44.3)	452-648	0.002*
Corneal parameters					
CV, mm^3	57.7 (3.7)	51.1-68.7	59.7 (2.6)	53.7-66.7	0.009*
CCT, µm	526 (30.5)	456-593	547.9 (27.9)	491-618	0.007
K1, D	42.6 (6.2)	36.3-47.5	45.1 (3.5)	41.6-63	0.025*
K2, D	44.3 (1.5)	40.60-49.3	46.6 (3.9)	43.5-66.2	0.001*
Km, D	44 (1.5)	40.30-48.4	45.9 (3.6)	43.4-66.4	0.004*

Abbreviations: SSc, systemic sclerosis; SFCT, subfoveal choroidal thickness; N750, 750 µm nasal; N1500, 1500 µm nasal; T750 µm, 750 µm temporal; T1500, 1500 µm temporal; ST1000, scleral thickness at a distance of 1000 m from scleral spur (SS); ST2000, scleral thickness at a distance of 2000 m from SS; ST3000, scleral thickness at a distance of 3000 m from SS; CCT, ccntral corneal thickness; CV, corneal volume; D, diopter; SD, standard deviation; K1, flat keratometry; K2, steep keratometry; Km, mean keratometry.

*P <0.05: statistically significant.

TABLE 2 Comparison of ocular parameters according to steroid use and organ involvement

Ocular Parameters	Medical treatment			Digital ulcer			Pulmonary involvement	
	With steroid	Without steroid		Presence	Absence		Presence	Absence
	Mean (SD)	Mean (SD)	*P*	Mean (SD)	Mean (SD)	*P*	Mean (SD)	Mean (SD)
SFCT, μm	202 (23)	214 (38.9)	0.426	208 (40.6)	214.3 (33.9)	0.622	203.4 (33.7)	226.7 (37.1)
T750, μm	191 (78)	212.9 (39)	0.272	200 (62)	213.4 (39.5)	0.438	206.8 (32.8)	210.9 (70.6)
T1500, μm	216 (35)	219.3 (38)	0.836	217 (35.4)	219.3 (38.7)	0.891	214 (32.8)	226.7 (43.3)
N750, μm	216 (25)	211 (41.2)	0.795	209 (44.2)	215.1 (34.5)	0.644	201.5 (38)	232 (30.9)
N1500, μm	208 (39)	221 (43.6)	0.448	215 (39.6)	221.7 (45)	0.648	206.9 (38)	240 (42)
ST1000, μm	626 (70)	610 (96.1)	0.658	584 (74.4)	633.1 (96.4)	0.104	575 (68.6)	680.2 (86.7)
ST2000, μm	639 (91)	604.2 (80)	0.293	604 (85.3)	616 (82.7)	0.660	581 (74.3)	663.2 (72)
ST3000, μm	635 (94)	608 (79.9)	0.408	594 (79.1)	636.7 (84)	0.241	579.8 (77)	672.3 (55.8)
K1, D	42.9 (1)	42.5 (7)	0.876	41.3 (9.8)	43.4 (1)	0.334	42 (7.5)	43.6 (1.5)
K2, D	43.5 (0.8)	44.5 (1.6)	0.093	44.8 (1.5)	44 (1.5)	0.108	44.4 (1.6)	44.2 (1.4)
Km, D	43.2 (0.9)	44.2 (1.5)	0.102	44.4 (1.4)	43 (1.5)	0.196	44.1 (1.5)	43.9 (1.4)
CV, mm^3	57.3 (1.8)	57.9 (4.1)	0.694	58.1 (3.4)	57.5 (4)	0.670	58.2 (3.7)	57 (3.8)
CCT, μm	527 (21)	525 (32.7)	0.886	523 (28.4)	527 (32.3)	0.708	530 (30.1)	519.2 (31)

Abbreviations: SFCT, subfoveal choroidal thickness; N750, 750 μm nasal; N1500, 1500 μm nasal; T750 μm, 750 μm temporal; T1500, 1500 μm temporal; ST, scleral thickness; ST1000, scleral thickness at a distance of 1000 m from scleral spur (SS); ST2000, scleral thickness at a distance of 2000 m from SS; ST3000, scleral thickness at a distance of 3000 m from SS; CCT, central corneal thickness; CV, corneal volume; D, diopter; SD, standard deviation; CVS, cardiovascular system; K1, flat keratometry; K2, steep keratometry; Km: mean keratometry.

*P <0.05, statistically significant.

(T750.0) and 1500 μm (T1500.0) temporal and 750 μm (N750.0) and 1500 μm (N1500.0) nasal to the fovea (Figure 3).

2.2 | Scleroderma Health Assessment Questionnaire (SHAQ)

The Scleroderma Health Assessment Questionnaire (SHAQ), which has been validated in Turkish patients, was used to evaluate health-related QoL.[24] The SHAQ was constructed by the addition of the five following questions related to symptoms: "In the past week, how much have your—Raynaud phenomenon, digital ulcers, gastrointestinal symptoms, lung symptoms, and overall scleroderma symptoms—interfered with your activity?" The answer is marked on a VAS with a length of 15 cm. The ends of the line are "does not interfere" and "very severe limitations." The final VAS score is calculated by multiplying the value by 0.2. The score ranges from 0 to 3 representing a minimum to maximum limitation, respectively.

2.3 | Definition of Organ Involvement

The presence of isolated pulmonary hypertension and/or pulmonary interstitial fibrosis was considered pulmonary manifestation. The pulmonary hypertension was defined as mean pulmonary artery pressure >20 mm Hg at rest as measured by right heart catheterization. In addition, when right ventricular systolic pressure >40 mm Hg was detected on echocardiography, the diagnosis of pulmonary hypertension was suspected. But pulmonary arterial hypertension is a rare form of pulmonary hypertension characterized by a progressive obliterative vasculopathy of the distal pulmonary arterial circulation. It was defined as pulmonary capillary wedge pressure of 15 mm Hg or less and pulmonary vascular resistance at least 3 Wood Units.[25] The definition of pulmonary interstitial fibrosis was established as SSc-associated interstitial lung disease after the exclusion of other probable causes of lung fibrosis. Chest X-ray and pulmonary function test-based parameters (usually forced vital capacity less than 80%) defined suspected interstitial lung disease.[26] High-resolution CT imaging has become the main method in the evaluation of pulmonary interstitial fibrosis. Compared with chest radiographs, high-resolution CT can detect more subtle structural abnormalities in the lung tissue at earlier disease stages.

Cardiac diseases may present with non-specific symptoms such as chest pain, lipothymia, syncope, and palpitations, which can also be seen in other diseases. However, cardiac involvement was defined in the presence of rhythm or conduction disorders on electrocardiography and diastolic dysfunction on echocardiography.

Muscular involvement was defined by proximal muscle weakness and increased serum levels of muscle enzymes (creatinine phosphokinase, lactate dehydrogenase, and aldolase) and

	Muscular involvement			CVS involvement		
	Presence	Absence		Presence	Absence	
P	Mean (SD)	Mean (SD)	*P*	Mean (SD)	Mean (SD)	*P*
0.056	205 (25.6)	213.5 (38.5)	0.580	205 (37.2)	220 (34.3)	0.197
0.809	193.5 (18)	211.6 (53.5)	0.387	197.1 (55.5)	222 (37.3)	0.122
0.315	200.2 (21.9)	222 (38.6)	0.147	210.1 (34.6)	229.2 (38)	0.114
0.015*	181.8 (32)	219 (36.3)	**0.015***	203.9 (41.7)	223 (30.9)	0.113
0.018*	200.4 (35.3)	223(43.4)	0.201	204 (39)	237 (40.7)	0.018*
<0.001*	539 (39.8)	630 (90.7)	**0.014***	571 (68)	665(89.7)	0.001*
0.002*	529.8 (16.3)	630 (80.6)	**<0.001***	588 (78)	640 (81.2)	0.046*
<0.001*	546.1 (33)	629.2 (83)	**<0.001***	587 (80)	647 (75)	0.024*
0.460	43.5 (2.2)	42.4 (6.8)	0.668	41.5 (8.1)	43.9 (1.4)	0.412
0.640	44.5 (2.5)	44.3 (1.3)	0.741	44 (1.5)	44.6 (1.5)	0.655
0.700	44 (2.3)	44 (1.3)	0.937	43.7 (1.6)	44.3 (1.4)	0.227
0.351	58.3 (5.7)	57.6 (3.3)	0.659	57.3 (3.4)	58.3 (4.2)	0.248
0.301	535 (37.2)	524 (29.1)	0.399	524 (28)	528.5 (34)	0.260

electromyography-confirmed myopathy and muscle biopsy/ magnetic resonance imaging demonstrated myositis.[27]

2.4 | Statistical analysis

All statistical analyses of the study were carried out using SPSS version 22.0 for Windows (IBM, Armonk, NY, USA). Continuous variables were expressed as the mean ± standard deviation or the median (minimum and maximum values), and categorical variables were expressed as number and percentage. Demographic characteristics were presented using descriptive statistics. The Kolmogorov-Smirnov test was used to test the normality assumption of the data. Nonparametric tests were used for the statistical evaluation of non-normally distributed data. The independent samples *t* test and χ^2 test were used for the analysis of two-group differences in measured parameters. Correlations between variables were analyzed using Pearson's or Spearman's correlation coefficients. A *P* value less than 0.05 was considered statistically significant.

We targeted a sample size based on discerning differences in ST among groups as the primary outcome. The sample size capable of detecting a change of the difference between groups was estimated using the mean and expected standard deviation of change in ST data obtained from a previous study[28] (ST for Group 1: 573.40 ± 45.39 vs ST for Group 2: 544.61 ± 47.47). The effect size obtained in this study was found to be medium (Cohen's d = 0.619). As a result of the power analysis carried out considering that a lower level of effect size could also be obtained, a sample size of at least 72 patients (at least 36 individuals for each group) was estimated to provide 80% power at a confidence interval of 95% for a medium effect size value (Cohen's d = 0.6).

3 | RESULTS

The mean age of the 38 patients with SSc consisting of 34 females (89%) and 4 males (11%) was 48 years, while the mean age of the 40 healthy participants consisting of 27 females (67.5%) and 13 males (32.5%) was 42.9 years. There was no significant difference between the groups in terms of age and gender distribution (*P* =0.074, *P* =0.881, respectively).

The age-matched and disease duration-matched comparison of the ocular parameters is shown in Table 1. There were significant differences between SSc patients and healthy controls in terms of mean CT values measured from nasal or temporal points (at N750: 212 versus 405 μm [*P* <0.001]; at N1500: 219 versus 464 μm [*P* <0.001]; at T750: 208 versus 440 μm [*P* <0.001]; and at T1500: 219 versus 441 μm [*P* <0.001]. Likewise, the SSc group had a lower mean SFCT than the healthy control group, which was also statistically significant (212 vs 405 μm; *P* =0.003).

TABLE 3 Correlation of component of SHAQ with scleral thickness at three levels

	ST100		ST2000		ST3000	
	P	*r*	*P*	*r*	*P*	*r*
RP-VAS	<0.001*	−0.588	<0.001*	−0.522	0.001*	−0.508
DU-VAS	<0.001*	−0.577	0.004*	−0.459	0.004*	−0.460
Digestive-VAS	<0.001*	−0.546	0.013*	−0.398	0.045*	−0.328
Pulmonary-VAS	<0.001*	−0.559	0.005*	−0.451	0.016*	−0.389
Overall disease severity-VAS	0.754	−0.053	0.997	0.001	0.596	0.089
SHAQ-global	0.006*	−0.437	0.005*	−0.449	0.008*	−0.426

Abbreviations: ST, scleral thickness; SHAQ, Scleroderma Health Assessment Questionnaire; RP, Raynaud's phenomenon; VAS, visual analogue scale; DU, digital ulcer; *r*, Spearman's rho coefficient.

*P <0.05, statistically significant.

The SSc group had a thicker ST than the control group. This difference was significant at all distances (P=0.008, P=0.001, P=0.002, respectively). The SSc group had mean K1, K2, and Km values of 43, 44, and 44 diopters, respectively, while the healthy controls had mean K1, K2, and Km values of 45, 46, and 46 diopters, respectively. There was a significant difference between the SSc and healthy control groups in terms of K1, K2, Km, CV, and CCT parameters (P=0.025, P=0.001, P=0.004, P=0.007, and P=0.009, respectively) (Table 1).

The patients with SSc were grouped among themselves based on the medical treatment, presence of digital ulcer, and organ involvement (Table 2). Those with muscular, pulmonary, and cardiac involvement had statistically significantly thinner ST at three levels than those without muscular, pulmonary, and cardiac involvement (P=0.014, P <0.001, P =0.001, respectively).

Among the ocular parameters, only ST had a statistically significant correlation with the SHAQ-global and its components. There was a weak-moderate negative correlation between ST and the components of this scale (RP-VAS, DU-VAS, pulmonary symptoms-VAS, digestive symptoms-VAS) and SHAQ-global at three levels (Table 3).

4 | DISCUSSION

The results of the present study showed that ST was thicker but CT and corneas were thinner in patients with SSc. In addition, ST was associated with a health assessment questionnaire at all three levels. When SSc patients were grouped based on the presence or absence of organ involvement, those with pulmonary, cardiac, or muscular involvement were found to have thinner ST. Although choroidal and corneal parameters have been evaluated in SSc patients in the literature, ST has not been evaluated. Therefore, this study is the first to evaluate the correlation of all ocular parameters with health-related QoL.

The cornea is susceptible to be affected by connective tissue diseases due to its rich collagen structure. The fact that type 1 collagen is dominant in human corneal structure compared with other collagen types and the effect of interleukin-35 (IL-35) on type 1 collagen in SSc dermal fibroblasts has not yet been determined is a point to be taken into account.[29,30] This condition may alter the biochemical structure or thickness of the cornea. Many studies support this theory. Serup et al found increased central CT in patients with SSc compared with healthy controls.[31] Nagy et al, on the other hand, found that pachymetric values (corneal anterior surface, corneal volume, and anterior chamber measurements) were statistically significantly lower in the SSc group than in the control group.[32] Similarly, another study reported thinner CT in the SSc group than in the control group.[33] SSc patients in our study had significantly lower corneal parameters (K1, K2, Km, CCT, CV) than healthy controls. This suggests that biochemical and ultrastructural changes occur in the cornea as a result of the immunological dysregulation process.[32]

In the literature, there are studies investigating choroidal involvement in patients with SSc. This anatomical structure has a critical role because it has a highly vascular structure, regulates the temperature in the eye, especially in the fovea, and supplies oxygen to the retina.[34] Grennan and Forrester found that 50 per cent of SSc patients had hypoperfusion in the choroidal capillaries.[35] Kraus et al found retinal pigment epithelial atrophy secondary to choroidal hypoperfusion in 26.3% of patients with SSc.[36] However, there are studies stating that choroidal and central foveal thicknesses are not different from healthy controls [17]. SSc patients in our study had significantly thinner CT than healthy controls. Endothelial cell injury, basement membrane thickening, and pericyte loss in choroidal vessels, which have been shown in histological studies, may explain why the thickness changes.[37]

Although scleritis and episcleritis have been reported in patients with SSc in the literature, no studies have evaluated ST. Scleral thickening was observed secondary to edema and inflammatory cell infiltration, especially in the case of scleritis.[38,39] Although another study found no scleritis, it reported thicker ST in patients with systemic lupus erythematosus compared with healthy controls.[28] Our study similarly showed thicker ST at all three levels compared with healthy control. There are several important reasons for this. First, the sclera is mainly composed of 90% type 1 collagen and 5% type III collagen.[40] In patients with SSc, the cellular infiltration process occurs in the early period, whereas the fibrotic process occurs in the late period. In the early period, the ratio of type 1/type 3 collagen in the body has been shown to change secondary to cellular infiltration (lymphocyte, macrophage, fibroblast).[40] So ST may increase due to scleral

edema and cellular infiltration in the early phase. Furthermore, fibroblastic transformation, breakdown of proteoglycan linkages, and degeneration of collagen fibrils in the sclera may alter its thickness.[38] Therefore, thicker ST of SSc patients compared with healthy controls despite having no ophthalmologic symptoms also suggests subclinical inflammation. In summary, biochemical and structural changes in the sclera may have caused an increase in thickness. However, histological studies are needed to verify this result.

There are a limited number of studies that review the relationship between demographic data, clinical parameters, medical treatment, and ocular parameters in rheumatologic diseases. Coskun et al stated that age, gender, and the form of the disease did not affect the CT.[41] Aydin et al reported that CT was not associated with organ involvement.[17] Our study also showed that organ involvement did not affect the CT. Kaya et al reported that steroid use and disease activity had no effect on ST in patients with systemic lupus erythematosus.[28] Although there was no association between the use of steroids and ST, there was a correlation between the health assessment questionnaire and ST in our study. Moreover, SSc patients with organ involvement (pulmonary, cardiac, muscle) had thinner ST than those without organ involvement. This may be related to the cytokine levels released as a result of immunological dysregulation, because T-helper cells have been shown to be effective in the pathophysiology and activity of SSc. It has been reported that increased serum levels of T helper type 17 increase fibroblast proliferation and aggregate cytokine release, so causing severe fibrosis.[42] Likewise, another study reported that IL-6 and IL-10 were variably associated with internal organ involvement.[43] A similar study showed that increased serum levels of IL-1β and IL-6 in SSc patients caused the active inflammation phase, whereas IL-4 caused fibrotic activation.[44] Therefore, the thinner ST thickness of the patients with a poor functional status and organ involvement may be the result of higher serum cytokine levels and higher severity of secondary fibrosis of the sclera.

There is a limited number of studies in the literature reviewing the relationship between ocular involvement and QoL in patients with SSc. Two published studies showed that ocular symptoms decrease the QoL.[45,46] Another study reported that ocular superficial diseases had a moderate effect on the QoL.[47] Interestingly, although there was no involvement in any of the ocular parameters studied in our study, only ST was correlated with the QoL among them. In addition, patients with organ involvement (muscular, pulmonary, and cardiovascular) had statistically thinner ST than those without organ involvement. This indicates that organ involvement or SSc-specific symptoms that negatively affect the QoL may have an associational relationship with scleral thinning (despite the absence of any scleral involvement or scleritis), either causal or non-causal that would need more studies to confirm.

4.1 | Limitations

Due to the cross-sectional nature of the study, it could not be determined whether the patients who were evaluated in the study had scleritis later. Furthermore, evaluating ST only on the temporal side is another limitation of our study, because the radius of the scleral curvature has been found to be different from the different scleral points.[28] Moreover, the study period had to be shortened to minimize the potential risk of exposure to coronavirus disease 2019 because the study was conducted during the pandemic.

5 | CONCLUSION

Ocular involvement leads to serious problems in patients with SSc. Therefore, early diagnosis has a crucial role. Despite not having ocular involvement, SSc patients had thicker ST but thinner CT and corneal parameters than healthy controls in our study. This may indicate subclinical inflammation and connective tissue involvement in patients with SSc. AS-OCT and Oculus Pentacam can be used for screening SSc patients as they are useful tools for the detection of ocular involvement. Furthermore, only ST was affected by organ involvement and QoL among the ocular parameters. However, further studies are needed for the verification or clarification of this result.

ACKNOWLEDGEMENT

We thank the Department of Rheumatology, Pamukkale University Faculty of Medicine, which supported this study by providing data of patients diagnosed with SSc.

CONFLICT OF INTEREST

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

ORCID

Serdar Kaymaz https://orcid.org/0000-0002-6958-5436

REFERENCES

1. Desbois AC, Cacoub P. Systemic sclerosis: an update in 2016. *Autoimmun Rev*. 2016;15:417-426.
2. Smith V, Scire CA, Talarico R, et al. Systemic sclerosis: state of the art on clinical practice guidelines. *RMD Open*. 2019. https://doi.org/10.1136/rmdopen-2018-000782
3. Mostmans Y, Cutulo M, Giddelo C, et al. The role of endothelial cells in the vasculopathy of systemic sclerosis: a systematic review. *Autoimmun Rev*. 2017;16:774-786.
4. Abraham DJ, Krieg T, Distler J, Distler O. Overview of pathogenesis of systemic sclerosis. *Rheumatology*. 2009;48:3-7.
5. Elhai M, Meune C, Boubaya M, et al. Mapping and predicting mortality from systemic sclerosis. *Ann Rheum Dis*. 2017;76:1897-1905.
6. Smith V, Van Praet JT, Vandooren B, et al. Rituximab in diffuse cutaneous systemic sclerosis: an open-label clinical and histopathological study. *Ann Rheum Dis*. 2010;69:193-197.
7. Raja J, Denton CP. Cytokines in the immunopathology of systemic sclerosis. *Semin Immunopathol*. 2015;37:543-557.
8. West RH, Barnett AJ. Ocular involvement in scleroderma. *Br J Ophthalmol*. 1979;63:845-847.
9. Kirkham TH. Scleroderma and Sjogren's syndrome. *Br J Ophthalmol*. 1969;53:131-133.
10. Gomes Bde A, Santhiago MR, Magalhães P, Kara-Junior N, Azevedo MN, Moraes HV Jr. Ocular findings in patients with systemic sclerosis. *Clinics (Sao Paulo)*. 2011;66:379-385.
11. Kanski JJ, Bowling B, Nischal KK, Pearson A. *Clinical Ophthalmology: A Systematic Approach*, 7th ed. Edinburgh; New York: Elsevier/Saunders; 2011:219-220.

12. Hamideh F, Prete PE. Ophthalmologic manifestations of rheumatic diseases. *Semin Arthritis Rheum*. 2001;30:217-241.
13. De Andrés J, García-Delpech S, Pérez VL, et al. Bilateral infusion pump implants as therapy for refractory corneal ulcers in a patient with CREST syndrome: an interdisciplinary approach. *Arch Ophthalmol*. 2008;126:964-967.
14. Sii F, Lee GA, Sanfilippo P, Stephensen DC. Pellucid marginal degeneration and scleroderma. *Clin Exp Optom*. 2004;87:180-184.
15. Jawad ZY, Faiq I. Ocular manifestations of systemic sclerosis: a descriptive cross-sectional study from Iraq. *IOSR Journal of Nursing and Health Science*. 2017;06(04):94-97. https://doi.org/10.9790/1959-0604019497
16. Kreps EO, Carton C, Cutolo M, et al. Ocular involvement in systemic sclerosis: A systematic literature review, it's not all scleroderma that meets the eye. *Semin Arthritis Rheum*. 2019;49:119-125.
17. Aydin E, Atik S, Koc F, et al. Choroidal and central foveal thickness in patients with scleroderma and its systemic associations. *Clin Exp Optom*. 2017;100:656-662.
18. Coudrillier B, Pijanka J, Jefferys J, et al. Collagen Structure and Mechanical Properties of the Human Sclera: Analysis for the Effects of Age. *Journal of Biomechanical Engineering*. 2015;137(4). https://doi.org/10.1115/1.4029430
19. Read SA, Alonso-Caneiro D, Vincent SJ, et al. Anterior eye tissue morphology: Scleral and conjunctival thickness in children and young adults. *Sci Rep*. 2016;6:33796.
20. Tailor R, Gupta A, Herrick A, Kwartz J. Ocular manifestations of scleroderma. *Surv Ophthalmol*. 2009;54:292-304.
21. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Subcommittee for scleroderma criteria of the American Rheumatism Association. Diagnostic and Therapeutic Criteria Committee. *Arthritis Rheum*. 1980;23:581-590.
22. LeRoy EC, Black C, Fleischmajer R, et al. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. *J Rheumatol*. 1988;15:202-205.
23. Manjunath V, Taha M, Fujimoto JG, Duker JS. Choroidal thickness in normal eyes measured using Cirrus HD optical coherence tomography. *Am J Ophthalmol*. 2010;150:325-329.
24. Temiz Karadag D, Karakas F, Tekeoglu S, Yazici A, Isik OO, Cefle A. Validation of Turkish version of the Scleroderma Health Assessment Questionnaire. *Clin Rheumatol*. 2019;38:1917-1923.
25. Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J*. 2019;53:1801913. https://doi.org/10.1183/13993003.01913-2018
26. Hunzelmann N, Genth E, Krieg T, et al. Registry of the German Network for Systemic Scleroderma. The registry of the German Network for Systemic Scleroderma: frequency of disease subsets and patterns of organ involvement. *Rheumatology (Oxford)*. 2008;47(8):1185-1192. https://doi.org/10.1093/rheumatology/ken179
27. Lóránd V, Czirják L, Minier T. Musculoskeletal involvement in systemic sclerosis. *Presse Med*. 2014;43:315-328.
28. Kaya H, Karasu U, Martin Ç, Taşçi M, Pekel G. Measurements of scleral thickness and corneal optic densitometry in patients with systemic lupus erythematosus. *Medicine*. 2020;99(31):e21467. https://doi.org/10.1097/MD.0000000000021467
29. Atamas SP, Luzina IG, Ingels J, et al. Stimulation with type I collagen induces changes in gene expression in peripheral blood mononuclear cells from patients with diffuse cutaneous systemic sclerosis (scleroderma). *Clin Exp Immunol*. 2010;161:426-435.
30. Nakayasu K, Tanaka M, Konomi H, Hayashi T. Distribution of types I, II, III, IV and V collagen in normal and keratoconus corneas. *Ophthalmic Res*. 1986;18:1-10.
31. Serup L, Serup J, Hagdrup HK. Increased central cornea thickness in systemic sclerosis. *Acta Ophthalmol (Copenh)*. 1984;62:69-74.
32. Nagy A, Rentka A, Nemeth G, et al. Corneal Manifestations of Systemic Sclerosis. *Ocul Immunol Inflamm*. 2019;27:968-977.
33. Şahin M, Yüksel H, Şahin A, et al. Evaluation of the Anterior Segment Parameters of the Patients with Scleroderma. *Ocul Immunol Inflamm*. 2017;25:233-238.
34. Munch IC, Altuntas C, Li XQ, Jackson GR, Klefter ON, Larsen M. Dark adaptation in relation to choroidal thickness in healthy young subjects: a cross-sectional, observational study. *BMC Ophthalmology*. 2016;16:105. https://doi.org/10.1186/s12886-016-0273-6
35. Grennan DM, Forrester J. Involvement of the eye in SLE and scleroderma. A study using fluorescein angiography in addition to clinical ophthalmic assessment. *Ann Rheum Dis*. 1977;36:152-156.
36. Kraus A, Guerra-Bautista G, Espinoza G, et al. Defects of the retinal pigment epithelium in scleroderma. *Br J Rheumatol*. 1991;30:112-114.
37. Maclean H, Guthrie W. Retinopathy in scleroderma. *Trans Ophthalmol Soc UK*. 1970;89:209-220.
38. Arellanes-Garcia L, Del Carmen P-D, Garza-Leon M. Refractive changes in patients with autoimmune scleritis. *J Ophthalmic Inflamm Infect*. 2011;1:173-175.
39. Shoughy SS, Jaroudi MO, Kozak I, Tabbara KF. Optical coherence tomography in the diagnosis of scleritis and episcleritis. *Am J Ophthalmol*. 2015;159:1045-1049.
40. Coudrillier B, Pijanka J, Jefferys J, et al. Collagen structure and mechanical properties of the human sclera: analysis for the effects of age. *J Biomech Eng*. 2015;137:041006.
41. Coşkun E, Zengin O, Kenan S, et al. Evaluation of choroidal thickness in patients with scleroderma. *Eye (Lond)*. 2016;30:588-592.
42. Xing X, Li A, Tan H, Zhou Y. IFN-γ^+ IL-17$^+$ Th17 cells regulate fibrosis through secreting IL-21 in systemic scleroderma. *J Cell Mol Med*. 2020;24:13600-13608.
43. Scala E, Pallotta S, Frezzolini A, et al. Cytokine and chemokine levels in systemic sclerosis: relationship with cutaneous and internal organ involvement. *Clin Exp Immunol*. 2004;138:540-546.
44. Khadilkar PV, Khopkar US, Nadkar MY, et al. Fibrotic Cytokine Interplay in Evaluation of Disease Activity in Treatment Naïve Systemic Sclerosis Patients from Western India. *J Assoc Physicians India*. 2019;67:26-30.
45. Gomes Bde A, Santhiago MR, Magalhães P, Kara-Junior N, Azevedo MN, Moraes HV Jr. Ocular fndings in patients with systemic sclerosis. *Clinics (Sao Paulo)*. 2011;66:379-385. https://doi.org/10.1590/s1807-59322011000300003
46. Hunzelmann N, Genth E, Krieg T, et al. The registry of the German Network for Systemic Scleroderma: frequency of disease subsets and patterns of organ involvement. *Rheumatology (Oxford)*. 2008;47:1185-1192.
47. Gomes DAF, Santhiago MR, de Azevedo MNL, Moraes HV. Evaluation of dry eye signs and symptoms in patients with systemic sclerosis. *Graefes Arch Clin Exp Ophthalmol*. 2012;250:1051-1056.

How to cite this article: Kaymaz S, Halil Y, Kaya H, Karasu U, Cobankara V. The relationship of ocular parameters with clinical parameters and disease-related quality of life in patients with systemic sclerosis: A cross-sectional study. *Int J Rheum Dis*. 2021;24:1308–1316. https://doi.org/10.1111/1756-185X.14216

Received: 27 June 2021 | Revised: 8 July 2021 | Accepted: 19 July 2021

DOI: 10.1111/1756-185X.14194

NOVEL HYPOTHESIS

International Journal of Rheumatic Diseases

WILEY

A bond between rheumatic diseases and cancer in the elderly: The interleukin-6 pathway

Giuseppe Carlo Iorio[1] | Antonio Ammendolia[2] | Nicola Marotta[2] | Umberto Ricardi[1] | Alessandro de Sire[2]

[1]Department of Oncology, Radiation Oncology, University of Turin, Turin, Italy

[2]Department of Medical and Surgical Sciences, University of Catanzaro "Magna Graecia", Catanzaro, Italy

Correspondence
Alessandro de Sire, Physical and Rehabilitative Medicine, Department of Medical and Surgical Sciences, University of Catanzaro "Magna Graecia", Viale Europa, Catanzaro 88100, Italy.
Email: alessandro.desire@unicz.it

Abstract

Interleukin (IL)-6 is a soluble factor secreted by T lymphocytes, involved in antibody generation by B lymphocytes. The IL-6 pathway has risen as a pivotal pathway implicated in immune regulation and dysregulation in various rheumatic diseases. Nonetheless, elevated IL-6 levels can also play a role in cancer. Targeting the IL-6 pathway has led to innovative therapeutic approaches for rheumatic diseases and for COVID-19, particularly in the elderly. Indeed, tocilizumab, an agent targeting IL-6, has recently amassed significant attention as a promising univocal agent for different conditions. In this viewpoint, we sought to recall and describe the common pathway among osteoarthritis, rheumatoid arthritis, and cancer, suggesting that anti-IL-6 may be considered a jack-of-all-trades against inflammaging in the elderly.

KEYWORDS

aging, cancer, COVID-19, osteoarthritis, rheumatoid arthritis

1 | INFLAMMAGING AND INTERLEUKIN (IL)-6

Inflammaging is a low-grade, clinically undetectable inflammation in the elderly due to a progressive age-related increase of serum levels of pro-inflammatory cytokines (i.e., IL-1, IL-6, and tumor necrosis factor [TNF]-α), provoked by a continuous antigenic load and stress.[1] Among these pro-inflammatory cytokines, IL-6 has gained a remarkable research interest, since its pathway has resulted as crucially implicated in immune regulation in several diseases, such as the rheumatic ones.[1] Nonetheless, elevated IL-6 levels may also play a role in cancer.[2] Indeed, although the link between inflammation and cancer has been historically debated, IL-6 has been reported to be involved in inflammation-associated tumorigenesis, and a role for IL-6 has emerged in several oncological scenarios.[3] All these conditions, rheumatic diseases, as osteoarthritis (OA) and rheumatoid arthritis (RA), and cancer, typically arise among older people.[4-6] Thus, the elderly typically represents a population with various comorbidities, and, interestingly, a common cytokine-based pro-inflammatory path is bonding these age-related conditions (Figure 1).

The current coronavirus disease 19 (COVID-19) pandemic has placed under the spotlight the role of the cytokine release syndrome and IL-6, with the advent of targeted therapies in this setting.[7] Indeed, a hyperinflammation state, dependent on cytokine release syndrome (CRS) and IL-6, has been linked with the COVID-19 fatality rate.[8]

Targeting the IL-6 pathway might lead to innovative therapeutic approaches not only for rheumatic diseases[9,10] and cancer[11] but also for COVID-19.[7] In this context, the COVID-19 pandemic has drastically affected the management and treatment strategies of rheumatic diseases as well as cancer.[12-14]

Therefore, given the enhanced relevance during the present pandemic, we sought to recall the common pro-inflammatory bond between these age-related conditions, rheumatic diseases, and cancer, focusing on the IL-6 role and its targeting with potential implications for future therapeutic approaches.

© 2021 Asia Pacific League of Associations for Rheumatology and John Wiley & Sons Australia, Ltd.

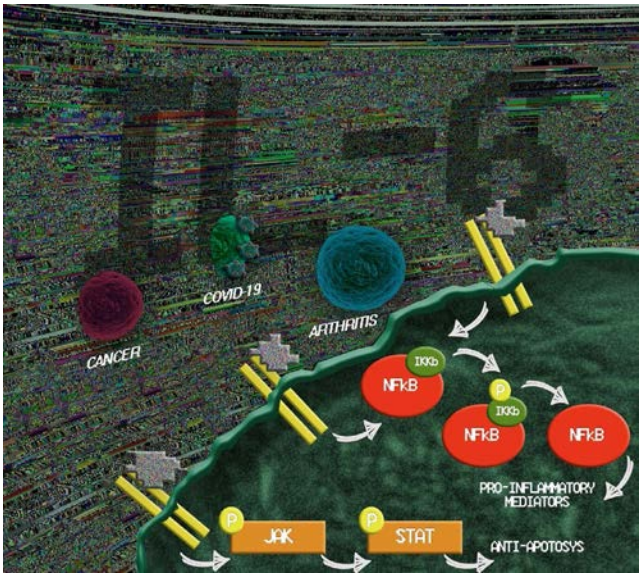

FIGURE 1 Interleukin (IL)-6 signaling interaction with the immune-modulation system. IL-6 is a B cell differentiation switcher that can be synthesized by an ample variety of cells, including monocytes, lymphocytes, fibroblasts, endothelial cells, and some cancer cells. The IL-6 receptor (IL-6R, CD126) can subsist as a soluble or transmembrane form; the membrane-bound molecule of IL-6R is an 80 kDa protein that expresses the extracellular binding site and a minimal cytoplasmic domain. This receptor, unlike its mediator, is expressed only by leukocytes and hepatocytes. IL-6R changes its conformation after binding IL-6, providing the enrollment of a glycoprotein Gp130, a cytoplasmic mediator, also known as CD130. In this scenario, Gp130 becomes the IL-6R/IL-6 complex activated mediator, sharing the molecular pathway of other molecules such as IL-11, IL-27, IL-31, cardiotropin-1 (CTF1), cardiotropin-like cytokine (CLC), ciliary neurotrophic factor (CNTF), oncostatin M and leukemia inhibitory factor (LIF). Gp130 overexpresses the tyrosine kinase pathway Janus-activated kinases (JAKs) and tyrosine kinases, promoting phosphorylation and activation of signal transducers and activators of transcriptions 1 and 3 (STAT1 and STAT3). STAT3 is not a unique transducer for IL-6, as STAT3 is a target gene for anti-apoptotic pathways, thus acting as an angiogenic mediator, tumor, and metastatic growth factor. Furthermore, the JAKs and IL-6 signaling might stimulate the PI3K/AKT (protein kinase B), RAS, and mitogen-activated protein kinase pathways, thus upregulating anti-apoptosis and cell survival. NFκB, nuclear factor κB

2 | RHEUMATIC DISEASES AND IL-6

OA is considered a chronic, low-grade inflammatory disease with a high cytokine content, involving the entire joint rather than the cartilage surface.[15-18]

OA etiopathogenic pathways can include epigenetic modifications, cellular senescence, and an age-related rise in a resulting continuous pro-inflammatory state, defined as "inflammaging".[1,18,19] Synovial fluid contains a variety of pro-inflammatory cytokines, at low concentrations (IL-1β, TNF) or at high concentrations (IL-6).[15] Therefore, biological drugs that inhibit inflammatory mediators, such as IL-1, TNF-α, and IL-6, have been proposed to block cartilage catabolism.[20] Indeed, targeted inhibition of these cytokines has been hypothesized to down-regulate chemotactic cascades and matrix enzyme proteases, preventing and delaying the progression of OA disease.[20]

RA is an autoimmune disease exhibited in chronic and progressive inflammatory tissues and joints disorder which often involves irreversible joint damage and systemic complications.[21]

This severe disease progression is correlated with IL-6/IL-6R complex elevated levels in the synovium of RA patients. IL-6 generated by bone marrow stromal cells can stimulate the receptor activator of nuclear factor-κB ligand (RANKL), critical for the differentiation and up-regulation of osteoclasts and bone resorption.[22] In RA, IL-6 stimulating vascular endothelial growth factor (VEGF) could modulate vascular permeability, enhancing inflammation recruitment into the tissues, aggravating the damage.[23] Thus, the plan of IL-6 inhibitor regimens for RA, the most prevalent chronic autoimmune disorder afflicting predominantly the joints, rose in the early 1990s; the principal purpose was alleviating symptoms like fever, fatigue, pain, joint damage, anemia.[21] IL-6 might become the key target of the acute phase response in RA, by modulating lymphocyte differentiation and influencing all the aforementioned clinical manifestations.

3 | CANCER AND IL-6

In terms of cancer pathogenesis, overexpressed IL-6 leads to Janus-activated kinase / signal transducer and activator of transcription 3 (JAK/STAT3) signaling hyperactivation, often associated with dismal patient outcomes.[2] The IL-6/JAK/STAT3 aberrant hyperactivation significantly impacts the tumor microenvironment acting as a driver of tumor cell proliferation and scattering capacity and as well suppressing the anti-tumor immune response.[2]

Specifically, STAT3 hyperactivation has been related to chemotherapy and radiotherapy (RT) resistance, given its crucial role in the interaction between tumor-associated macrophages and tumors.[24] Tumor-associated macrophages are major supportive components within neoplasms, characterized by many functions that might facilitate tumor outgrowth. Tumor-associated macrophages' elevated numbers are associated with poor cancer prognosis.[25] Thus, targeting IL-6 may pave the way to enhanced tumor control.[26]

The interplay between IL-6 and RT has been investigated in head and neck cancer (HNC).[24,27] Of interest, in a series of 26 HNC patients, serum levels of pro-inflammatory markers, such as IL-6, were observed to increase after RT and chemo-radiotherapy.[27]

Thereupon, paradoxically, oncological treatments may favor a tumor-promoting pro-inflammatory microenvironment.[27] Accordingly, Matsuoka et al.[24] hypothesized improved outcomes, such as treatment response and survival, in oral squamous cell carcinoma patients, with the addition of tocilizumab to RT, given its capacity to limit the IL-6 effect in reducing radiation-induced DNA damage.

Moreover, this treatment-induced pro-inflammatory microenvironment could lead to lymphocyte deficiency.[28] Lymphopenia is associated with an increased risk of opportunistic infections (a significant implication during the present pandemic), and worse oncologic outcomes due to the lymphocytes' essential roles within the anti-tumor immune response.[29,30]

Finally, the present times may represent a boost for further investigation regarding IL-6 targeting in cancer patients.

4 | CONCLUSIONS

Considering inflammation as a common denominator for aging, rheumatic diseases, and cancer, we highlighted the need to guide treatments against the cytokine storm. By the present viewpoint, we sought to recall the role played by IL-6 for rheumatic diseases and cancer, with enhanced relevance during the COVID-19 era. We are aware that future studies are necessary to better investigate the bond between rheumatic diseases and cancer in elderly. Therefore, we could affirm that anti-IL-6 might be considered a jack-of-all-trades against inflammaging, potentially paving the way to future synergistic treatment perspectives.

ORCID

Giuseppe Carlo Iorio https://orcid.org/0000-0003-1390-4191
Antonio Ammendolia https://orcid.org/0000-0002-2828-2455
Nicola Marotta https://orcid.org/0000-0002-5568-7909
Umberto Ricardi https://orcid.org/0000-0003-4406-7621
Alessandro de Sire https://orcid.org/0000-0002-5541-8346

REFERENCES

1. Franceschi C, Bonafè M, Valensin S, et al. Inflamm-aging: an evolutionary perspective on immunosenescence. *Ann N Y Acad Sci*. 2000;908(1):244-254. https://doi.org/10.1111/j.1749-6632.2000.tb06651.x
2. Weber R, Groth C, Lasser S, et al. IL-6 as a major regulator of MDSC activity and possible target for cancer immunotherapy. *Cell Immunol*. 2021;359:104254. https://doi.org/10.1016/j.cellimm.2020.104254
3. Yao X, Huang J, Zhong H, et al. Targeting interleukin-6 in inflammatory autoimmune diseases and cancers. *Pharmacol Ther*. 2014;141(2):125-139. https://doi.org/10.1016/j.pharmthera.2013.09.004
4. Bernetti A, Agostini F, Alviti F, et al. New Viscoelastic Hydrogel Hymovis MO.RE. Single intra-articular injection for the treatment of knee osteoarthritis in sportsmen: safety and efficacy study results. *Front Pharmacol*. 2021;12:673988. https://doi.org/10.3389/fphar.2021.673988
5. Serhal L, Lwin MN, Holroyd C, et al. Rheumatoid arthritis in the elderly: characteristics and treatment considerations. *Autoimmun Rev*. 2020;19(6):102528. https://doi.org/10.1016/j.autrev.2020.102528
6. Laconi E, Marongiu F, DeGregori J. Cancer as a disease of old age: changing mutational and microenvironmental landscapes. *Br J Cancer*. 2020;122(7):943-952. https://doi.org/10.1038/s41416-019-0721-1
7. West TA, Malik S, Nalpantidis A, et al. Tocilizumab for severe COVID-19 pneumonia: case series of 5 Australian patients. *Int J Rheum Dis*. 2020;23(8):1030-1039. https://doi.org/10.1111/1756-185X.13913
8. Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet*. 2020;395(10229):1033-1034. https://doi.org/10.1016/S0140-6736(20)30628-0
9. Hassen LM, Almaghlouth IA, Hassen IM, et al. Impact of COVID-19 outbreak on rheumatic patients' perceptions and behaviors: a cross-sectional study. *Int J Rheum Dis*. 2020;23(11):1541-1549. https://doi.org/10.1111/1756-185X.13959
10. de Sire A. Are corticosteroids effective as adjunctive therapy in children with septic arthritis? A Cochrane Review summary with commentary. *Int J Rheum Dis*. 2020;23(10):1426-1429. https://doi.org/10.1111/1756-185X.13903
11. Ascierto PA, Fox B, Urba W, et al. Insights from immuno-oncology: the Society for Immunotherapy of Cancer Statement on access to IL-6-targeting therapies for COVID-19. *J Immunother Cancer*. 2020;8(1):e000878. https://doi.org/10.1136/jitc-2020-000878
12. Mikuls TR, Johnson SR, Fraenkel L, et al. American College of Rheumatology guidance for the management of rheumatic disease in adult patients during the COVID-19 pandemic: version 1. *Arthritis Rheumatol*. 2020;72(8):1241-1251. https://doi.org/10.1002/art.41301
13. de Sire A, Andrenelli E, Negrini F, Lazzarini SG, Patrini M, Ceravolo MG. Rehabilitation and COVID-19: the Cochrane Rehabilitation 2020 rapid living systematic review. Update as of August 31st, 2020. *Eur J Phys Rehabil Med*. 2020;56(6):839-845. https://doi.org/10.23736/S1973-9087.20.06614-9
14. Slotman BJ, Cremades V, Kirby AM, Ricardi U. European radiation oncology after one year of COVID-19 pandemic. *Clin Transl Radiat Oncol*. 2021;28(1):141–143. https://doi:10.1016/j.ctro.2021.03.011
15. Tam LS, Tanaka Y, Handa R, et al. Updated APLAR consensus statements on care for patients with rheumatic diseases during the COVID-19 pandemic. *Int J Rheum Dis*. 2021;24(6):733-745. https://doi.org/10.1111/1756-185X.14124
16. de Sire A, Marotta N, Marinaro C, et al. Role of physical exercise and nutraceuticals in modulating molecular pathways of osteoarthritis. *Int J Mol Sci*. 2021;22(11):5722. https://doi.org/10.3390/ijms22115722
17. Jargin SV. Chondroprotectives used for the treatment of knee osteoarthritis: a comment. *Int J Rheum Dis*. 2021;24(3):459-461. https://doi.org/10.1111/1756-185X.14071
18. de Sire A, de Sire R, Petito V, et al. Gut–joint axis: the role of physical exercise on gut microbiota modulation in older people with osteoarthritis. *Nutrients*. 2020;12(2):574. https://doi.org/10.3390/nu12020574
19. Pietrobon AJ, Teixeira FME, Sato MN. Immunosenescence and inflammaging: risk factors of severe COVID-19 in older people. *Front Immunol*. 2020;11:579220. https://doi.org/10.3389/fimmu.2020.579220
20. Kumar A, Palit P, Thomas S, et al. Osteoarthritis: prognosis and emerging therapeutic approach for disease management. *Drug Dev Res*. 2021;82(1):49-58. https://doi.org/10.1002/ddr.21741
21. Serhal L, Lwin MN, Holroyd C, et al. Rheumatoid arthritis in the elderly: Characteristics and treatment considerations. *Autoimmun Rev*. 2020;19(6):102528. https://doi.org/10.1016/j.autrev.2020.102528
22. Palmqvist P, Persson E, Conaway HH, et al. IL-6, Leukemia inhibitory factor, and oncostatin M Stimulate bone resorption and regulate the expression of receptor activator of NF-κB ligand, osteoprotegerin, and receptor activator of NF-κB in mouse calvariae. *J Immunol*. 2002;169(6):3353-3362. https://doi.org/10.4049/jimmunol.169.6.3353
23. Lamas JR, Rodríguez-Rodríguez L, Tornero-Esteban P, et al. Alternative splicing and proteolytic rupture contribute to the generation of soluble IL-6 receptors (sIL-6R) in rheumatoid arthritis. *Cytokine*. 2013;61(3):720-723. https://doi.org/10.1016/j.cyto.2012.12.025

24. Matsuoka Y, Nakayama H, Yoshida R, et al. IL-6 controls resistance to radiation by suppressing oxidative stress via the Nrf2-antioxidant pathway in oral squamous cell carcinoma. *Br J Cancer*. 2016;115(10):1234-1244. https://doi.org/10.1038/bjc.2016.327
25. Pollard JW. Tumour-educated macrophages promote tumour progression and metastasis. *Nat Rev Cancer*. 2004;4(1):71-78. https://doi.org/10.1038/nrc1256
26. Iorio GC, Ricardi U, Franco P. The importance of IL-6 blockade beyond the COVID-19 pandemic: consideration for cancer care. *Radiother Oncol*. 2020;151:24-25. https://doi.org/10.1016/j.radonc.2020.07.018
27. Kiprian D, Czarkowska-Paczek B, Wyczalkowska-Tomasik A, et al. Radiotherapy and radiochemotherapy increase serum levels of pro-inflammatory interleukin-6 and C-reactive protein in patients with head and neck cancers. *Transl Cancer Res*. 2018;7:41-47. https://doi.org/10.21037/tcr.2017.12.23
28. Liao YC, Liang WG, Chen FW, et al. IL-19 induces production of IL-6 and TNF-alpha and results in cell apoptosis through TNF-alpha. *J Immunol*. 2002;169(8):4288-4297. https://doi.org/10.4049/jimmunol.169.8.4288
29. Iorio GC, Ricardi U, Dal Pra A. Radiation-induced lymphopenia beyond the COVID-19 pandemic. *Front Oncol*. 2020;10(18):617302. https://doi.org/10.3389/fonc.2020.617302
30. Tanriverdi O. Lymphopenia that may develop in patients treated with temozolomide and immune control check-point inhibitor may be a high risk for mortality during the COVID-19 outbreak. *Med Oncol*. 2020;37:51. https://doi.org/10.1007/s12032-020-01376-8

How to cite this article: Iorio GC, Ammendolia A, Marotta N, Ricardi U, de Sire A. A bond between rheumatic diseases and cancer in the elderly: The interleukin-6 pathway. *Int J Rheum Dis*. 2021;24:1317–1320. https://doi.org/10.1111/1756-185X.14194

Received: 6 August 2021 | Revised: 18 August 2021 | Accepted: 20 August 2021

DOI: 10.1111/1756-185X.14212

EXPERT COMMENTS

International Journal of Rheumatic Diseases

WILEY

Recent advances in pediatric rheumatology: April to June 2021

Prabal Barman | **Archan Sil** | **Surjit Singh**

Pediatric Allergy Immunology Unit, Advanced Pediatrics Center, Post Graduate Institute of Medical Education and Research, Chandigarh, India

Correspondence
Surjit Singh, Department of Pediatrics and Chief, Allergy Immunology Unit, Advanced Pediatrics Center, Post Graduate Institute of Medical Education and Research, Chandigarh, India.
Email: surjitsinghpgi@rediffmail.com

1 | IGG AND IGA AUTOANTIBODIES AGAINST L1 ORF1P EXPRESSED IN GRANULOCYTES CORRELATE WITH GRANULOCYTE CONSUMPTION AND DISEASE ACTIVITY IN PEDIATRIC SYSTEMIC LUPUS ERYTHEMATOSUS

Ukadike K, Ni K, Wang X, Taylor M, LaCava J, Pachman L, Eckert M, Stevens A, Lood C, Mustelin T. *Arthritis Res Ther* 2021 May 29; 23(1): 153. 10.1186/s13075-021-02538-3.

Systemic lupus erythematosus (SLE) is characterized by various autoantibodies in association with Type 1 interferons. It has been reported in recent literature that SLE patients have autoantibodies of immunoglobulin G class (IgG) produced against RNA-binding p40 (ORF1p) protein that is coded by L1 retroelement. In this multicenter study from the USA, Ukadike et al. analyzed the presence of these autoantibodies in pediatric SLE (pSLE). In their cohort of 30 pSLE patients, the authors reported that both IgG and immunoglobulin A (IgA) autoantibodies against p40/ORF1p were elevated in comparison to healthy controls and disease controls (juvenile dermatomyositis; juvenile idiopathic arthritis). They also correlated well with disease activity. It was also observed that neutrophil activation and death markers correlated with these autoantibodies and indirectly with disease activity, thereby indicating that p40 may be expressed by neutrophils. Although the sample size is small, this study is an important addition to the list of novel biomarkers for defining disease activity in pSLE.

2 | THE IMPACT OF SERUM ANTI-NEUTROPHIL CYTOPLASMIC ANTIBODY ON CLINICAL CHARACTERISTICS AND OUTCOMES IN PEDIATRIC-ONSET SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS

Gau C, Tseng M, Wu C, Yang H, Huang J. *Front Med (Lausanne)* 2021 Apr 16; 8: 647510. 10.3389/fmed.2021.647510.

SLE is an autoimmune disorder with multi-system involvement. It is characterized by development of several autoantibodies that may, at times, include anti-neutrophil cytoplasmic antibodies (ANCAs). Recent studies in adults suggest that SLE patients with ANCA positivity are more likely to have renal involvement and increased disease activity. However, there is paucity of literature on this aspect in pSLE. Gau et al. conducted a retrospective case-control study from Taiwan involving 70 pSLE patients – 9 among these were also ANCA positive. The authors reported that pSLE patients who were ANCA positive had increased incidence of hematuria and lacked the typical renal biopsy findings. However, there was no discernible difference with respect to other clinical parameters including renal involvement. This study provides a new perspective to pSLE.

© 2021 Asia Pacific League of Associations for Rheumatology and John Wiley & Sons Australia, Ltd.

3 | FINDINGS AND FEASIBILITY OF MAJOR SALIVARY GLAND ULTRASOUND IN CHILDHOOD-ONSET SYSTEMIC LUPUS ERYTHEMATOSUS: A PILOT STUDY

McDonald J, Vega-Fernandez P, Ting T. *Pediatr Rheumatol Online J* 2021 May 17; 19(1): 73. 10.1186/s12969-021-00561-x.

SLE in children (cSLE) is a multisystemic autoimmune disorder associated with multiple autoantibodies. At times, cSLE can present in conjunction with other autoimmune disorders like Sjögren's syndrome (SS). SS remains an underdiagnosed entity in children because diagnosis depends on the classical clinical manifestations of xerostomia and keratoconjunctivitis sicca that are uncommon in the pediatric population. Further, invasive tests like parotid sialography and salivary scintigraphy are rarely performed in children. However, salivary gland ultrasound (SGUS) can be a useful non-invasive diagnostic modality to look for salivary gland involvement in patients with cSLE. McDonald et al. have carried out a cross-sectional study on 31 patients with cSLE (without diagnosis of SS) at Cincinnati Children's Hospital Medical Center, USA, to determine anomalies in salivary gland compatible with the diagnosis of secondary SS. Among 31 cSLE patients, 11 (35%) showed abnormal findings on SGUS. Significant statistical correlations were noted between SGUS positive scores and presence of anti-Ro, anti-La antibodies, and mean immunoglobulin G value at diagnosis. The authors suggest that SGUS is a useful diagnostic modality for detecting early secondary SS in patients with cSLE.

4 | IDENTIFICATION OF A SHARED GENETIC RISK *LOCUS* FOR KAWASAKI DISEASE AND IGA VASCULITIS BY A CROSS-PHENOTYPE META-ANALYSIS

Carmona E, García-Giménez J, López-Mejías R, Khor C, Lee J-K, Taskiran E, Ozen S, Hocevar A, Liu L, Gorenjak M, Potoènik U, Kiryluk K, Ortego-Centeno N, Cid M, Hernández-Rodríguez J, Castañeda S, González-Gay M, Burgner D, Martín J, Márquez A, Spanish IgA Vasculitis Consortium and International Kawasaki Disease Genetics Consortium. *Rheumatology (Oxford)* 2021 May 16; keab443. 10.1093/rheumatology/keab443

Kawasaki disease (KD) and IgA vasculitis (IgAV) are the 2 commonest vasculitides in children. Recent studies suggest a probable common genetic overlap in pathogenesis of these conditions. Carmona et al. provide the first cross-disease meta-analysis using genome-wide association studies from previously published data. Authors discovered a unique intronic variant, rs3743841, located in *NAGPA* gene, that had attained genome-wide significance and had pleiotropic effects on evolution of these 2 conditions. In addition, this variant also represented the most significant non-human leukocyte antigen signal described in relation to IgAV. This study has important clinical implications as it suggests a common mechanism in pathogenesis of these 2 disorders. However, as the genetic footprint of KD varies among different ethnicities, it is necessary to gather data from other populations.

5 | THE "INTERMEDIATE" CD14 + CD16 + MONOCYTE SUBPOPULATION PLAYS A ROLE IN IVIG RESPONSIVENESS OF CHILDREN WITH KAWASAKI DISEASE

Kim YS, Yang HJ, Kee SJ, Choi I, Ha K, Ki KK, Jeong IS, Cho HJ. *Pediatr Rheumatol Online J* 2021 May 31; 19(1): 76. 10.1186/s12969-021-00573-7.

KD is now the most common cause of acquired heart disease in children in developed countries. Cardiac complications are more common in children with KD who develop intravenous immunoglobulin (IVIg) resistance. Studies carried out over the last 2 decades have described different risk factors associated with IVIg resistance in KD. Kim et al. conducted this single-center, prospective study from South Korea to reveal whether there was any correlation between CD14+CD16+ intermediate monocytes and IVIg responsiveness in children with KD. They enrolled 62 KD patients, 20 healthy controls without fever and 15 controls with fever. Monocyte subtypes were assayed by flow cytometry. The authors reported that intermediate monocytes were significantly reduced before IVIg infusion in patients who subsequently developed IVIg resistance compared to those who responded to IVIg. While a decreasing trend of intermediate monocytes was noted in the IVIg-responsive group after IVIg infusion, the resistant group showed increasing trend. Low pre-IVIg level of intermediate monocytes with significant increase after IVIg infusion predicted IVIg resistance. However, the results of this study need to be replicated in children from other ethnicities before firm conclusions can be drawn.

6 | CLINICAL FEATURES AND OUTCOMES OF 76 PATIENTS WITH COVID-19-RELATED MULTI-SYSTEM INFLAMMATORY SYNDROME IN CHILDREN

Haslak F, Barut K, Durak C, Aliyeva A, Yildiz M, Guliyeva V, Varol SE, Cebeci SO, Aygun F, Varli YZ, Ozel A, Onan SH, Kocoglu U, Erol M, Karagozlu F, Ulug N, Dedeoglu R, Sahin S, Adrovic A, Oztunc F, Kasapcopur O. *Clin Rheumatol* 2021 Jun 5: 1–12. 10.1007/s10067-021-05780-x.

Multi-system inflammatory syndrome in children (MIS-C) is an inflammatory condition that develops after SARS-CoV-2 infection. It is characterized by fever, multisystemic involvement and raised inflammatory markers. The term MIS-C was coined by the Centers for Disease Control and Prevention in May 2020. Haslak et al. conducted this multi-centric cross-sectional study from 3 pediatric referral centers in Turkey to define the clinical phenotype and sequelae in 76 children with MIS-C. Among 76 patients (24 female; mean age 8.17 ± 4.42 years), 27 (35.5%) required pediatric intensive care unit admission. Predominant systems involved were cardiovascular and gastrointestinal. There was 1 mortality. While higher initial procalcitonin values were associated with prolonged hospital stay, low serum albumin values at time of admission and increased age were significant risk factors for admission to intensive care unit. This

study provides useful guidelines to clinicians in predicting severe MIS-C cases.

7 | SYSTEMATIC REVIEW OF CHILDHOOD-ONSET POLYARTERITIS NODOSA AND DADA2

Cuceoglu M, Sener S, Batu E, Akca U, Demir S, Sag E, Atalay E, Balık Z, Basaran O, Bilginer Y, Ozen S. *Semin Arthritis Rheum* 2021 Apr 19; 51(3): 559-564. 10.1016/j.semarthrit.2021.04.009.

Since the first description of deficiency of adenosine deaminase 2 (DADA2) in 2014, the clinical approach to children with polyarteritis nodosa (PAN) has undergone a paradigm shift. Cuceoglu et al. present a detailed critique of pediatric PAN and DADA2. The authors report on 28 publications that described 613 pediatric patients with PAN and 26 publications that described 207 pediatric patients with DADA2. It was found that while children with DADA2 had more frequent involvement of nervous, gastrointestinal and cardiac systems, testicular involvement and constitutional symptoms were more prominent in children with PAN. In their own cohort of 34 PAN and 18 DADA2 children, the authors noted that DADA2 patients had a younger age at onset with history of consanguinity in parents and clinical features of livedo reticularis, stroke, lymphopenia and hypogammaglobulinemia. PAN, on the other hand, was characterized by panniculitis and thrombocytosis. It is important to differentiate these conditions as treatment modalities are completely different - anti-tumor necrosis agents in DADA2, and corticosteroids (in conjunction with cyclophosphamide/azathioprine) in PAN. This is an important study for pediatric rheumatologists.

8 | GENETIC AND IMMUNOLOGIC FINDINGS IN CHILDREN WITH RECURRENT APHTHOUS STOMATITIS WITH SYSTEMIC INFLAMMATION

Girardelli M, Valencic E, Moressa V, Margagliotta R, Tesser A, Pastore S, Spadola O, Athanasakis E, Severini GM, Taddio A, Tommasini A. *Pediatr Rheumatol Online J* 2021 May 10; 19(1): 70. 10.1186/s12969-021-00552-y.

Although recurrent aphthous stomatitis (RAS) is usually a benign and self-limiting entity in children, it may at times, be associated with inflammatory diseases such as Behçet's disease (BD), inflammatory bowel disease and SLE. Moreover, cases of RAS with very early age at onset may be associated with monogenic defects. In this single-center study from Italy, Girardelli et al. enrolled 15 patients with RAS (below 18 years of age) who had signs of systemic inflammation. The patients were subjected to lymphocyte subset analysis, gene sequencing and interferon scoring. Clinical diagnosis of BD, incomplete BD, BD/SLE overlap and SLE was made in 8, 5, 1 and 1 patients respectively. Immunological investigations showed increased proportion of natural killer cells (23%) and reduced B cells (5%) in 1 patient. Pathogenic variants identified on genetic testing were *STAT1* gain of function mutation (GOF), *TNFAIP3* mutation (A20 haploinsufficiency), *DNASE1L3* and *PTPN22*. One patient with *TNFAIP3*, 2 patients with *STAT1* GOF and 3 patients without any genetic defect had high interferon scores. This study shows that a subset of children with RAS may warrant detailed genetic and immunological analyses as this may impact therapeutic decision making.

9 | CLINICAL SIGNIFICANCE OF INTERLEUKIN-18 FOR THE DIAGNOSIS AND PREDICTION OF DISEASE COURSE IN SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS

Mizuta M, Shimizu M, Inoue N, Ikawa Y, Nakagishi Y, Yasuoka R, Iwata N, Yachie A. *Rheumatology (Oxford)* 2021 May 14; 60(5): 2421-2426. 10.1093/rheumatology/keaa634.

Systemic juvenile idiopathic arthritis (s-JIA) is an inflammatory disorder characterized by quotidian fever, evanescent rashes, generalized lymphadenopathy, hepatosplenomegaly and serositis. Arthritis may or may not be a part of initial presentation. Although its etiology is not known, proinflammatory cytokines (eg, interleukin [IL]-1, IL-6 and IL-18) have been shown to have an important role in pathogenesis of s-JIA. In this prospective study, Mizuta et al. have investigated the role of IL-18 as a marker for diagnosis of s-JIA and for predicting its course. The authors assayed serum IL-18 levels in 116 patients with s-JIA, 151 with other diseases and 20 controls. A cut-off level of 4800 pg/mL was found to be predictive of a diagnosis of s-JIA. While a steady decline of serum IL-18 level was seen during remission in patients with monocyclic course, patients with chronic course showed persistently raised IL-18 levels even during remission. Serum IL-18 levels correlated well with flares and remissions in children with polycyclic course. IL-18 levels of ≤ 595 pg/mL correlated well with disease remission. This study suggests that serum IL-18 may be a useful biomarker for monitoring disease activity and predicting remission in children with s-JIA. This is a landmark study that is likely to be referred to for clinical decision making.

10 | BONE MINERAL DENSITY AND EXPLANATORY FACTORS IN CHILDREN AND ADULTS WITH JUVENILE DERMATOMYOSITIS AT LONG TERM FOLLOW-UP: A CROSS SECTIONAL STUDY

Marstein HS, Godang K, Flato B, Sjaastad I, Bollerslev J, Sanner H. *Pediatr Rheumatol Online J* 2021 Apr 26; 19(1): 56. 10.1186/s12969-021-00543-z.

Juvenile dermatomyositis (JDM) is the commonest inflammatory myopathy in children. It can adversely impact bone health in the long run. In this cross-sectional study from Norway, Marstein et al. compared bone mineral density (BMD) in 59 patients with JDM with

matched controls. The authors also evaluated bone turnover markers in context of BMD. It was found that BMD Z-scores (<−1 *SD*) were reduced in all patients. The Z-scores correlated negatively with increased duration of prednisolone use during follow-up, high inflammatory markers and elevated interferon gamma-induced protein 10 (IP-10). While the adverse effects of steroids on BMD are well known, Marstein et al. have shown that high inflammatory markers and elevated interferon gamma-induced protein 10 also independently impact bone density. This aspect may be overlooked in clinical practice, especially when steroids have been discontinued in JDM.

11 | RUXOLITINIB TREATMENT PERMITS LOWER CUMULATIVE GLUCOCORTICOID DOSING IN CHILDREN WITH SECONDARY HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

Chi Y, Liu R, Zhou ZX, Shi XD, Ding YC, Li JG. *Pediatr Rheumatol Online J* 2021 Apr 1; 19(1): 49. 10.1186/s12969-021-00534-0.

Hemophagocytic lymphohistiocytosis (HLH) is a severe, life-threatening disorder characterized by uncontrolled proliferation of histiocytes leading to systemic inflammatory responses. While genetic defects are the major causes of primary HLH, secondary HLH is associated with infection, connective tissue disease and malignancy. Ruxolitinib, a Janus-associated kinase 1/2 inhibitor, has been shown to improve survival in mice models with secondary HLH. In this retrospective study, Chi et al. analyzed 11 children with secondary HLH who received ruxolitinib (group R) and compared the results with 11 age-matched controls with HLH who underwent conventional treatment (group C). Indications for ruxolitinib included persistence of fever even after methylprednisolone pulses and intravenous immunoglobulin (3 patients) and major organ involvement despite conventional treatment with dexamethasone, etoposide and cyclosporine (4 patients). In 4 patients with HLH, ruxolitinib alone was used as primary therapy. Group R patients showed more rapid reduction of body temperature and lower glucocorticoid dosage requirement in comparison to group C. There was no adverse drug reaction noted with ruxolitinib during treatment or on follow-up over 2.5 years. Ruxolitinib can be an effective alternative in controlling fever and inflammation in patients with secondary HLH and it has also been shown to be effective as a glucocorticoid sparing agent. Although this novel therapeutic agent may impact clinical management in HLH, further studies with larger sample size would be necessary.

12 | IGG4-RELATED DISEASE IN PEDIATRIC PATIENTS: A SINGLE-CENTER EXPERIENCE

Akca Ü, Atalay E, Cüceoğlu M, Şener S, Balık Z, Başaran Ö, Batu E, Karadag Ö, Özen S, Bilginer Y. *Rheumatol Int* 2021 May 12. 10.1007/s00296-021-04885-5.

Immunoglobulin G4-related disease (IgG4-RD) is a rare, chronic inflammatory disorder that may affect virtually any organ system. In this retrospective study from Ankara, Turkey, Akca et al. evaluated 8 children (including 4 girls) with IgG4-RD. All patients had varied clinical manifestations with the most common being ophthalmic involvement (n=6), followed by lymphadenopathy (n=1), sialadenitis, pancreatitis, ulcerative colitis, and pulmonary manifestations (n=1). Serum IgG4 was increased in only 3 patients. The predominant histopathological feature (n=7) was fibrosis and lymphoplasmacytic infiltrates. The authors also alluded to various treatment regimens used in these children – largely corticosteroids, followed by steroid-sparing agents in the form of azathioprine, methotrexate and rituximab. In one case of severe orbital disease, radiotherapy was used as a last resort as she did not respond to conventional therapy. This is an important study on IgG4-RD and its multifaceted nature and prompts increased awareness on the subject.

13 | WHOLE-BODY MRI QUANTIFICATION FOR ASSESSMENT OF BONE LESIONS IN CHRONIC NONBACTERIAL OSTEOMYELITIS PATIENTS TREATED WITH PAMIDRONATE: A PREVALENCE, REPRODUCIBILITY, AND RESPONSIVENESS STUDY

Panwar J, Tolend M, Lim L, Tse SM, Doria AS, Laxer RM, Stimec J. *J Rheumatol* 2021 May 1; 48(5): 751-759. 10.3899/jrheum.200329.

Chronic nonbacterial osteomyelitis (CNO) is an uncommon autoinflammatory syndrome characterized by tender osteitis. Whole-body magnetic resonance imaging (WB-MRI) is the preferred imaging modality for diagnosing and following-up patients with CNO. However, there is paucity of literature with regard to objective assessment of treatment response to therapy using WB-MRI. In this single-center study involving 32 children with CNO, 88 WB-MRI scans were analyzed by 2 radiologists who were blinded to the clinical details. Lesions were scored before and after pamidronate therapy. The authors noted good response to pamidronate, especially for vertebral lesions. They also observed that WB-MRI has a high degree of reliability in objectively quantifying and assessing response to treatment and can be used in monitoring disease activity. This is an important study for pediatric rheumatologists.

ORCID

Surjit Singh https://orcid.org/0000-0002-6716-1883

How to cite this article: Barman P, Sil A, Singh S. Recent advances in pediatric rheumatology: April to June 2021. *Int J Rheum Dis*. 2021;24:1321–1324. https://doi.org/10.1111/1756-185X.14212

Received: 5 July 2021 | Revised: 20 July 2021 | Accepted: 12 August 2021

DOI: 10.1111/1756-185X.14208

APLAR GRAND ROUND CASE

International Journal of Rheumatic Diseases | WILEY

Kawasaki disease with dilatation of the common bile duct: A case report and review of literature

Atsushi Morita[1] | Kazuo Imagawa[1,2] | Takumi Ishiodori[1] | Manabu Tagawa[1,2] | Hidetoshi Takada[1,2]

[1]Department of Pediatrics, University of Tsukuba Hospital, Tsukuba, Japan

[2]Department of Child Health, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan

Correspondence
Kazuo Imagawa, Department of Pediatrics, University of Tsukuba Hospital, 2-1-1 Amakubo, Tsukuba, Ibaraki 305-8576, Japan.
Email: imagawa-tuk@md.tsukuba.ac.jp

Funding information
This work is supported by the Japan Society for the Promotion of Science, under Grant Number 17K16240 and 20K08251 to Kazuo Imagawa.

Abstract

Background: Kawasaki disease (KD) is a syndrome that results in acute systemic vasculitis and is a major cause of acquired heart disease in developed countries. KD is diagnosed based on certain characteristic symptoms and echocardiogram results. It has been reported that abdominal ultrasound is of value in supporting the diagnosis of KD. Nevertheless, abdominal ultrasound is not a routine procedure in KD. Moreover, dilatation of the common bile duct (CBD) has been rarely reported in previous cases.

Case presentation: A 4-year-old boy presented with fever and markedly high transaminase level (aspartate aminotransferase, 5323 U/L; alanine aminotransferase, 1554 U/L). The patient was diagnosed as having KD based on characteristic symptoms and echocardiogram findings. Ultrasound revealed dilatation of the CBD as well as cervical lymphadenopathy resembling a cluster of grapes, thickening of the gallbladder wall, and increased periportal echogenicity throughout the liver parenchyma. The patient received initial treatment with intravenous immunoglobulin at day 4 of fever and second-line treatment with intravenous immunoglobulin and prednisolone because of recurrent fever on day 6. Dilatation of the CBD was improved from 6.6 mm on day 4 to 3.1 mm on day 8. Although re-dilatation was observed, it gradually diminished and normalized (4.3 mm on day 28, 4.0 mm on day 63, 3.3 mm on day 105, and 2.8 mm on day 182).

Conclusion: This case highlights the usefulness of abdominal ultrasound and the importance of considering dilatation of the CBD as one of the complications of KD.

KEYWORDS

abdominal ultrasound, cholangitis, cholecystitis, cytokine, hepatobiliary abnormalities, interleukin-6, ultrasonography

1 | INTRODUCTION

Kawasaki disease (KD) is a syndrome that results in acute systemic vasculitis, affecting mainly infants and children, and is a major cause of acquired heart disease in developed countries.[1] Although KD was first described by Tomisaku Kawasaki in 1967,[2-4] the cause of the disease is still unknown. Therefore, to date, KD is diagnosed based on certain characteristic symptoms and echocardiogram results.[5]

It has been reported that neck and abdominal ultrasound is of value in supporting the diagnosis of KD; for instance, characteristics such as cervical lymphadenopathy resembling a cluster of grapes,[6] severe dilatation of the gallbladder—called hydrops of the

© 2021 Asia Pacific League of Associations for Rheumatology and John Wiley & Sons Australia, Ltd

gallbladder,[7] thickening of gallbladder wall,[8] and segmental bowel-wall thickening[9] support the diagnosis of KD. Nevertheless, abdominal ultrasound is not a routine procedure in KD. Moreover, dilatation of the common bile duct (CBD) has been rarely reported.

Herein, we report the case of a 4-year-old boy with KD, and with various ultrasound findings including dilatation of the CBD during the acute phase of the disease.

2 | CASE PRESENTATION

A 4-year-old boy was admitted to our hospital because of markedly high levels of transaminase. The patient had been well until 3 days before admission, when a runny nose and fever were noted. On the day of symptom onset, the patient was evaluated by his primary-care pediatrician and was diagnosed as having bronchitis. After which, the patient experienced nausea and vomiting and was taken to the emergency department at another hospital. At the other hospital, the patient did not appear ill but had redness in the pharynx and cervical lymphadenopathy. The blood test results showed high transaminase levels, after which he was transferred to our hospital.

On arrival, the patient appeared ill and was febrile, with a body temperature of 40.4°C. His blood pressure was 97/48 mm Hg, pulse rate was 148 beats per minute, respiratory rate was 28 breaths per minute, with oxygen saturation of 96% while breathing ambient air. Physical examination revealed bilateral conjunctival congestion, erythema around the navel, reddening and indurative edema of palms, and cervical lymphadenopathy. There was no evidence of reddening of the lips, strawberry tongue, and redness at the site of bacille Calmette-Guèrin inoculation. The blood test results showed markedly high level of transaminase with acute inflammatory response (white blood cell count, 16 400/μL; erythrocyte sedimentation rate, 50 mm/h; C-reactive protein, 157 mg/L; aspartate aminotransferase, 5323 U/L; alanine aminotransferase, 1554 U/L; total bilirubin, 1.5 mg/dL; γ-glutamyl transpeptidase, 149 U/L; and total bile acid, 381.1 μmol/L). There was no evidence of viral hepatitis (negative results of hepatitis A virus antibody, hepatitis B surface antigen, hepatitis C virus antibody, and polymerase chain reaction for Epstein-Barr virus, cytomegalovirus, herpes simplex viruses 1 and 2, and human herpes virus 6) or autoimmune hepatitis. No bacterial growth was detected in any of the cultures. Some cytokines were measured using cytokine bead assay (BD™ CBA kit, Becton Dickinson, Franklin Lakes, NJ, USA); interleukin-6 (IL-6) level increased to 87.7 pg/mL (reference value <7.0 pg/mL), IL-10 increased to 32.0 pg/mL (reference value <5.0 pg/mL), whereas IL-1β and tumor necrosis factor-α levels were normal. Although the echocardiogram showed normal cardiac function with no evidence of valve regurgitation, slight dilatation of the left main trunk was observed (Figure 1). Ultrasonographic evaluation of cervical lymph nodes revealed multiple hypoechoic-enlarged nodes, which resembled a cluster of grapes (Figure 2A). An abdominal ultrasound showed thickening of the gallbladder wall, increased periportal echogenicity throughout the liver parenchyma, and dilatation of the CBD with a maximum diameter of 6.6 mm at the intrapancreatic region (4-year-old standard value, 2.3 mm, upper limit, 3.7 mm)[10] (Figure 2B-D). No evidence of biliary calculus and pancreatitis was observed.

After admission, intravenous administration of cefotaxime was initiated; however, it was ineffective. On the next day of hospitalization (day 4 of fever), reddening of lips was observed and the patient was diagnosed with KD based on the presence of five principal symptoms.[5] Intravenous immunoglobulin (2 g/kg) was administered as initial therapy. Oral aspirin was not administered because of the high transaminase level. A Kobayashi score of 8 suggested that the patient was at high risk of intravenous immunoglobulin resistance.[11] Viral hepatitis could not be completely ruled out at this point; therefore, steroid administration was avoided. The patient's fever rapidly decreased with the initiation of treatment, and transaminase level gradually improved. However, the patient's fever relapsed on day 6, so intravenous immunoglobulin (2 g/kg) and intravenous prednisolone (2 mg/kg/day) were administered as second-line therapy. Flurbiprofen, which is used as an alternative to oral aspirin in Japan when high transaminase levels are observed,[12] was also administered

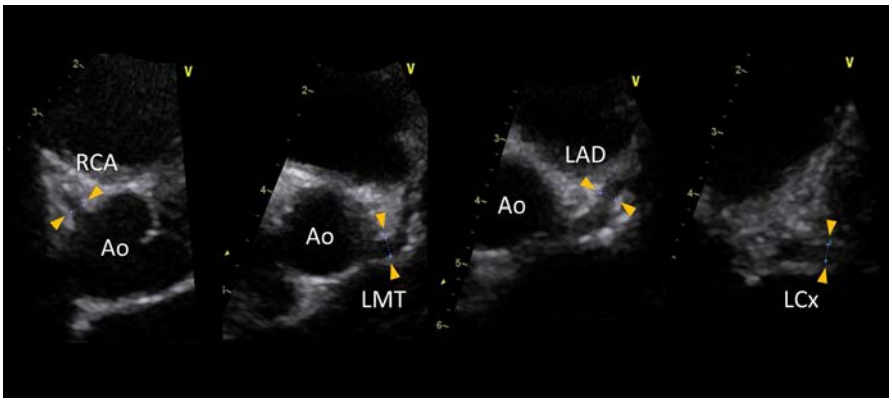

FIGURE 1 Echocardiogram of the patient, performed on day 4. Slight dilatation of the LMT was recognized. No evidence of valve regurgitation and cardiac dysfunction was observed. Each measured value was as follows: RCA (seg1): 2.2 mm (Z = 0.75), LMT (seg5): 3.4 mm (Z = 2.91), LAD (seg6): 2.6 mm (Z = 1.90), LCx (seg11): 2.5 mm (Z = 2.08). Abbreviations: Ao, aorta; LAD, left anterior descending artery; LCx, left circumflex artery; LMT, left main trunk; RCA, right coronary artery; Z, Z score

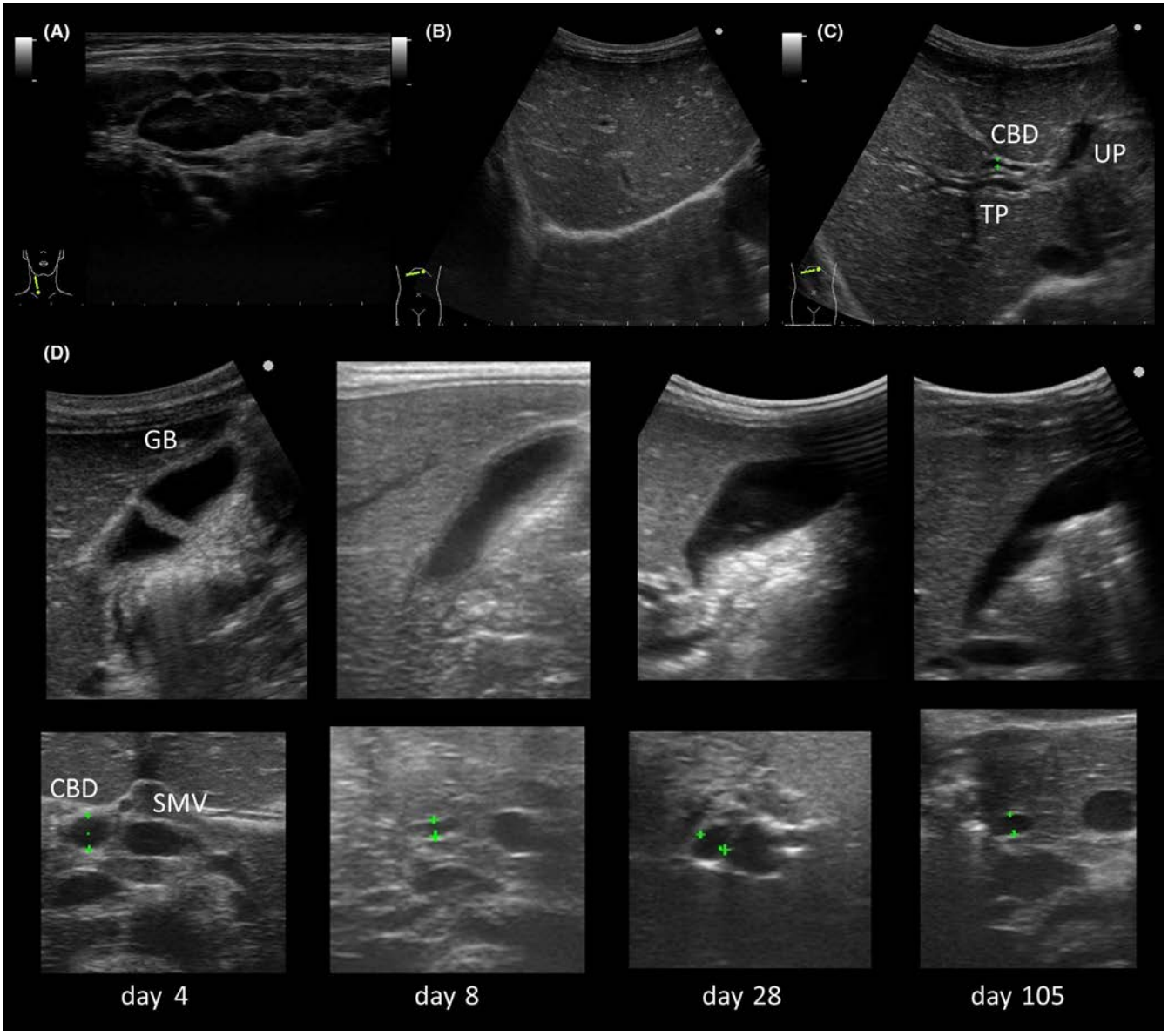

FIGURE 2 Neck and abdominal ultrasound and shift of maximum diameter of the common bile duct, performed on day 4. Neck ultrasound showed multiple hypoechoic-enlarged nodes which resembled a cluster of grapes (A). Abdominal ultrasound showed increased periportal echogenicity throughout the liver parenchyma (B), dilatation of common bile duct (C, D) and thickening of gallbladder wall (D). The maximum diameter of the common bile duct shifted as follows: day 4: 6.6 mm, day 8: 3.1 mm, day 28: 4.3 mm, day 63: 4.0 mm, day 105: 3.3 mm, and day 182: 2.8 mm (4-year-old standard value is 2.3 mm, upper limit is 3.7 mm).[9] All tests were performed in a fasting state. Thickening of the gallbladder wall remained on day 8, but it improved after day 28. Abbreviations: CBD, common bile duct; GB, gallbladder; SMV, superior mesenteric vein; TP, transverse portion of the portal vein; UP, umbilical portion of the portal vein

because the transaminase level remained high (aspartate aminotransferase, 171 IU/L; alanine aminotransferase, 468 IU/L). The patient maintained a defervesced state after second-line therapy. Oral medication was switched from flurbiprofen to oral aspirin (5 mg/kg/day) on day 10 (aspartate aminotransferase, 45 IU/L; alanine aminotransferase, 171 IU/L), and prednisolone administration was simultaneously changed from intravenous to oral because the patient's C-reactive protein level normalized. Following which, prednisolone administration was tapered in 5-day steps—from 2 mg/kg/day to 1 mg/kg/day to 0.5 mg/kg/day. Membranous desquamation appeared on the fingertips on day 15.

The maximum diameter of the CBD reduced from 6.6 mm on day 4 to 3.1 mm on day 8. Although re-dilatation was observed, it gradually diminished and normalized (4.3 mm on day 28, 4.0 mm on day 63, 3.3 mm on day 105, and 2.8 mm on day 182). The thickening of the gallbladder wall was persistent on day 8; however, it improved after day 28. All abdominal ultrasound tests were performed in a fasting state (Figure 2D). No exacerbation of coronary lesions was observed.

3 | DISCUSSION

Our patient was diagnosed with acute KD and showed dilatation of the CBD. Very few reports are available on biliary dilatation in KD patients (Table 1). To the best of our knowledge, only one Japanese study has previously reported on a case of acute-phase KD (only available in the Japanese literature),[13] and our case is the first of its kind to be reported in an international journal.

A Japanese report evaluated the hepatobiliary system using abdominal ultrasound in 68 patients with KD every 3 or 4 days.[13] Of the 68 patients, 20 had dilatation of the gallbladder, and among them, four patients had thickening of the gallbladder wall and three had dilatation of the CBD in acute phase. All three patients with dilatation of the CBD had high transaminase level and cholestasis. Dilatation of the CBD regressed spontaneously in 2 weeks to 1 month (Table 1, cases A1-A3). In the present case, the peak value of alanine aminotransferase and the maximum diameter of the CBD were most severe, and took longer to normalize.

In the subacute phase, which is also rare, a total of three cases of biliary dilatation have been reported.[14,15] Petersen et al[14] reported on a 10-year-old with painless jaundice and elevated amylase level, along with dilatation of the CBD and hydrops of the gallbladder. On endoscopic retrograde cholangiopancreatography, the patient had string-like stenosis in the pre-papillary CBD (Table 1, case S1). Cherry et al reported two cases; one was of a 6-year-old boy who experienced recurrent abdominal pain, jaundice, and persistent elevation of transaminases with dilatation of the CBD. On computed tomography, the patient had CBD stenosis at the level of the pancreatic head (Table 1, case S2). The other case was of a 3-year-old boy who developed pancreatitis. On magnetic resonance cholangiopancreatography, the patient had dilatation of the CBD with tapering near the ampulla of Vater, consistent with stenosis (Table 1, case S3).[15] One of the three cases underwent CBD stent placement, the others spontaneously improved. It is not described whether dilatation of the CBD in the subacute phase was also present in the acute phase. Although abdominal ultrasound as well as computed tomography, magnetic resonance cholangiopancreatography, and endoscopic retrograde cholangiopancreatography are not routine procedures for KD, past cases along with the present case suggest that the presentation of the CBD dilatation in KD may be quite latent if not investigated thoroughly.

Our patient also showed increased levels of transaminase and γ-glutamyl transpeptidase with thickening of the gallbladder wall, increased periportal echogenicity throughout the liver parenchyma, along with dilatation of the CBD detected by abdominal ultrasound, which suggested cholecystitis and intrahepatic/extrahepatic cholangitis. Although there have been few pathological investigations that consider hepatobiliary abnormalities in KD, it has been reported that patients with dilatation of the gallbladder and thickening of the gallbladder wall showed neutrophil infiltration around the gallbladder wall, cystic duct mucosa, and bile duct epithelial cells.[16,17] Actually, 62.7% of patients with acute phase KD show an increased γ-glutamyl transpeptidase level and 40.3% show an increase in alanine aminotransferase level.[18] These findings indicate that KD may lead to cholecystitis and intrahepatic/extrahepatic cholangitis. The relationship between these pathological conditions and ultrasound findings remains unclear. However, it is presumed that inflammation of the cystic duct results in obstruction, causing hydrops of the gallbladder.[13] In addition, our case suggests that thickening of the gallbladder wall, increased periportal echogenicity throughout the liver parenchyma, and dilatation of the CBD also relate to inflammation and subsequent edema and obstruction at each location (Figure 3).

Our patient demonstrated IL-6 elevation detected using a cytokine bead assay (BD™ CBA kit). Interleukin-6 was discovered as a hepatocyte-stimulating factor 2 induced in acute liver inflammation.[19] It reduces gene expression of excretory transporters such

TABLE 1 Cases of CBD dilatation in Kawasaki disease

Case	Age (year)	Period of dilatation (day)	Peak value				Maximum diameter of CBD (mm)	Reference
			ALT (U/mL)	GGT (U/mL)	T-Bil (mf/dL)	D-Bil (mg/dL)		
Cases of dilatation of CBD in acute phase								
A1	5	9-33	120	46	2.5	1.7	5.0	13
A2	3	6-30	226	220	6.7	6.2	3.0	13
A3	2	6-14	348	109	5.2	4.5	3.0	13
A4	4	4-63	1554	149	1.5	0.9	6.6	Present case
Case of dilatation of CBD in subacute phase								
S1	10	19-67	n/a	n/a	8.7	n/a	n/a	14
S2	6	37-97[a]	601	364	8.7	6.3	9.0	15
S3	3	21-51	165	240	6.0	3.8	n/a	15

Abbreviations: ALT, alanine aminotransferase; CBD, common bile duct; D-Bil, direct bilirubin; GGT, γ-glutamyl transpeptidase; T-Bil, total bilirubin.
[a]CBD stent was placed on day 37 and removed 2 months after the placement.

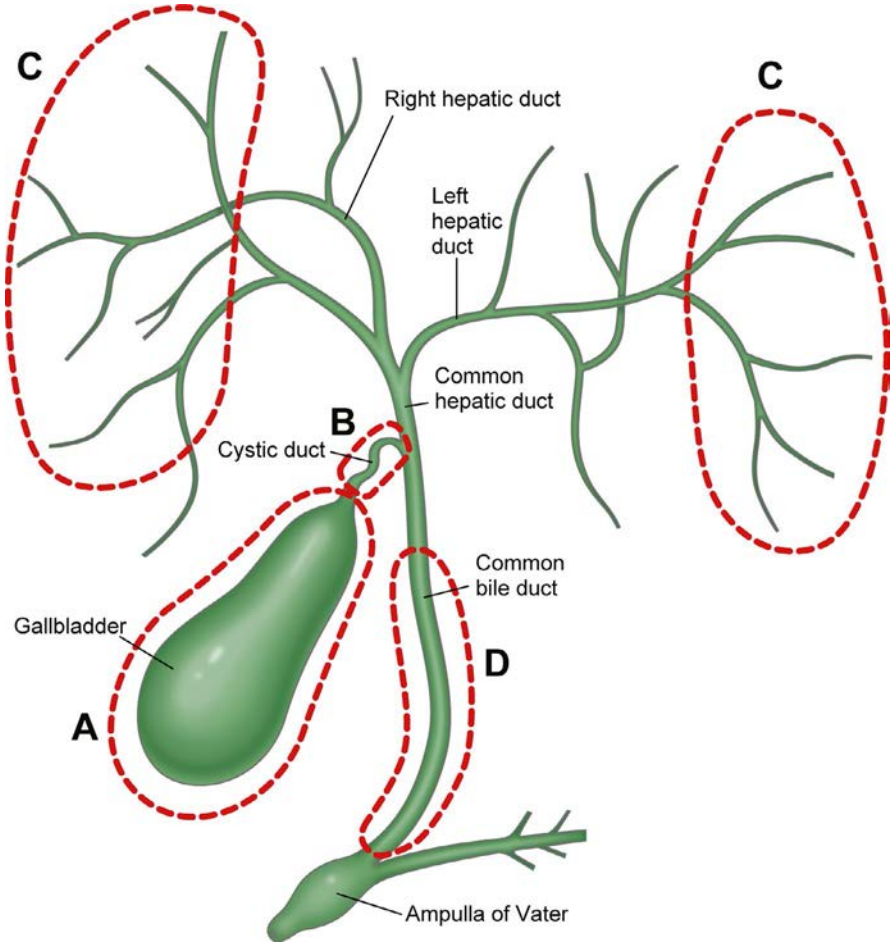

FIGURE 3 Hepatobiliary abnormalities and abdominal ultrasound findings in Kawasaki disease. All abdominal ultrasound findings are presumed due to inflammation and subsequent edema and obstruction at each location. (A) Thickening of the gallbladder wall. Gallbladder swelling due to decreased contractility. (B) Hydrops of the gallbladder due to obstruction of cystic duct. (C) Increased periportal echogenicity throughout the liver parenchyma. (D) Dilatation of the common bile duct

as the bile salt export pump ABCB11 and multidrug-resistance-associated protein 2 in primary human hepatocyte cell lines,[20] which impair the secretion of bile acids into the bile ducts. Bile acids were also elevated in our patient. Elevated IL-6 may have contributed to cholestasis and led to hepatobiliary abnormalities in KD.

4 | CONCLUSION

This case of a 4-year-old with dilatation of the CBD in acute KD highlights the usefulness of abdominal ultrasound and the importance of considering dilatation of the CBD as one of the complications of KD. Abdominal ultrasound is not a routine procedure in KD, so it is possible that CBD dilatation in KD may remain latent if not investigated thoroughly. Further prospective studies to support these findings are warranted.

ACKNOWLEDGEMENTS

We would like to thank Editage (https://www.editage.com/) for editing and reviewing this manuscript for English language.

CONFLICT OF INTEREST

None of the authors have any financial or non-financial competing interests to declare in relation to this manuscript.

AUTHOR CONTRIBUTIONS

AM and KI made substantial contributions to the conception or design of the work. AM and TI contributed to the acquisition, analysis, or interpretation of ultrasound findings for the work.KI and MT contributed to the acquisition, analysis, or interpretation of comprehensive data for the work. AM and KI drafted the work and HT revised the work critically for important intellectual content. Final approval of the version to be published was provided by AM, KI, TI, MT, and HT.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the ethics committee of the University of Tsukuba Hospital. Written informed consent was obtained from the patient's parents.

CONSENT FOR PUBLICATION

Written informed consent was obtained from the patient's parents.

ORCID

Kazuo Imagawa https://orcid.org/0000-0002-2512-6043

REFERENCES

1. McCrindle BW, Rowley AH, Newburger JW, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a

scientific statement for health professionals from the American Heart Association. *Circulation*. 2017;135:e927-e999.
2. Kawasaki T. Acute febrile mucocutaneous syndrome with lymphoid involvement with specific desquamation of the fingers and toes in children. *J Jpn Allergol*. 1967;16:178-222.
3. Kawasaki T, Kosaki F, Okawa S, Shigematsu I, Yanagawa H. A new infantile acute febrile mucocutaneous lymph node syndrome (MLNS) prevailing in Japan. *Pediatrics*. 1974;54:271-276.
4. Kawasaki T, Singh S. Kawasaki disease - the journey over 50 years: 1967–2017. *Int J Rheum Dis*. 2018;21:7-9.
5. Kobayashi T, Ayusawa M, Suzuki H, et al. Revision of diagnostic guidelines for Kawasaki disease (6th revised edition). *Pediatr Int*. 2020;62(10):1135-1138.
6. Tashiro N, Matsubara T, Uchida M, Katayama K, Ichiyama T, Furukawa S. Ultrasonographic evaluation of cervical lymph nodes in Kawasaki disease. *Pediatrics*. 2002;109:E77-E87.
7. Suddleson EA, Reid B, Woolley MM, Takahashi M. Hydrops of the gallbladder associated with Kawasaki syndrome. *J Pediatr Surg*. 1987;22:956-959.
8. Bader-Meunier B, Hadchouel M, Fabre M, Arnoud MD, Dommergues JP. Intrahepatic bile duct damage in children with Kawasaki disease. *J Pediatr*. 1992;120:750-752.
9. Maurer K, Unsinn KM, Waltner-Romen M, Geiger R, Gassner I. Segmental bowel-wall thickening on abdominal ultrasonography: an additional diagnostic sign in Kawasaki disease. *Pediatr Radiol*. 2008;38:1013-1016.
10. Hamada Y, Ando H, Kamisawa T, et al. Diagnostic criteria for congenital biliary dilatation 2015. *J Hepatobiliary Pancreat Sci*. 2016;23:342-346.
11. Kobayashi T, Inoue Y, Takeuchi K, et al. Prediction of intravenous immunoglobulin unresponsiveness in patients with Kawasaki disease. *Circulation*. 2006;113:2606-2612.
12. Tanoshima R, Hashimoto R, Suzuki T, Ishiguro A, Kobayashi T. Effectiveness of antiplatelet therapy for Kawasaki disease: a systematic review. *Eur J Pediatr*. 2019;178:947-955.
13. Ka K, Maeda K. The Hepatobiliary system in Kawasaki disease (in Japanese). *J Jpn Pediatr Soc*. 1989;93:1852-1859.
14. Petersen C, Mildenberger H, Jablonski M. Painless cholestasis in Kawasaki syndrome-associated with pancreatitis. *Pediatr Surg Int*. 1994;9:118-119.
15. Cherry R, Naon H, Cohen H, Takahashi M, Kaminsky C, Mason W. Common bile duct stenosis and pancreatitis in Kawasaki disease: two cases and a review of the literature. *Pediatr Infect Dis J*. 2010;29:571-573.
16. Mercer S, Carpenter B. Surgical complications of Kawasaki disease. *J Pediatr Surg*. 1981;16:444-448.
17. Edwards KM, Glick AD, Greene HL. Intrahepatic cholangitis associated with mucocutaneous lymph node syndrome. *J Pediatr Gastroenterol Nutr*. 1985;4:140-142.
18. Tremoulet AH, Jain S, Chandrasekar D, Sun X, Sato Y, Burns JC. Evolution of laboratory values in patients with Kawasaki disease. *Pediatr Infect Dis J*. 2011;30:1022-1026.
19. Gauldie J, Richards C, Harnish D, Lansdorp P, Baumann H. Interferon beta 2/B-cell stimulatory factor type 2 shares identity with monocyte-derived hepatocyte-stimulating factor and regulates the major acute phase protein response in liver cells. *Proc Natl Acad Sci USA*. 1987;84:7251-7255.
20. Diao L, Li N, Brayman TG, Hotz KJ, Lai Y. Regulation of MRP2/ABCC2 and BSEP/ABCB11 expression in sandwich cultured human and rat hepatocytes exposed to inflammatory cytokines TNF-{alpha}, IL-6, and IL-1{beta}. *J Biol Chem*. 2010;285:31185-31192.

How to cite this article: Morita A, Imagawa K, Ishiodori T, Tagawa M, Takada H. Kawasaki disease with dilatation of the common bile duct: A case report and review of literature. *Int J Rheum Dis*. 2021;24:1325–1330. https://doi.org/10.1111/1756-185X.14208

Received: 11 August 2021 | Revised: 26 August 2021 | Accepted: 28 August 2021

DOI: 10.1111/1756-185X.14214

International Journal of Rheumatic Diseases | WILEY

COCHRANE CORNER

What are the benefits and harms of belimumab for patients with systemic lupus erythematosus?: A Cochrane Review summary with commentary

Giovanni Iolascon

University of Campania "Luigi Vanvitelli", Naples, Italy

Correspondence
Giovanni Iolascon, University of Campania "Luigi Vanvitelli", Naples, Italy.
Email: giovanni.iolascon@unicampania.it

Keywords: belimumab, Cochrane Review summary, systemic lupus erythematosus

Cochrane Rehabilitation

http://rehabilitation.cochrane.org

The aim of this commentary is to discuss the published Cochrane Review "Belimumab for systemic lupus erythematosus"[1] by Singh et al.,[a] under the direct supervision of Cochrane Musculoskeletal Group. This Cochrane Corner is produced in agreement with *International Journal of Rheumatic Diseases* by Cochrane Rehabilitation.

1 | BACKGROUND

Systemic lupus erythematosus (SLE) is a multisystemic autoimmune disease associated with significant morbidity and mortality. Genetic, immunological, endocrine, and environmental factors contribute to the etiopathogenesis of SLE.[2] Clinical features of SLE vary from a mild phenotype to a very severe multiorgan involvement, characterizing a life-threatening disease with no cure.[3] Poor functioning and quality of life frequently affect people with SLE, requiring a multidisciplinary approach, that includes specific physical and lifestyle measures, particularly to avoid flare-ups of the disease.[4]

Furthermore, several drugs such as glucocorticoids (GCs), antimalarials or cytotoxic drugs are largely used to treat mild to severe manifestations in this disease, often causing significant adverse events.[4] To date, new therapeutic strategies to treat the acute phase of SLE are available, such as anifrolumab and belimumab. This latter was the first biologic disease-modifying anti-rheumatic drug (DMARD) approved for SLE. Belimumab is a human monoclonal antibody directed against cytokine B-lymphocyte stimulator (BLyS).[5]

2 | BELIMUMAB FOR SYSTEMIC LUPUS ERYTHEMATOSUS

(Jasvinder A Singh, Nipam P Shah, Amy S Mudano, 2021).

2.1 | What is the aim of this Cochrane Review?

The aim of this Cochrane Review was to assess the benefits and harms of belimumab (alone or in combination with other drugs) in SLE.

2.2 | What was studied in the Cochrane Review?

The population addressed in this review was people with SLE according to the American College of Rheumatology classification criteria.[6] The intervention studied was belimumab alone or in

[a]This summary is based on a Cochrane Review previously published in the Cochrane Database of Systematic Reviews 2021, Issue 2, Art. No.:CD010668, DOI: 10.1002/14651858.CD010668.pub2 (see www.cochranelibrary.com for information). Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and Cochrane Database of Systematic Reviews should be consulted for the most recent version of the review.

The views expressed in the summary with commentary are those of the Cochrane Corner author and do not represent the Cochrane Library or Wiley.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.
© 2021 The Authors. *International Journal of Rheumatic Diseases* published by Asia Pacific League of Associations for Rheumatology and John Wiley & Sons Australia, Ltd.

combination with other immunosuppressive drugs or another biologic, compared to placebo or other DMARDs, DMARD combinations, or biologics.

The major outcomes investigated were: intensity of disease assessed through the reduction of at least 4 points on Safety of Estrogen in Lupus National Assessment (SELENA) - Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score, change in health-related quality of life (HR-QoL), glucocorticoid sparing (prednisone dose reduced by 50% or more), participants with at least 1 serious adverse event (AE) or serious infection, withdrawals due to AEs and deaths.

2.3 | What was the search methodology and search date of the Cochrane Review?

The Information Specialist searched for studies that had been published from inception to 25 September 2019. The search methods for identification of studies were: Cochrane Central Register of Controlled Trials (CENTRAL; August 2019) in the Cochrane Library; MEDLINE Ovid; Embase Classic +Embase; CINAHL (Cumulative Index to Nursing and Allied Health Literature); Web of Science; and the World Health Organization (WHO) International Clinical Trials Registry Platform.

2.4 | What are the main results of the Cochrane Review?

The review included 6 randomized controlled trials (RCTs) involving a total of 2917 people, aged from 22 to 80 years and the majority were women. The risk of bias was generally low except for attrition bias, which was high in two-thirds of the studies. All RCTs compared belimumab to placebo. Some studies contained multiple dose comparisons and various follow-up lengths (from 84 days to 76 weeks).

This Cochrane systematic review showed that people on belimumab 10 mg/kg (Food and Drug Administration [FDA]-approved dose) versus those receiving placebo experienced:

- statistically significant reduction in SELENA - SLEDAI score (at least 4 points), with an absolute risk difference of 13% better in the treated group (95% confidence interval [CI] 8%-17%) (risk ratio [RR] 1.33, 95% CI 1.22-1.45 [high-certainty evidence]) (4 studies with 2666 participants)
- no clinically meaningful difference in terms of HR-QoL, with a mean difference of 1.6 points, 95% CI 0.30-2.90 (moderate-certainty evidence) (2 studies with 801 participants)
- statistically significant reduction of GC dose (at least 50%), with a RR of 1.59 (95% CI 1.17-2.15); 11% better absolute difference (95% CI 4%-18%) (high-certainty evidence) (2 studies with 537 participants)
- no significant difference in the number of participants who experienced serious AEs with an absolute risk difference of 2% less (RR 0.87, 95% CI: 0.68-1.11) (5 studies with 2890 participants) or deaths (0% of absolute risk difference; Peto odds ratio 1.15, 95% CI 0.41-3.25) (6 studies with 2917 participants) (low-certainty evidence), as well as for serious infections (0% of absolute risk difference; RR 1.01, 95% CI: 0.66-1.54) (4 studies with 2185 participants) and numbers of AEs that caused people to withdraw (1% of absolute risk difference; RR 0.82, 95% CI: 0.63-1.07) (5 studies with 2890 participants) (moderate-certainty evidence).

2.5 | What did the authors conclude?

Compared to placebo, belimumab (10 mg/kg) probably reduces SLE intensity and glucocorticoid doses, while data about QoL and safety (AE, infections, withdrawals due to AE and death) are inconclusive.

3 | WHAT ARE THE IMPLICATIONS OF THE COCHRANE EVIDENCE FOR PRACTICE IN RHEUMATOLOGY?

SLE is a disabling chronic autoimmune disease with high clinical variability and mortality.[7] The fluctuating disease course characterized by sudden flares interspersed with a period of remission represents a huge challenge to the clinician.[8] For patients affected by SLE, the pharmacological control of disease activity is the main goal, even if this target is not so commonly obtained in daily practice.[9] In this scenario, the biologic therapies, particularly belimumab, are showing promising results in the clinical management of SLE.[9] Based on Cochrane Systematic Review evidence, belimumab showed benefits in terms of modifying SLE disease activity. Moreover, this drug promotes GC sparing, which might further avoid bone and muscle impairments due to the chronic use of high-dose GC.[10] However, its safety profile is still unclear, also due to the short-term duration of the included trials, and therefore long-term studies should clarify this unmet outcome. Moreover, investigating the efficacy and/or effectiveness of belimumab versus an active comparator should be an interesting topic for both research and clinical practice.

ACKNOWLEDGEMENTS

The author thanks Cochrane Rehabilitation and Cochrane Musculoskeletal Group for reviewing the contents of the Cochrane Corner.

CONFLICT OF INTEREST

The author declares no conflicts of interest.

ORCID

Giovanni Iolascon https://orcid.org/0000-0002-0976-925X

REFERENCES

1. Singh JA, Shah NP, Mudano AS. Belimumab for systemic lupus erythematosus. *Cochrane Database Syst Rev*. 2021;2(2):CD010668. https://doi.org/10.1002/14651858.CD010668.pub2

2. Justiz Vaillant AA, Goyal A, Bansal P, et al. *Systemic Lupus Erythematosus. [Updated 2020 Dec 30]*. In: StatPearls [Internet]. StatPearls Publishing; 2021 Jan-. https://www.ncbi.nlm.nih.gov/books/NBK535405/
3. Kiriakidou M, Ching CL. Systemic lupus erythematosus. *Ann Intern Med*. 2020;172(11):ITC81-ITC96. https://doi.org/10.7326/AITC202006020
4. Fanouriakis A, Kostopoulou M, Alunno A, et al. 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus. *Ann Rheum Dis*. 2019;78(6):736-745. https://doi.org/10.1136/annrheumdis-2019-215089
5. Parodis I, Axelsson M, Gunnarsson I. Belimumab for systemic lupus erythematosus: a practice-based view. *Lupus*. 2013;22(4):372-380. https://doi.org/10.1177/0961203313476154
6. Aringer M, Costenbader K, Daikh D, et al. 2019 European League Against Rheumatism/American College of Rheumatology Classification Criteria for systemic lupus erythematosus. *Arthritis Rheumatol*. 2019;71(9):1400-1412. https://doi.org/10.1002/art.40930. Epub 2019 Aug 6. PMID: 31385462; PMCID: PMC6827566
7. Kaul A, Gordon C, Crow MK, et al. Systemic lupus erythematosus. *Nat Rev Dis Primers*. 2016;2:16039. doi:https://doi.org/10.1038/nrdp.2016.39
8. Shaikh MF, Jordan N, D'Cruz DP. Systemic lupus erythematosus. *Clin Med (London, England)*. 2017;17(1):78-83. https://doi.org/10.7861/clinmedicine.17-1-78
9. He J, Li Z. An era of biological treatment in systemic lupus erythematosus. *Clin Rheumatol*. 2018;37(1):1-3. https://doi.org/10.1007/s10067-017-3933-x
10. Porta S, Danza A, Arias Saavedra M, et al. Glucocorticoids in systemic lupus erythematosus. Ten questions and some issues. *J Clin Med*. 2020;9(9):2709. https://doi.org/10.3390/jcm9092709

DOI: 10.1111/1756-185X.14190

International Journal of Rheumatic Diseases

WILEY

Your help is needed in the fight against COVID-19: Please contribute to the COVID-19 Global rheumatology alliance registry

The COVID-19 Global Rheumatology Alliance is a global collaboration of rheumatologists, scientists, patients and organisations all committed to addressing the issues in rheumatology created by the COVID-19 global pandemic. To date the alliance has published important data on the effect of COVID-19 infection on outcomes and the effect of rheumatic medications on COVID-19 outcomes.

We currently have 3520 cases from all over the world but we still need to collect many more cases and we need cases from all around the world including the Asia-Pacific region. We are hoping for more cases from the Asia-Pacific region because this is currently under-represented in the registry.

To contribute we ask that you provide details of the case, rheumatic diagnosis details, treatments, and the outcome of the case.

You can join the mailing list for the COVID-19 Global Rheumatology Alliance by signing up on our webpage (top right hand corner)

For more information please visit our website at www.rheum-covid.org, if you have questions or issues and would like to know more information please email rheum.covid@gmail.com.

© 2021 Asia Pacific League of Associations for Rheumatology and John Wiley & Sons Australia, Ltd