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ORIGINAL ARTICLE

Efficacy of Tofacitinib in Takayasu Arteritis Refractory to Biologic DMARDs—A Multicentre Study in Indian Patients

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ABSTRACT

Background: The management of patients with Takayasu arteritis (TAK), especially those who are refractory to biologic disease-modifying anti-rheumatic drugs (DMARDs), is challenging.

Objective: We determined the efficacy of tofacitinib in patients with TAK who could not achieve or maintain stable disease despite biologic DMARDs (bDMARD-NR).

Methods: Details of consecutive patients with TAK treated with originator/generic tofacitinib at 5 centres in India were recorded retrospectively from the medical records. The activity of the disease was assessed using multiple domains including Indian Takayasu arteritis score (ITAS), C-reactive protein (CRP) and imaging. Active disease was defined by either (i) ITAS-A(CRP) ≥ 3 wherein both ITAS and CRP each contributed at least 1 point to the final score; or (ii) clinical ITAS score > 1 in the presence of imaging activity even without raised CRP. The parameters between patients with good response and no response to treatment were compared.

Results: Altogether, 33 patients (30 females) with a mean age of 28.9 ± 7.6 years and a disease duration of 39.0 (15.8–72.0) months who received tofacitinib were included. Sixteen patients (54.5%) who failed anti-TNF agents [$n = 14$, (42.4%)] or tocilizumab [$n = 14$, (42.4%)] were classified as bDMARD-NR. During a follow-up of 15.0 (6.5–20.0) months, 23 (69.7%) satisfied the above composite criteria for inactive disease using clinical, laboratory, and imaging parameters. Among bDMARD-NR, 14 (77.8%) achieved inactive disease. Four patients discontinued tofacitinib due to adverse drug events. No predictors of response were identified.

Conclusion: Tofacitinib may be an effective option in a subset of patients who fail to attain stable disease state despite use of csDMARDs and bDMARDs.

1 | Introduction

Takayasu arteritis (TAK) is a granulomatous large vessel vasculitis characterized by inflammation-induced fibrosis and stenosis of the aorta and its direct branches [1, 2]. Active inflammation during the initial stages results in fibrotic narrowing of large arteries. Although upto 80% of the patients achieve initial remission with glucocorticoids and immunosuppressive agents,

tapering of steroids is frequently associated with relapses in as many as half of them [3, 4].

Tofacitinib is a targeted synthetic DMARD (disease modifying anti-rheumatic drugs) which preferentially inhibits Janus kinase 1 (JAK1) or JAK3 and uses signal transducer and activator of transcription (STAT) as intermediary signaling molecules. The JAK/STAT pathway is a major signaling pathway for multiple proinflammatory cytokines including interleukin-6 (IL6) and interferon-γ. This pathway is implicated in the pathogenesis of multiple systemic autoimmune diseases including TAK [5, 6]. Interleukin-6 (IL6) is an established target for the treatment of patients with Takayasu arteritis. The JAK/STAT pathway has been observed to mediate IL-6 driven vascular fibrosis in TAK [7]. JAK inhibitors can suppress tissue-resident memory T cell driven microvascular angiogenesis and can shift the T-helper cell profile from Th1 and Th17 cells to T-regulatory cells in animal models of large vessel vasculitis and TAK respectively [8]. Various case reports and a cohort study suggest the utility of tofacitinib in the treatment of patients with refractory TAK. While individual case reports have suggested its utility in patients with TAK refractory to biologics, the majority of patients recruited in the prospective cohort study were refractory to conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs) [9–19]. In this study, we have determined the efficacy of tofacitinib in the management of patients who are unable to achieve or maintain a stable disease state with multiple lines of csDMARDs and biologic DMARDs (bDMARDs).

2 | Materials and Methods

2.1 | Ethical Approval of the Study Protocol

This study was approved by the institutional review and ethics committee of Christian Medical College, Vellore (IRB no. 15825, 25.10.2023). The study conformed to the principles outlined in the Declaration of Helsinki 1964 and its later amendments. The written informed consent was not taken due to the retrospective nature of the study.

2.2 | Patients

This is a multicentre retrospective study based on information collected from the medical records of patients with a medical diagnosis of TAK during November 2019 to June 2023. Consecutive adult patients aged > 16 years, satisfying the American College of Rheumatology (ACR)1990 criteria for TAK and being treated with either originator or generic tofacitinib at 5 centres in India were included in the study [20]. Only patients who satisfied the definition of refractory disease (detailed below) were included in the study.

The details regarding demographics, clinical presentation, disease duration, disease activity as assessed by the Indian Takayasu Activity Score 2010 (ITAS 2010) or NIH score, laboratory markers including C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), vascular imaging, treatment, and response to treatment were captured at every visit of the patient [21, 22]. The disease was subcategorised into 5 types by angiography as per Numano's classification [23].

2.3 | Study Definitions

The definition of activity and response in individual domains was as follows:

a. Clinical activity: Presence of new clinical symptoms as documented by ITAS 2010 > 1. Accordingly, clinically stable disease was defined as ITAS 2010 score of ≤ 1.

b. Laboratory activity: Presence of persistently raised CRP for 2 consecutive visits. Response was defined as achievement of CRP values below 10 mg/L, while any decrease in CRP not amounting to normalization was defined as partial laboratory response.

c. Imaging activity: new areas or progression of existing areas of arterial wall thickening/stenosis/aneurysms in angiography or active uptake in ^{18}FDG PETCT imaging.

Overall, the disease was considered active in the presence of (i) ITAS-A (CRP) score of ≥ 3 wherein both ITAS and CRP each contributed at least 1 point to the final score or (ii) In the absence of laboratory activity but presence of imaging activity, a clinical ITAS score of > 1 was also considered active.

Relapse was defined as attainment of ITAS = 0 followed by return of disease activity as described above. Response was defined as either attainment of inactive disease or clinically stable disease with partial response in other domains and no evidence of progression in imaging. Non-response was failure to achieve inactive disease state as described above. Any decrease in CRP not amounting to normalization was defined as partial laboratory response. Clinically stable disease was defined as ITAS 2010 score of ≤ 1.

The refractory disease was defined as failure to achieve or maintain inactive disease without steroids with at least one conventional synthetic DMARD (csDMARD). If the patients received prior biological agents (bDMARD) in addition to csDMARDs, they were classified as bDMARD nonresponders (bDMARD NR).

2.4 | Statistical Analysis

The data is presented as mean ± SD or median (Interquartile range) according to the distribution of data. The total number of patients enrolled in the study or various groups was used to calculate percentage. The baseline parameters between patients with a good response and no response to treatment were compared using Fischer's exact test or Mann Whitney test. The graphs were plotted using R studio vs. 4.2.0.

3 | Results

During the study period, among 34 patients who received tofacitinib, 33 were classified as refractory TAK and were included in the study. The single patient who received tofacitinib as 1st line immunosuppressant and died within 3 months of initiation of the drug was excluded from the study. Among 33 patients (30, 90.9% females) with a mean age of 28.9 ± 7.6 years and a median disease

duration of 39.0 (15.8–72.0) months, tofacitinib was received in the dose of 5 mg twice daily (Table 1). Supra-diaphragmatic aorta and its branches were involved in 32 (97.0%) along with infra-diaphragmatic branches in 23 (69.7%) patients. The majority (22, 66.7%) patients had type 5 disease followed by type 2 disease in 18.2%, type 1 disease in 9.1%, and type 3 and 4 disease, each in 1 (3.0%) patient. Three (9.1%) and 2 (6.1%) of patients had pulmonary and coronary artery involvement, respectively. Three (9.1%) of patients had aneurysmal disease. The presenting symptoms included constitutional symptoms, carotidynia, ischemic features, aortic regurgitation, and cardiac failure in 14 (42.4%), 9 (27.3%), 19 (55.9%), 6 (18.2%) and 3 (9.1%) patients, respectively. The median ESR, CRP, ITAS score, and steroid dose at initiation of tofacitinib were 39.0 (24.0–57.5) mm/1st hr., 25.0 (9.5–53.5) mg/L, 1 (0–2.5) and 7.5 (3.8–12.5) mg/day, respectively. All patients received prior systemic steroids. The majority ($n = 30$, 91%) patients had active disease with at least one conventional or biologic DMARD while 3 (9%) patients required repeated increases in the dose of steroids to maintain the stable disease prior to starting tofacitinib. The patients received a median of 2 (1–3.5) lines of immunosuppression before being initiated on tofacitinib. The indication for initiating tofacitinib was clinically active disease and persistent laboratory activity in 23 (69.7%) and 19 (57.6%) patients, respectively, while 7 (21.2%) had angiography evidence of active or progressive disease despite non-biologics or biologic DMARDs.

Prior to receiving tofacitinib, 18 patients (54.5%) failed biologics including anti-TNF agents [$n = 14$, (42.4%)] and tocilizumab [$n = 14$, (42.4%)]. Ten of these patients failed both the above biologic agents (30.3%).

3.1 | Response to Tofacitinib (Figure 1)

3.1.1 | All Patients

Among 33 patients included in the study, 18 patients were bDMARD-NR. During a follow-up of 15.0 (6.5–20.0) months, 23 (69.7%) among enrolled patients satisfied the composite criteria for inactive disease using clinical, laboratory, and imaging parameters.

The drug was discontinued by the physician due to a lack of induction of response and adverse events in 5 (15.2%) and 4 (12.1%)

TABLE 1 | Demography and disease activity parameters of patients given tofacitinib at the index visit.

	csDMARD-NR	bDMARD-NR
At baseline (*n*)	15	18
Age at inclusion (years)	29.1 ± 7.2	28.7 ± 8.2
Age at onset (years)	26.4 ± 7.5	23.5 ± 7.7
Duration of symptoms (months) median (IQR)	19.0 (5.0–15.0)	54.0 (29.8–96.0)
Prior 2nd line immunosuppressants (*n*), median (IQR), range	1.0 (1.0–2.0), 1–3	3.0 (2–4), 2–7
Mycophenolate (*n*, %)	9, 60.0	15, 83.3
Methotrexate (*n*, %)	7, 46.7	13, 72.2
Azathioprine (*n*, %)	3, 20.0	2, 11.1
Calcineurin Inhibitors (*n*, %)	0	2, 11.1
Leflunomide (*n*, %)	1, 6.7	0
Cyclophosphamide (*n*, %)	1, 6.7	1, 5.6
Tocilizumab (*n*, %)	0	14, 77.8
Anti-TNF agents (*n*, %)	0	14, 77.8
Steroid dose (mg/day) median (IQR), range	10.0 (5.0–15.0), 2.5–25.0	5.0 (2.5–10.0)
Concomitant immunosuppressants, *n* (%)	9 (60.0)	13 (76.5)
Methotrexate, *n* (%)	6 (40.0)	12 (70.6)
Mycophenolate, *n* (%)	2 (13.3)	0
Tacrolimus, *n* (%)	0	1 (5.9)
Leflunomide, *n* (%)	1 (6.7)	0
ESR (mm/1st hour) median (IQR), range	39.0 (27.0–51.0), 10.0–80.0	40.0 (22.8–74.8), 10.0–140.0
CRP (mg/L) median (IQR), range	24.0 (7.2–42.9), 1.8–79.4	26.0 (9.8–73.3), 0.2–109.0
ITAS median (IQR), range	2.0 (0–5.0), 0–8	0.0 (0–2.0), 0–12
ITAS-CRP median (IQR), range	4.0 (3–5), 1–11	5.0 (2.0–4.0), 1–15

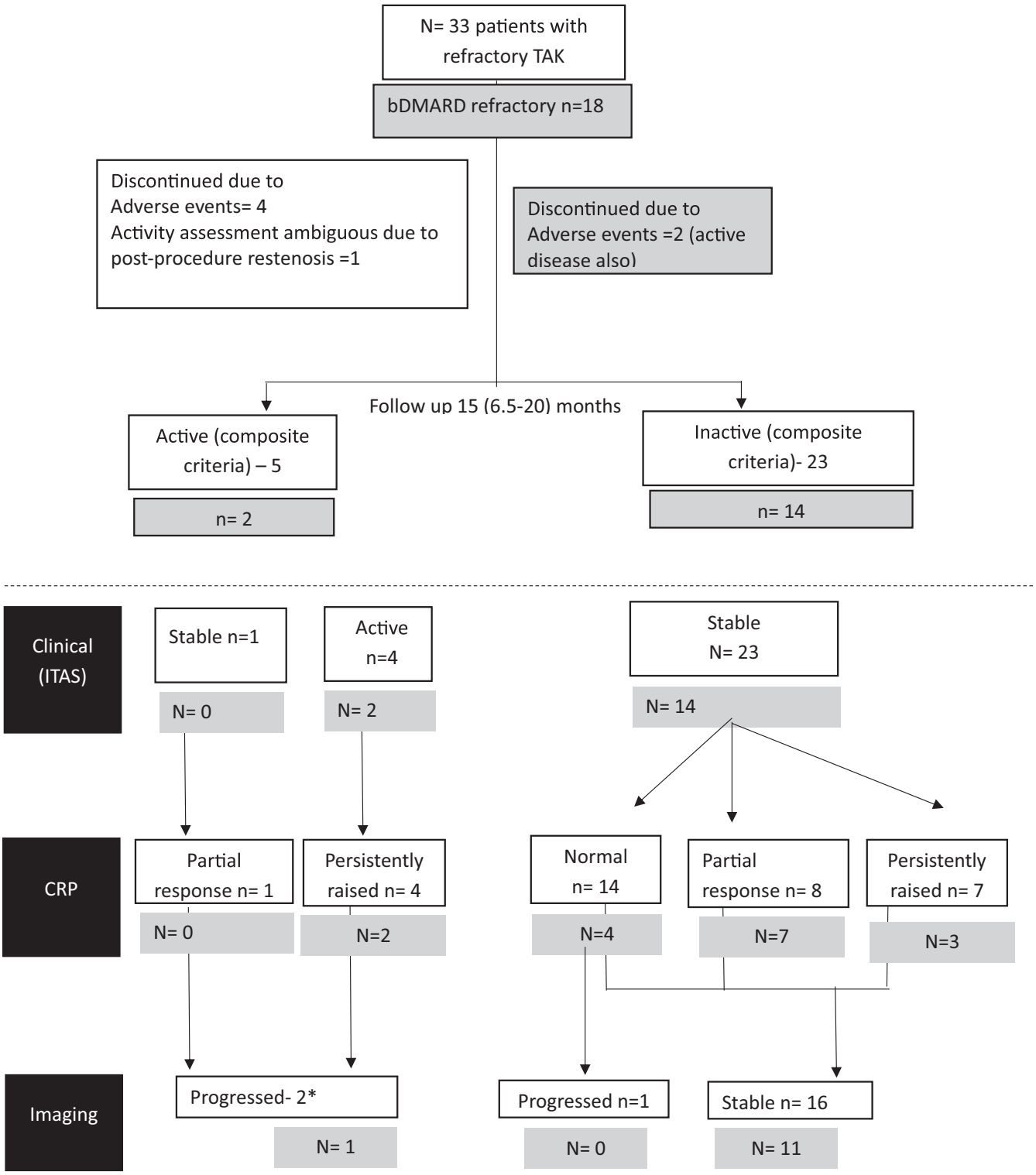

FIGURE 1 | Flow chart depicting the activity status of patients with refractory TAK initiated on tofacitinib. The shaded boxes represent biologic DMARD non responders, white boxes indicate all patients. *1 patient discontinued tofacitinib.

patients, respectively. The adverse events included myocardial infarction in 1, new onset QuantiFERON TB positivity, and herpes zoster and transaminitis in 1 patient each. The disease activity could not be determined with certainty in 1 patient who had an increase in ITAS score, which was attributed to the in-stent restenosis of a previously revascularized vessel. Due to ambiguity in assessing imaging activity, this patient was not included in the outcome analysis.

3.1.2 | Response in Individual Domains of Activity (Table 2; Figure S1)

Altogether, 28 patients were able to continue the drug without adverse events and had no ambiguity in the assessment of disease activity. Among them, 23 patients attained inactive disease by the composite outcome measure. All 23 patients who attained inactive disease achieved clinically stable disease with clinical

ITAS of ≤1, while 5 patients still qualified for the criteria for clinically active disease (Table 2). One patient who attained stable disease switched to azathioprine to facilitate planning for pregnancy.

The inflammatory markers normalized ($n=14$, 50%) or reduced significantly ($n=8$, 28.6%), while 6 (21.4%) patients had persistently raised CRP. Twenty-one of these 28 patients (75%) underwent repeat vascular imaging during follow up at a median follow up of 15 (12.5 to 21.0) months. Stable disease was observed in 17 (81%) patients, while 3 (14.3%) had evidence of disease progression (Table 2). Among 3 patients who had angiographic progression, only one had evidence of clinical and laboratory activity requiring re-switching to biologics. Another patient had only clinical activity without laboratory activity, while one discontinued Tofa due to adverse events.

Since the follow up imaging was not available in 10 out of 28 patients, the efficacy analysis in these patients was based on clinical and laboratory response. All but one patient had concordance between clinical and laboratory assessment. One single patient had isolated high CRP without evidence of clinical activity and hence was considered as inactive for outcome analysis.

The ITAS, ESR, CRP values, and daily steroid dose for the responder group of patients decreased significantly at the last visit as compared with the index visit, while no significant change was observed in the non-responder group (Table S1).

3.2 | Outcomes of bDMARD-NR (Figure S1)

Among 18 patients who failed prior biologics, 2 discontinued the drug due to suspected cardiac events and latent tuberculosis. Both these patients failed to achieve inactive disease after the initiation of tofacitinib. During a median follow-up of 16 (9.0–24.0) months in the remaining patients, 14 (77.8%) with bDMARD-NR achieved inactive disease as per composite criteria. Four patients, including those who discontinued Tofa due to adverse events, did not achieve an inactive disease state. Clinical ITAS ≤1 was achieved in 14 (77.8%) patients. Complete or partial and no laboratory response was observed in 13 (63.2%) while persistent laboratory activity was present in 5 (27.8%) patients. Among 12 patients who had repeat angiograms, the disease was stable in 11 while 1 had evidence of active disease. The median dose of steroids decreased from 5 (2.5–10) mg/day at baseline to 3 (0–13.1) mg/day at the last visit (Figure 1). The CRP values decreased from 21.5 (9.3–84.8) mg/L to 15.5 (7.5–31.4) mg/L while ESR did not show a significant change [40 (22.3–80.3) to 44 (16–56) mm/1st hour].

3.3 | Outcome in csDMARD NR (Figure 1)

Among csDMARD refractory patients ($n=15$), tofacitinib was discontinued due to adverse events in 2 (13.3%) patients. At the last follow-up, 9 out of 15 (60%) patients were in an inactive disease state as per our definition. The analysis of treatment response in individual domains showed 12/15 patients (80%) were in a clinically stable state while 3 had clinically active disease. The CRP normalized or decreased in 10 (66.7%) and 1 patient respectively while 4 patients (26.7%) had persistently raised CRP. Nine patients underwent follow-up imaging which showed non-progressive disease in 6, while 3 had angiographic progression during follow-up. One patient had evidence of in-stent restenosis.

Predictors of non-response: The univariate analysis did not identify any predictors of response to tofacitinib.

4 | Discussion

In this series, 69.7% attained inactive disease status as per our definition as well as clinically stable disease. This is thus far the largest series to explore the efficacy of tofacitinib in TAK patients who are bDMARD-NR, wherein 87.5% of patients refractory to biologic DMARDs achieved an inactive state with tofacitinib. The disease activity assessment in this study was based on all three domains of disease activity which is similar to the concept of recently proposed Takayasu arteritis integrated disease activity index (TAIDAI) that requires clinical and laboratory assessment of disease activity to be supported by the imaging assessment by PET and vice versa [24]. The clinical and laboratory component of activity was measured together by the composite ITAS-A CRP score. This being a retrospective study, various imaging techniques, including CT angiogram, MR angiogram, conventional peripheral angiography, or FDG-PET CT, were used for assessment of vascular involvement. However, the same imaging modality was used at the baseline visit as well as follow-up for an individual patient.

The pooled efficacy of tofacitinib in bDMARD refractory patients with TAK is reported to be approximately 64.1% in published case reports ($n=13$ patients, 7 studies) [11–13, 15–18] (Tables 3 and 4). The two studies conducted in the East China cohort have reported complete remission in 85.2% and 88.57% of patients who received tofacitinib as an add-on immunosuppressant to high-dose corticosteroids, which was significantly higher than the figures in patients treated with methotrexate or leflunomide. At 12 months, 88.5% of patients were relapse-free with stable or improved imaging in 70.4% and 22.2% respectively

TABLE 2 | Response to tofacitinib in individual domains of disease activity (including patients who discontinued tofacitinib due to adverse events).

	Active/progression*	Inactive*	Ambiguous/partial response
Clinical assessment	6 (18.2%)	27 (81.8%)	1 (3%)
Laboratory assessment (CRP)	8 (24.2%)	14 (42.4%)	11 (33.3%) (partial response)
Imaging	3 (9.1%)	17 (51.5%)	1 (3%) (in stent-restenosis)

*by composite outcome cirteria.

TABLE 3 | Cohort studies in patients with Takayasu arteritis treated with tofacitinib.

Study	Type of study	Number and type of patients on TOF	Biologic refractory (bDMARD NR), *n*	Age in years (mean ± SD)	Disease duration (months)	Median baseline CRP (mg/L)	Baseline median ESR (mm/1st h)	Initial GCs (mg/day)	Follow up duration (months)	Clinical and lab response	Angiographic outcome	Adverse events with TOFA
Kong et al. China 2021	OLS comparing TOF and MTX	27 (19 Refractory, 8 New)	3	31.11 ± 9.58	31 (10–72)	6.3 (1.3–32.6)	20 (2–42)	15 (12–30)	12	Complete response (88.46%) Laboratory markers normalization more in TOF	Stable lesions- 88.46% Improvement in 7.69%	3.5% Varicella Zoster 11.5% Transaminitis
Wang et al. China 2022	OLS comparing TOF and LEF	32 (23 refractory, 9 new)	NR	30.94 ± 9.03	30 (11–68.5)	7.05 (2.15–31.45)	20 (3.5–41.5)	15 (10–30)	12	Effectiveness rate was 71.88% Laboratory markers normalization more in TOF	Improved lesions in 9.38%	6.2% Varicella Zoster 3% Dyslipidemia
Present study 2023	Retrospective	33 (All refractory)	18	29.4 ± 8.1	39.0 (15.8–72)	24.5 (9.8–48.8)	41 (24.5–61.5)	7.5 (4.8–15.0)	15.0 (6.5–20.0)	Clinical response—67.6% CRP response—58.8%	Stable—16/21[a] (80%) patients 1 patient had stent restenosis	14.7% (death, MI, TB, HZ and transaminitis in 1 each)

Abbreviations: bDMARD NR, biologic DMARDS non-responders; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GCs, glucocorticoids; MTX, methotrexate, OLS, open label longitudinal study; Tofa, tofacitinib.
[a]Imaging available for 21 patients.

TABLE 4 | Case reports on refractory TAK patients treated with tofacitinib.

Study	Type of study	The type of patients included (*n*)	Previous immunosuppression ± GCs	Dose of tofacitinib & duration of study	Clinical response	Lab outcome normalization of Lab markers	Angiographic outcome (CTA/MRA/PET/Conv Angio)	Steroid dose (post TOF- mg of prednisolone or its equivalent)	Adverse events
Wang et al. 2022	Case Report	Refractory TAK *n* = 1	MTX, AZA	11 mg Extended release	Yes	Yes	Improved	5 mg	N/A
Jing Li et al. 2020	Case series	Refractory TAK *n* = 5	MTX (4/5) MMF (4/5) AZA (2/5) CYC (2/5) TCZ (4/5)	5 mg twice daily	3/5	2/4	3/5	Able to reduce prednisolone dose to ≤ 10 mg in only 2 patients	None
Kuwabara et al. 2020 Japan	Case report	Refractory TAK complicated with Ulcerative Colitis *n* = 1	TNFi TCZ	20 mg daily later tapered to 10 mg	Yes	N/A	Improved	8 mg	None
Plermo et al. 2020 Italy	Case report	Refractory TAK *n* = 2	Case-1: MTX, RTX, TNFi, TCZ Case-2: MTX, RTX, TNFi, AZA, MMF, TCZ	5 mg twice daily	No	No	1 improved other persisted	N/A	N/A
Sato et al. 2020 Japan	Case report	Refractory TAK complicated with UC *n* = 1	AZA, TNFi (GOL), Vedolizumab	20 mg initially	Yes	Yes	Improved	13 mg	N/A
Yamamura et al. 2020 Japan	Case report	Refractory TAK n=1	AZA, TCZ, TNFi, CSA	10 mg with MTX 10 mg weekly once	Yes	Yes	Improved	15 mg	N/A
Rios Rodriguez et al. 2020 Germany	Case report	TAK complicated with rAxSPA n=1	MTX, TCZ, IL17i, TNFi	10 mg with MTX 15 mg weekly once	Yes	Yes	Stable	0 mg	None
Ino et al. 2022 Japan	Case report	Refractory TAK n=1 naïve TAK n=1	AZA, TNFi	10 mg	Yes in 1	Yes in 1	Improved in 2	1–0 mg 2–12 mg	N/A

Abbreviations: ADA, adalimumab; AZA, azathioprine; CSA, cyclosporin; CYC, cyclophosphamide; LEF, eflunomide; MMF, mycophenolic acid; MTX, methotrexate; rAxSPA, radiographic axial spondyloarthritis; TCZ, tocilizumab; TNFi, NF inhibitors.

after tapering of steroids. No major safety concerns were noted [9, 19]. Although stabilization of clinical activity in that study was significantly better with tofacitinib as compared with methotrexate (56.52% CR, 34.78% relapse), the angiographic outcomes were not different between the two immunosuppressants. The response was better for the patients with lower baseline ESR and the presence of systemic symptoms.

The overall response in our cohort was slightly less than observed in the East China Takayasu cohort, which could be attributed to the ethnic differences, lower dose of steroids, and higher proportion of refractory and biologic refractory patients. However, in spite of a higher proportion of refractory patients (97%) in our study, more than 2/3rd of all included patients attained inactive disease after initiation of tofacitinib and were able to reduce steroids. Our study had a higher proportion of bDMARD IR as compared with the Chinese cohort, which had only 3 patients in this group. The response was interestingly better (77.8%) in patients who were refractory to anti-TNF agents and tocilizumab. This response was in spite of the use of a lower dose of steroids in our cohort (7.5 mg/day) as compared with the East China cohort (15 mg/day). There was no predictor or outcome identified in our study.

Our study, albeit limited by small sample size and lack of imaging for 10 patients due to retrospective design, suggests the role of tofacitinib in controlling disease activity and facilitating tapering of steroids in refractory TAK. Although the indication for use of tofacitinib was refractory disease, the number of prior conventional or biological DMARDs varied among patients, which may have added to the heterogeneity of response across different centres. Similarly, the concomitant use of different immunosuppressive agents may have impacted the outcome of this study. There is a need for a multiethnic randomized controlled trial to validate the outcomes of our study and previous studies. A subset of patients did not respond to the drug which suggests the need for studies focused on identifying clinical and laboratory predictors of response to tofacitinib.

5 | Conclusion

Tofacitinib may be an effective option in a subset of patients who have failed to attain stable disease in spite of csDMARDs and bDMARDs.

Author Contributions

Prabhu Vasanth and Ruchika Goel: planning of study, data collection and analysis, preparation of manuscript, revision of manuscript. All the other authors have contributed to data collection and review of manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

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

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LETTER TO THE EDITOR

Biologic Therapy in Rheumatology: Analysis of Multidisciplinary Teams' Performance in Kazakhstan

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Dear Editor,

Biologic disease-modifying antirheumatic drugs (bDMARDs) have significantly improved the management of inflammatory rheumatic diseases such as rheumatoid arthritis (RA), ankylosing spondylitis (AS), and psoriatic arthritis (PsA) [1–4]. In Kazakhstan, multidisciplinary groups (MDGs) have been established to oversee patient selection and monitor treatment with bDMARDs. However, data regarding the performance and challenges of these teams are limited.

As a pilot initiative, the first MDG was created in Almaty, where a structured referral protocol was implemented, incorporating disease activity assessment and adherence to national and international treatment guidelines. Clinical expertise and decision-making consistency among MDG members played a vital role in the quality of care.

We conducted a retrospective study analyzing MDG performance in nine regions of Kazakhstan. The study included 1358 patients receiving bDMARDs in 2023. Disease activity was assessed using validated indices: DAS28 for RA, BASDAI for AS, and DAPSA for PsA [2–4].

Among patients, 784 (66.3%) had RA, 461 (29.9%) had AS, and 53 (3.6%) had PsA. Golimumab was the most commonly used biologic (677 patients), followed by tocilizumab (120) and rituximab (27 cases), the latter primarily for systemic lupus erythematosus (SLE) and systemic sclerosis. Rituximab use was monitored through local registries, and patients with connective tissue diseases (CTDs) were included in a parallel observational study; however, detailed CTD data are not presented in this letter.

After six months of therapy, significant clinical improvement was observed:

1. DAS28 scores in RA reduced from 4.6–6.7 to 1.8–4.6.
2. BASDAI scores in AS declined from 3.1–10 to 1–6.6.
3. DAPSA scores in PsA decreased from 18–44 to 4–18.

Clinical response (as defined by standard thresholds) was observed in 96% of patients. Of the remaining 4% requiring therapy modification due to inefficacy, 2.7% experienced primary failure, and 1.3% secondary failure. Discontinuation due to adverse effects occurred in 1.6% of cases (e.g., infusion reactions, neutropenia, liver function abnormalities).

Access to bDMARDs varied substantially: Almaty had the highest coverage (877 patients), while Kostanay had the lowest (7 patients). Contributing factors included budget allocation disparities, uneven drug distribution, and the limited availability of IL-23 inhibitors. A lack of standardized referral pathways across regions further complicated equitable care.

To improve MDG efficiency and patient outcomes, we propose:

1. Establishing a national biologic therapy registry to systematically collect real-world data on efficacy, safety, and

clinical trajectories. Such registries serve as large-scale, prospective cohorts and provide valuable data on drug utilization and outcomes.

2. Developing unified referral protocols to ensure timely and evidence-based access to biologics.
3. Enhancing equity in access to bDMARDs through centralized procurement and resource distribution.

Finally, we acknowledge the potential link between rising autoimmune disease incidence and post-COVID-19 immune dysregulation. Preliminary data from Kazakhstan suggest this may be a growing concern requiring further investigation [5].

To improve long-term treatment outcomes and systematize data collection, the creation of national databases is essential. As discussed by Uslu et al. [6], national rheumatology registries play a pivotal role in monitoring the clinical course of rheumatic diseases, assessing the effectiveness and safety of biologic therapies, and generating real-world data that inform both clinical decision-making and health policy development. These registries serve as valuable prospective data sources for research and healthcare system planning.

Regional initiatives have demonstrated that strategic investments in rheumatology infrastructure can yield substantial improvements. For instance, the development of rheumatology services in the Atyrau Region—previously underserved—led to the establishment of a dedicated multidisciplinary team and improved patient access to bDMARDs. These outcomes were recently documented in a separate publication [7] and support the feasibility of scaling such models nationally [7].

Author Contributions

G.T. conceived and supervised the study. I.S. contributed to the study design and methodology. D.M. and Z.K. were responsible for data collection and verification. G.A. and D.E. participated in the analysis and interpretation of the data. C.B. contributed to drafting the manuscript. All authors reviewed and approved the final version of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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ORIGINAL ARTICLE

Efficacy and Safety of Rituximab in Connective Tissue Disease-Associated Thrombotic Thrombocytopenic Purpura/Thrombotic Microangiopathy

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Keywords: connective tissue disease | Rituximab | thrombotic microangiopathy | thrombotic thrombocytopenic purpura

ABSTRACT

Introduction: This study examined the efficacy and safety of Rituximab (RTX) treatment in connective tissue disease (CTD)-associated thrombocytopenic purpura (TTP) and thrombotic microangiopathy (TMA), using historical controls as comparators.

Methods: Patients who were admitted to our department from March 1, 2013 to March 31, 2021, and diagnosed with CTD-associated TTP/TMA refractory to plasma exchange were included in the study. A patient with treatment-resistant disease was treated with RTX in addition to high-dose glucocorticoid (GC) therapy (GC + RTX). As historical controls, we selected patients with CTD-associated TTP/TMA who were admitted to our center and treated with GC and immunosuppressants (IS) such as cyclophosphamide. The primary endpoint was the survival rate 52 weeks after the start of treatment.

Results: Fifteen patients were enrolled in the study (GC + RTX). As a control group, 11 patients were enrolled in the same manner (GC + IS). There were no significant differences in age or sex or laboratory tests between the two groups. The primary endpoint of survival rate was significantly higher in the GC + RTX group than in the GC + IS group. In the immunophenotyping analysis before treatment, among all subsets of immune cells, only plasmocytes were significantly elevated in TTP patients compared to healthy controls. Plasmocytes correlated with serum markers, suggesting increased B cell differentiation, which was markedly decreased after RTX treatment.

Conclusion: In CTD-associated TTP/TMA, B cells may affect pathology, and adding RTX to plasma exchange and GC therapy may be worth considering.

1 | Introduction

Thrombotic thrombocytopenic purpura (TTP) was first described by Moschcowitz in 1924 as a condition presenting with five characteristic features, but has since been shown to be associated with a decrease in a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) activity [1, 2]. Systemic lupus erythematosus (SLE) and other connective tissue diseases present with a variety of symptoms, but TTP is known to occur with worsening disease activity in connective tissue diseases [3, 4]. It is also known that, in some cases called thrombotic microangiopathy (TMA), the disease manifests similarly to TTP, even though ADAMTS13 activity is not reduced. Therefore, it is often referred to as connective tissue disease (CTD)-associated TTP/TMA. CTD-associated TTP/TMA is generally considered to

Summary

- It may be worth considering adding RTX to the treatment of patients with CTD-associated TTP/TMA who show little response to conventional treatments.
- Plasmocytes were inversely correlated with platelet counts and LDH levels in CTD-associated TTP/TMA patients.
- RTX may improve prognosis by affecting the pathogenesis of B cells, including plasmocytes.

have a poorer prognosis than typical TTP without underlying diseases [5]. Treatment of CTD-associated TTP/TMA is often combined with glucocorticoids and other immunosuppressive drugs because of the poor response to plasma exchange alone [6, 7]. However, there is no clarity regarding which immunosuppressants (IS) are most effective for CTD-associated TTP/TMA [4].

Rituximab (RTX) is a drug with established efficacy in CTD, including ANCA-associated vasculitis [8]. RTX is a molecularly targeted drug that targets CD20, depletes B cells, and suppresses antibody production, including autoantibody production. RTX has established efficacy in typical TTP [9–11] and has been covered by TTP insurance in Japan since August 2019. However, although there are case reports and single-arm reports reporting the effect of RTX on CTD-associated TTP/TMA [12–30], with some reports of exacerbations [31], there are no studies comparing an RTX-intervention group to a control group. In our department, RTX has been administered for CTD-associated refractory TTP/TMA after obtaining ethics committee approval and written consent. We enrolled patients with autoimmune diseases in a comprehensive immunophenotyping analysis registry (Flow study) to evaluate immune abnormalities in their peripheral blood [32–34]. In the present study, we investigated the safety and efficacy of RTX treatment for CTD-associated refractory TTP/TMA in our department in real-world settings compared with previous cases in which RTX was not used. Simultaneously, we examined the changes in immune abnormalities before and after RTX administration.

2 | Materials and Methods

2.1 | Study Design and Patients

Patients who were admitted to our department between March 1, 2013 and March 31, 2021, with a diagnosis of TTP/TMA associated with an exacerbation of CTD, and who received RTX were enrolled in the GC + RTX group. In this study, as in previous trials, TTP/TMA was diagnosed when ADAMTS13 activity was < 5%; the pentad of Moschcowitz was fulfilled; or microangiopathic hemolytic anemia, thrombocytopenia, elevated LDH (> 1.5 times the reference value), normal coagulation (PT-INR < 1.5, Fib > 100), and no severely elevated blood pressure (sBP < 180, dBP < 120) were observed [10, 30, 35, 36]. According to the current diagnostic criteria, a marked decrease in ADAMTS13 activity is essential for the diagnosis of TTP. However, ADAMTS13 has only recently become measurable in health insurance examinations. As this was a retrospective study, we examined TTP/TMA cases together, including TTP cases that exhibited a marked decrease in ADAMTS13 activity and TMA cases in which a marked decrease in ADAMTS13 activity could not be confirmed but showed clinical findings similar to those of TTP. We excluded cases of scleroderma renal crisis that responded to ACE inhibitors or ARBs and catastrophic antiphospholipid syndrome that responded to anticoagulant therapy. We defined patients who did not improve after five sessions of plasma exchange according to previous reports as refractory cases [10]. We retrospectively observed the outcomes of patients who received induction therapy with RTX in addition to high-dose glucocorticoid (GC) therapy for refractory cases at our hospital and affiliated hospital. RTX was administered at a dose of 500 mg per body once weekly for a total of four doses as the standard regimen. However, based on the patient's condition and blood test results, the dosing interval was extended up to 4 weeks, and the total number of doses was reduced accordingly. Plasma exchange was performed daily for the first three sessions, followed by 3–5 sessions per week thereafter. However, the frequency was reduced on certain occasions according to the patient's condition and blood test results. To optimize the efficacy of RTX, plasma exchange was withheld for 48 h following RTX administration. Historical control was defined as patients admitted to our hospital with a diagnosis of TTP/TMA associated with exacerbation of CTD. The diagnosis was made in the same manner as for the GC + RTX group, and refractory cases were defined in the same manner. Refractory cases during this period were treated with high-dose GC and IS other than RTX, and their outcomes were retrospectively monitored at our hospital and affiliated hospital. Patients who consented underwent additional comprehensive immunophenotyping analysis, which was performed in our department. This study was approved by the Ethics Committee of the Occupational Medical and Welfare University (H27-014, H23-005) and was conducted in accordance with the Declaration of Helsinki and Ethical Guidelines for Medical Research Involving Human Subjects of the Ministry of Health, Labor, and Welfare. Whenever RTX was administered to patients not covered by insurance, a clinical ethics application was submitted to the ethics committee of the hospital of the University of Occupational and Environmental Health, Japan for review and approval (2015-09), and consent was obtained from the patient.

2.2 | Assessment and Endpoints

The primary endpoint in this study was the survival rate 52 weeks after the initiation of induction therapy. The secondary endpoints included remission rate, plasma exchange independent rates, thrombocyte remission rates, hemodialysis-independent rates, and various blood tests (hemoglobin, platelet count, LDH, and Cre). Remission was defined as platelet normalization (> 150 000), LDH normality (< 1.5 × the upper limit of normal), and no TTP symptoms without plasma exchange [36]. In addition, comprehensive immunophenotyping analysis was performed to evaluate the changes before and after RTX treatment. Adverse events were defined as new events or unexpected worsening of a medical

condition, irrespective of cause, during the observation period as compared to before starting induction therapy. Severity was classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

2.3 | Flow Cytometric Analysis

Flow cytometric analysis was performed as previously described [32–34]. Briefly, peripheral blood mononuclear cells were isolated at the onset of TTP/TMA and approximately 6 months after RTX treatment. Peripheral blood mononuclear cells were resuspended in PBS/3% human IgG (Baxter International Inc., Vienna, Austria) to block Fc receptors and prevent nonspecific antibody binding, and then incubated for 15 min at 4°C in the dark. The cells were then washed with PBS containing 1% bovine serum albumin. Background fluorescence was assessed using the appropriate isotype- and fluorochrome-matched control monoclonal antibodies. After staining with the indicated antibodies, cells were analyzed by multicolor flow cytometry (FACSVerse; BD Biosciences, San Jose, CA, USA) and analyzed using FlowJo software (Tree Star, Ashland, OR, USA).

2.4 | Gating Strategy of Flow Cytometric Analysis

The phenotype of immune cell subsets was defined based on the HIP protocol of comprehensive eight-color flow cytometric analysis proposed by the National Institutes of Health (NIH)/the Federation of Clinical Immunology Societies (FOCIS), with some modifications for detecting Tfh cells [37]. Details of the gating strategy for the flow cytometric analysis are described in Table S1. The clones and names of the antibodies used in this study are listed in Table S2.

2.5 | Statistical Methods

Patient characteristics are expressed as mean (SD), median (interquartile range [IQR]), or number (%) of patients. Survival rates were assessed using the Kaplan–Meier method. Student's *t*-test and Mann–Whitney *U* test were used for between-group comparisons, and Fisher's exact test was used to compare categorical variables. The degree of contribution and contribution ratio were calculated using the bootstrap forest method. All reported *p* values were two-sided and were not adjusted for multiple testing. The level of statistical significance was set at $p < 0.05$. The last observation was used for patients whose laboratory values were not measured. All analyses were performed using JMP version 13.0 (SAS Institute Inc., Cary, NC, USA).

3 | Results

3.1 | Baseline Characteristics

Thirty-five cases were diagnosed with TTP/TMA, seven of which were due to causes other than CTD and 13 did not meet the definition of refractory disease (Figure S1). Of the remaining 15 patients, all received RTX. Finally, 15 patients were enrolled in the study as refractory CTD-associated TTP/TMA (GC + RTX group). Twenty-seven patients were diagnosed with TTP or TMA, five had TTP due to causes other than CTD, and 11 did not meet the definition of refractory disease. None of the patients were treated with RTX, and 11 patients were enrolled (GC + IS group).

Table 1 shows the baseline patient characteristics for both groups. There were no significant differences in age (GC + RTX/GC + IS:52 [40–68]/65 [50–73] years) or sex (percentage of women, GC + RTX/GC + IS:12 (80)/8 (72)) between the two groups. There were no significant differences in background CTD, although SLE accounted for more than 1/3 of the cases in both groups. No difference was observed between the two groups in the proportion of patients with other collagen diseases. In terms of treatment history, only one patient in the GC + RTX group had previously received RTX. All patients had microangiopathic hemolytic anemia and thrombocytopenia, and other Moschcowitz pentad, such as fever (10 (67)/5 (45)), central nervous system abnormalities (10 (67)/7 (64)), and renal dysfunction (13 (87)/7 (64)) did not differ between the two groups. French score (1 [0–1]/1 [1–1]), PLASMIC score (5 [5–6]/5 [5–6]), and severity score (3 [2–4]/2 [2–3]) also did not differ between the two groups [38, 39]. The SLICC Damage Index (1 [0–2]/1 [0–2]) at the time of diagnosis also did not differ between the two groups.

Laboratory parameters included Hb (82 [73–89]/82 [75–88] g/L), platelet count (5.8 [2.8–6.4]/2.6 [1.2–6.4] $\times 10^9$/L), LDH (621 [304–1027]/479 [345–778] U/L), Cre (144.1 [118.5–417.2]/172.4 [85.7–263.4] μmol/L), eGFR (24.50 [7.97–32.28]/22.87 [13.12–48.23] mL/min/1.7 m^2), haptoglobin (9 [9–53]/9 [9–66] mg/dL), and ADAMTS13 functional activity (37.2 [26.0–65.2]/27.5 [23.1–40.1]) were not significantly different. Ferritin (986 [368–9293]/3426 [216–5801]), an indicator of macrophage activation, did not differ between the two groups. No differences were observed in complement or autoantibody levels between the two groups.

There was no difference in the initial glucocorticoid dose (56 [50–65] mg/day/50 [40–68] mg/day) or glucocorticoid pulse therapy (10 (67) cases/9 (81) cases) between the two groups. No difference was observed between the two groups in the number of days from TTP/TMA diagnosis to the first plasma exchange. RTX was administered once in one case, twice in seven cases, three times in one case, and four times in six cases. In the GC + IS group, patients were treated with IVCY and AZA in addition to glucocorticoids.

3.2 | Effectiveness and Safety

The primary endpoint of the survival rate was 80.0% (12/15) in the GC + RTX group and 45.5% (5/11) in the GC + IS group after 52 weeks, which was significantly higher in the GC + RTX group than in the GC + IS group (Figure 1A). Deaths in the GC + RTX group included two from sepsis and one from intestinal perforation. In contrast, in the GC + IS group, there were two cases of lower gastrointestinal bleeding, one case of laryngeal hemorrhage, and three deaths due to sepsis (Table S3). The remission rate after 8 weeks did not differ between the two groups, nor did the cumulative remission rate after 52 weeks (Figure 1B,C). There was no difference in the thrombocyte remission rate between the

TABLE 1 | Baseline characteristics of patients with thrombotic microangiopathy in this study.

	GC + RTX $n = 15$	GC + IS; historical control $n = 11$
Age (years)	54.3 ± 16.0	61.3 ± 12.8
Sex (female)	12 (80)	8 (72)
The constitution of CTDs		
RA	0	1
SLE	6	4
IIM	3	2
SSc	2	1
MCTD	1	1
AOSD	1	1
PAN	0	1
MPA	2	0
Disease duration from onset of underlying disease (months)	57 [14–206]	6 [3–141]
Relapsing TTP/TMA	1 (7)	0 (0)
Coexistence of malignant tumors	1 (7)	0 (0)
Organ disorder; Moschcowitz's clinical pentad		
Microangiopathic hemolytic anemia	15 (100)	11 (100)
Thrombocytopenia	15 (100)	11 (100)
Fever	10 (67)	5 (45)
Central nervous system abnormalities	10 (67)	7 (64)
Renal dysfunction	13 (87)	7 (64)
The number of symptom combinations fulfilling the clinical pentad	4 [3–4]	3 [3–4]
French score	1 [0–1]	1 [1–1]
PLASMIC score	5 [5–6]	5 [5–6]
The severity index	3 [2–4]	2 [2–3]
Rose and Eldor score	5 [4–5]	5 [4–5]
Simple prognostic index	4 [2–4]	4 [4–4]
The French TMA Reference Center Score	2 [1–3]	2 [1–3]
Mortality In TTP Score (MITS)	3 [1–4]	3 [1–3]
Damage Index	1 [0–2]	1 [0–2]
Laboratory data		
Hemoglobin (g/L)	81 ± 107	80 ± 127
Platelet count ($\times 10^9$/L)	4.9 ± 2.4	4.0 ± 3.5
Creatinine (μmol/L)	222.2 ± 151.5	183.7 ± 115.6
eGFR (mL/min/1.7 m^2)	24.50 [7.97–32.28]	22.87 [13.12–48.23]
Ferritin (ng/mL)	986 [368–9293]	3426 [216–5801]
LDH (U/L)	621 [304–1027]	479 [345–778]

(Continues)

TABLE 1 | (Continued)

	GC + RTX $n = 15$	GC + IS; historical control $n = 11$
Haptoglobin (mg/dL)	9 [9–59]	9 [9–66]
ADAMTS13 functional activity (%)	37.2 [26.0–65.2]	27.5 [23.1–40.4]
PT-INR	1.07 [1.00–1.20]	1.14 [1.01–1.18]
APTT (s)	37.0 [26.0–44.3]	37.4 [23.7–55.0]
FDP (μg/mL)	10.9 [7.0–67.6]	10.5 [7.3–37.4]
Fibrinogen (mg/dL)	317 [246–410]	211 [135–303]
C3 (mg/dL)	59 [49–88]	61 [38–97]
C4 (mg/dL)	10 [7–19]	22[11–38]
CH50 (U/mL)	36 [27–59]	43 [26–52]
Rheumatoid factor (IU/mL)	10.4 [6.1–68.1]	7.5 [3.2–17.2]
Antinuclear antibody positive (a titer of ≥ 1:80)	10 (67)	7 (64)
Antiphospholipid antibodies positive	3 (20)	2 (18)
Anti-Ro antibodies positive	4 (27)	2 (18)
Anti-La antibodies positive	2 (13)	0 (0)
Anti-dsDNA antibodies positive	4 (27)	3 (27)
Anti-RNP antibodies positive	7 (47)	4 (36)
Anti-Sm antibodies positive	4 (27)	2 (18)
Anti-citrullinated protein antibodies positive	1 (7)	0 (0)
Anti-ARS antibodies positive	2 (13)	1 (9)
Anti-centromere antibodies positive	1 (7)	0 (0)
Anti-RNA polymerase III antibodies positive	0 (0)	1 (9)
Anti-myeloperoxidase-ANCA positive	2 (13)	0 (0)
Treatment		
Number of days from diagnosis to the first plasma exchange (days)	2 [2–4]	2 [1–4]
GC dose (mg/day, PSL equivalent)	56 [50–65]	50 [40–68]
Pulse glucocorticoid therapy	10 (67)	9 (81)
Immunosuppressants	RTX (15)	IVCY 5, Cyclosporine 1, Tacrolimus 1, Azathioprine 4

Note: The severity index was determined by the number of the following criteria: ADAMTS13 inhibitor 2 BU/mL or higher, renal dysfunction, neuropsychiatric disorder, cardiac disorder, intestinal disorder, deep bleeding or deep thrombus, failure to respond to GC treatment, and recurrent cases, as defined by the Ministry of Health, Labor and Welfare. Data are shown as mean ± standard deviation, median [quartile] or *n* (%). *p* values were determined using Student's *t*-test, the Wilcoxon rank-sum test or Fisher's exact probability test.

Abbreviations: ADAMTS13, a disintegrin-like and metalloproteinase with thrombospondin type 1 motifs 13; ANCA, anti-neutrophil cytoplasmic antibody; APTT, activated partial thromboplastin time; ARS, aminoacyl-tRNA synthetase; CH50, 50% hemolytic unit of complement; dsDNA, double-stranded deoxyribonucleic acid; FDP, fibrin/fibrinogen degradation products; GC, glucocorticoid; IVCY, intravenous cyclophosphamide pulse therapy; LDH, lactate dehydrogenase; PSL, prednisolone; PT-INR, prothrombin time-international normalized ratio; RNA, ribonucleic acid; RNP, ribonucleoprotein; Sm, Smith.

two groups during the observation period, nor was there any difference in the number of patients weaned off plasma exchange (Figure 1D,E). Seven patients in the GC + RTX group and six patients in the GC + IS group were started on hemodialysis at the onset of the disease, and five patients (71.4%) in the GC + RTX group and one patient (16.7%) in the GC + IS group were weaned off hemodialysis, with no difference between the two groups (Figure 1F). The platelet count improved in both groups; however, it improved significantly in the GC + RTX group after Week 8 and continued to improve at Week 52 (Figure 2A). Hgb was also significantly improved in the GC + RTX group after Week 8, and LDH was significantly improved in the GC + RTX group at Week 52; however, there was no significant difference in Cre between the two groups throughout the entire period (Figure 2B–D).

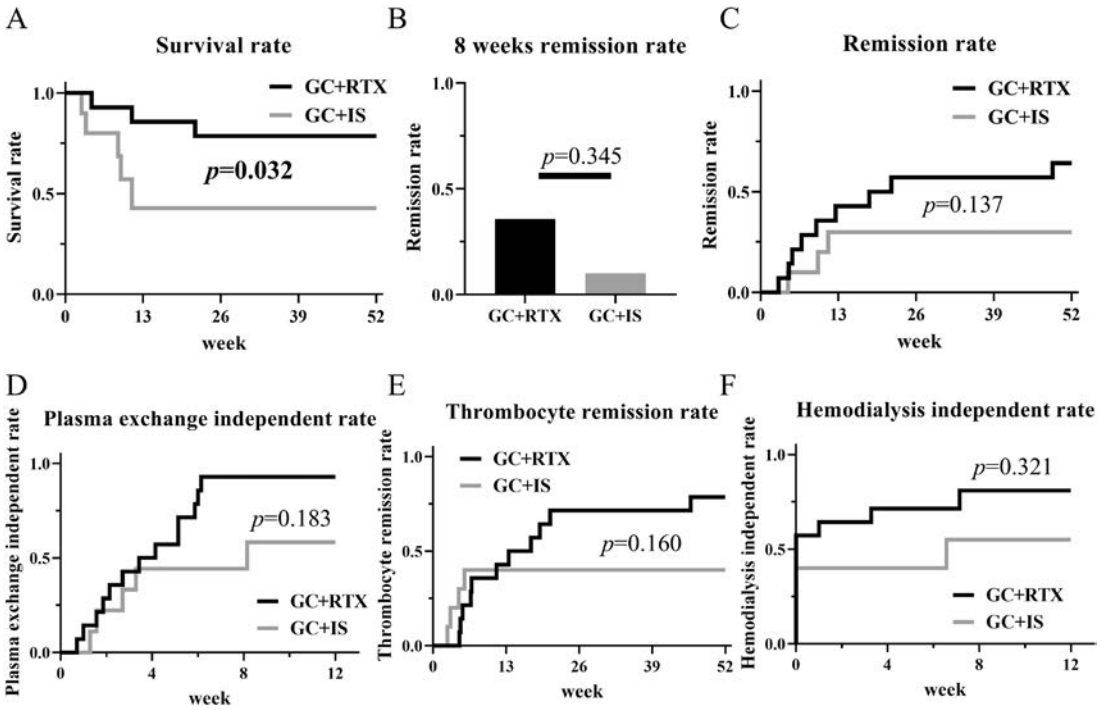

FIGURE 1 | (a) Survival rate up to 52 weeks. (b) Remission rate of patients treated with GC + RTX or patients treated with GC + IS at 8 weeks. (c) The remission rates up to 52 weeks after the introduction therapy. (d) Plasma exchange independent rates up to 12 weeks after the introduction therapy. (e) Thrombocyte remission rates up to 52 weeks after the introduction therapy. (f) Hemodialysis independent rates up to 12 weeks after the introduction therapy.

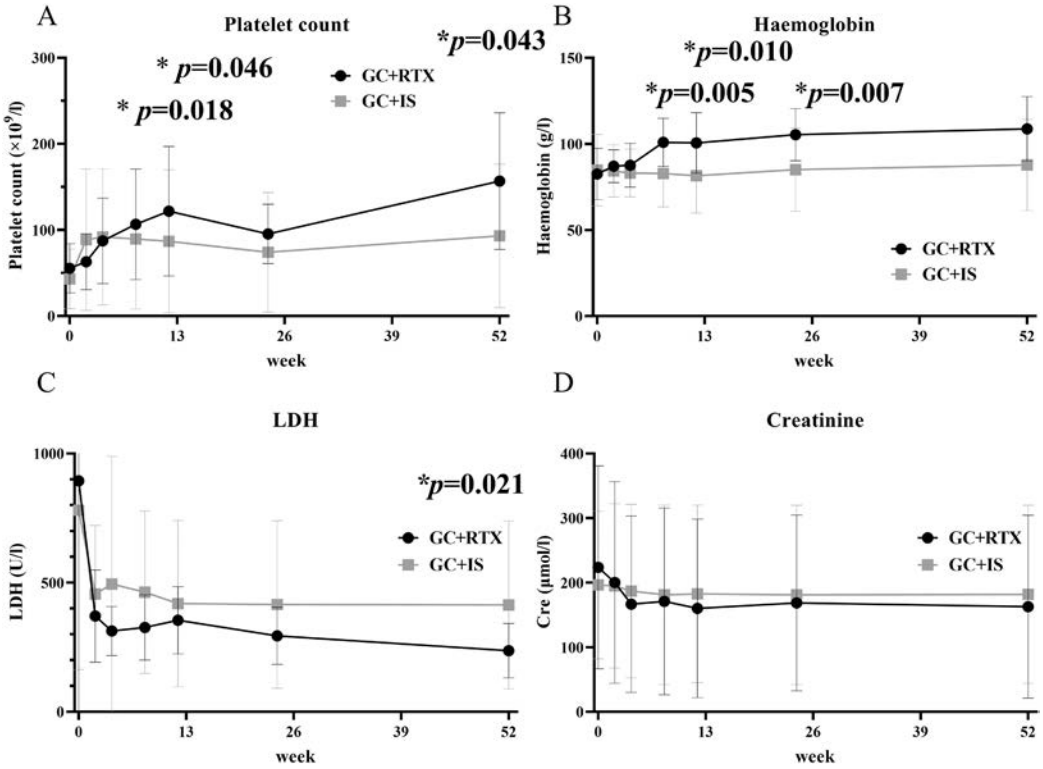

FIGURE 2 | (A) Change in platelet count(10^9/L) in TTP patients. (B) Change in hemoglobin (g/L) in TTP patients. (C) Change in lactate dehydrogenase (U/L) in TTP patients. (D) Change in Cre (μmol/L) in TTP patients. The points denote the mean value and the bars indicate the standard deviation. Cre; creatine; LDH; lactate dehydrogenase.

3.3 | Adverse Events

Adverse events occurred in all patients in the GC + RTX group during the observation period, but there was no difference compared to the GC + IS group. There was also no difference in serious adverse events (Table 2). In terms of CTCAE grade ≥ 3 adverse events, the all-cause mortality rate tended to be higher in the GC + IS group. Otherwise, there were no

TABLE 2 | Adverse events within 52 weeks after treatment.

	GC + RTX $n = 15$	GC + IS; historical control $n = 11$	p
All adverse events	15 (100)	11 (100)	1.000
Serious adverse events	14 (93)	11 (100)	1.000
Infection events	12 (80)	10 (91)	0.614
Serious infection events	11 (73)	8 (73)	1.000
Death (CTCAE grade 5 adverse events)	3 (20)	6 (63)	0.103
CTCAE grade 4 adverse events	2 (13)	3 (27)	0.617
CTCAE grade 3/4 adverse events	14 (93)	11 (100)	1.000
Adverse event of special interest			
Sepsis	3 (20)	3 (27)	0.674
Lung infection	8 (53)	6 (55)	1.000
Hepatitis B reactivation	0 (0)	0 (0)	1.000
Details of all adverse events			
Infection			
Sepsis	Grade 4; 1 Grade 5: 2	Grade 5: 3	
Lung infection	Grade 3; 7 Grade 4: 1	Grade 3; 3 Grade 4: 3	
Biliary tract infection	Grade 4; 1		
CMV infection reactivation	Grade 3; 5	Grade 3; 5	
Febrile neutropenia	Grade 3; 1	Grade 3; 1	
Urinary tract infection	Grade 3; 1		
Enterocolitis infectious	Grade 3; 1		
Shingles		Grade 3; 1	
Adverse drug reactions			
Colonic perforation	Grade 5; 1		
Lower gastrointestinal hemorrhage	Grade 4; 1	Grade 5; 2	
Laryngeal hemorrhage		Grade 5; 1	
Seizure	Grade 3; 1		
Uveitis	Grade 3; 1		
Thromboembolic event		Grade 3; 1	
Duodenal perforation		Grade 3; 1	
Malabsorption		Grade 3; 1	
Laboratory test abnormality			
ALT increased	Grade 3; 1		
ALP increased		Grade 3; 1	

Note: p values were determined by Fisher's exact probability test.

significant differences in the number of adverse events between the GC + RTX and GC + IS groups.

3.4 | Flow Cytometry Analysis

Figure 3 shows a heat map of cell counts by subset of various immune cells in the patients' peripheral blood compared to healthy controls. First, for $CD4^+$ T cells, most subsets were reduced or unchanged compared to healthy controls. As for $CD8^+$ T cells, although activated $CD8^+$ T cells and activated $CXCR3^+CCR6^-CD8^+$ T cells were also increased, these changes were not significant, and cell numbers decreased in most of the subsets. However, in B cells, plasmocytes were significantly elevated in TTP patients (23.5/μL) compared to healthy controls (3.1/μL) (Table S4). Plasmocytes were the

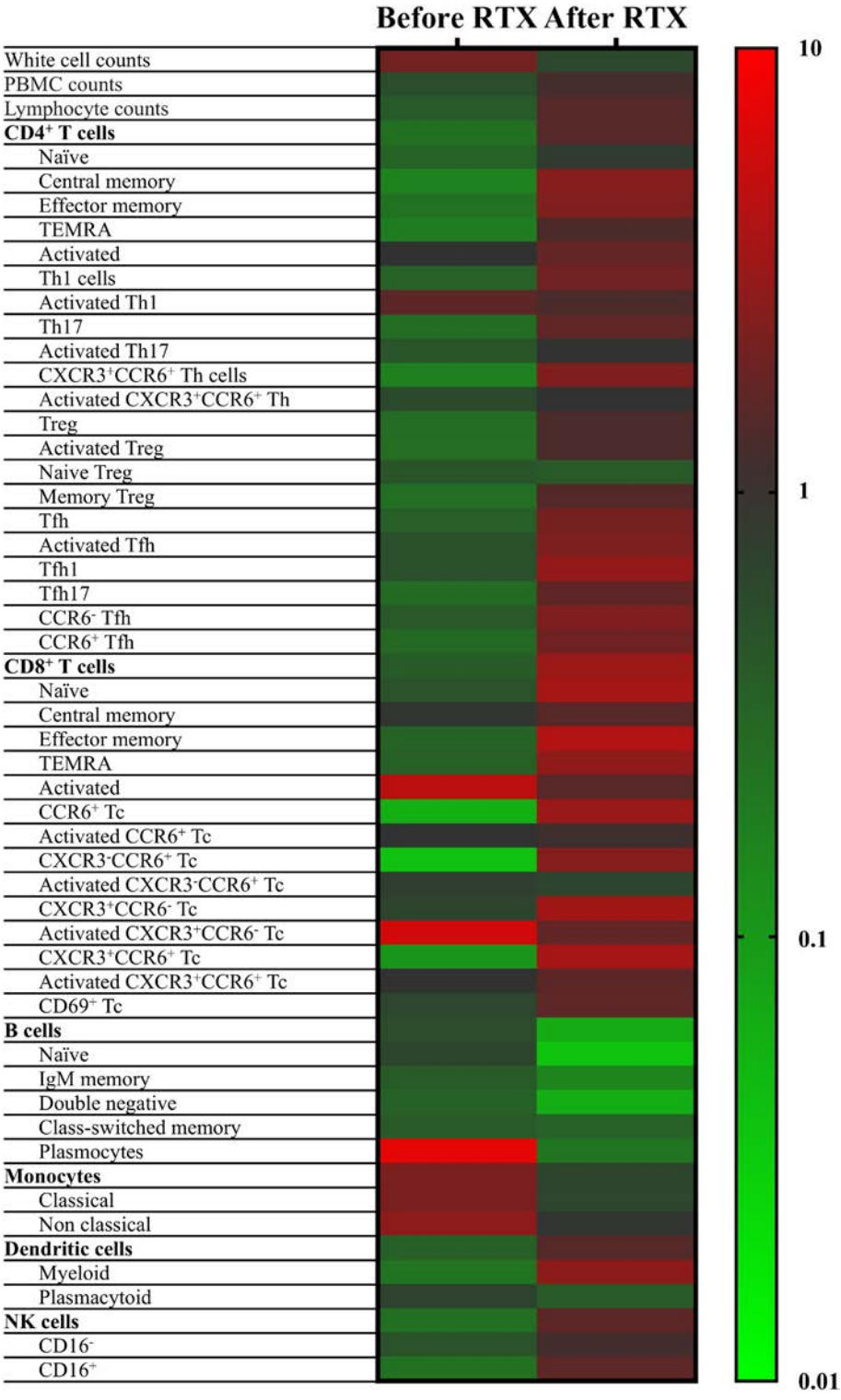

FIGURE 3 | The heat map shows the number of cells per various immune cell subsets in the peripheral blood compared to healthy controls. The left column shows the numbers before RTX treatment, and the right column shows the numbers after RTX treatment.

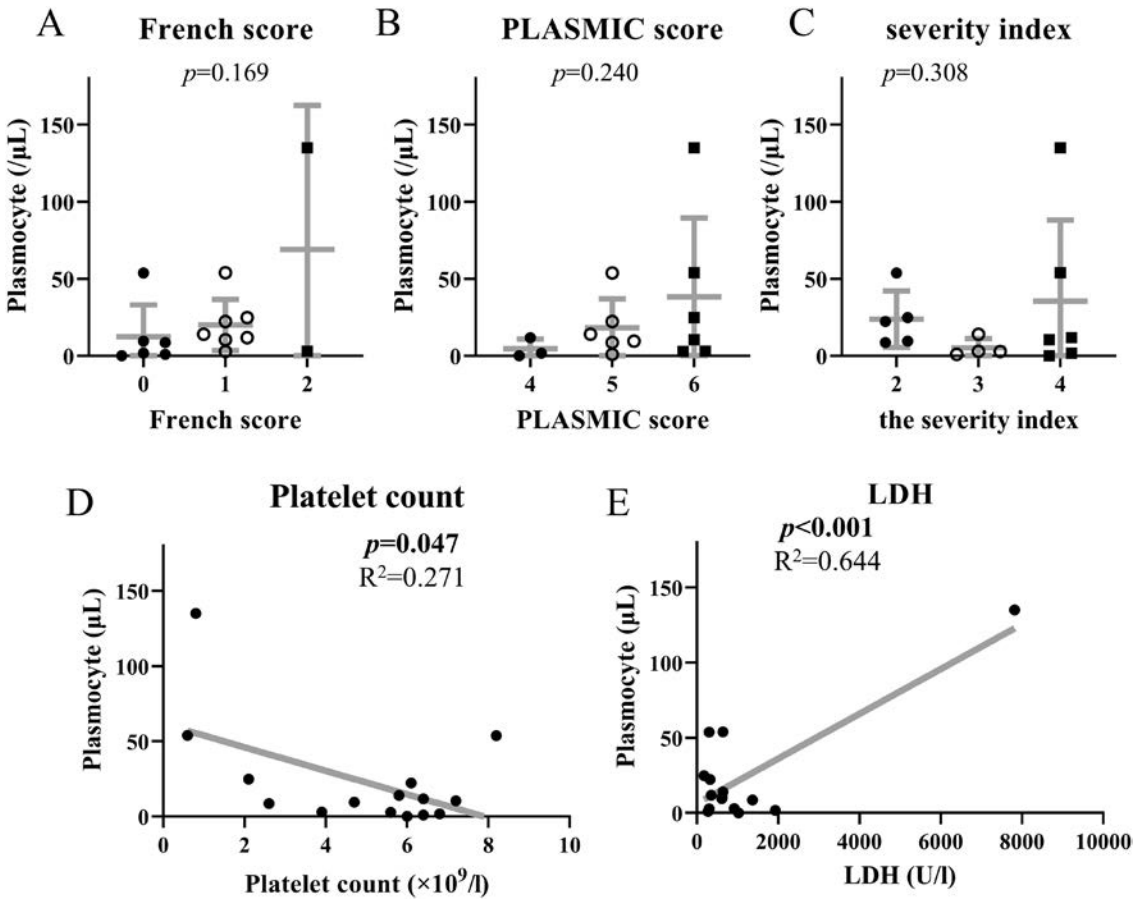

FIGURE 4 | (A) Comparison of plasmocyte with the severity index. (B) Comparison of plasmocyte with PLASMIC score. (C) Comparison of plasmocyte with French score. (D) Comparison of plasmocyte with platelet count. (E) Comparison of plasmocyte with LDH.

only subset that was also significantly increased in all cell subsets. Plasmocytes were not correlated with the severity score, PLASMIC score, or French score(Figure 4a–c), but were significantly inversely correlated with platelet count and significantly correlated with LDH (Figure 4d,e). This suggests that plasmocytes may be involved in the pathogenesis of TTP. In monocytes, all subsets were slightly increased, but not significantly different, and in DCs, all subsets were significantly lower in TTP than in healthy controls. Among NK cells, $CD16^+$ NK cells significantly decreased. These findings revealed that both the acquired and innate immune systems were abnormal in CTD-associated TTP/TMA. In particular, the acquired immune system has been found to exhibit abnormalities in plasmocyte differentiation.

RTX treatment decreased cell counts in all B cells, including plasmocytes (Figure 3; Table S5). With regard to T cells, both $CD4^+$ and $CD8^+$ T-cell counts recovered, with some subsets showing higher counts than in healthy controls. In the individual subset analysis, among $CD4^+$ T cells, effector memory $CD4^+$ T cells significantly recovered, and among $CD8^+$ T cells, $CXCR3^+CCR6^-$ $CD8^+$ T cells significantly recovered; however, no specific subset was biased toward recovery (Table S5). In the innate immune system, myeloid DCs, which were low before treatment, were significantly higher after treatment, although there were no significant changes in monocytes or NK cells.

4 | Discussion

This study examined the efficacy of adding RTX to plasma exchange and high-dose glucocorticoid therapy in refractory CTD-associated TTP/TMA in real-world settings.

CTD-associated TTP/TMA has been implicated in some autoimmune mechanisms, since the incidence of TMA in patients with CTD differs greatly from the incidence of TMA in the general population [40–42]. As mildly decreased ADAMTS13 activity is frequently observed in CTD-associated TTP/TMA, one hypothesis includes increased clearance by non-neutralizing antibodies. Other possible pathogeneses include vascular endothelial damage and complement hyperactivation due to abnormalities in complement regulatory factors, but the details are unspecified [43–45]. Although the treatment of CTD-associated TTP/TMA with glucocorticoids, cyclophosphamide, and other agents has been reported in a case report [6, 46, 47], many reports have used RTX, partly because RTX is effective in typical TTP [12–30].

The results suggest that adding RTX to GC therapy or performing plasma exchange for CTD-associated TTP/TMA may be worthwhile. In particular, focusing on the cause of death, there were no deaths due to hemorrhage associated with the progression of TTP/TMA in the GC + RTX group (Table S3). There was also a concern that RTX would increase deaths

from infections, but there was no difference in infection-related deaths between the two groups. Although the small sample size did not result in significant differences, there was a trend toward higher remission, thrombocyte remission, and weaning rates from plasma exchange in the GC + RTX group. Serum data also showed significant improvements in platelets, hemoglobin, and LDH from 8 to 52 weeks, suggesting the efficacy of RTX. In terms of renal function, there was no difference in Cre between the two groups, and the percentage of patients weaned from hemodialysis was not significantly different; however, more patients were weaned from hemodialysis with RTX. Regarding adverse events, because all patients were under immunosuppression, lung infections and CMV infection reactivation were more common, but there was no increase in infections or other adverse events in the GC + RTX group compared to the GC + IS group.

In the present study, we evaluated immunological abnormalities in CTD-associated TTP/TMA by performing a comprehensive immunophenotyping analysis of the peripheral blood prior to RTX. This is the first study to comprehensively evaluate immunophenotyping of the peripheral blood of patients with CTD-associated TTP/TMA. Although a decreased total lymphocyte count has been associated with poor prognosis of TTP in SLE [48], in the present case, lymphocytes were decreased in all patients, regardless of the underlying disease. This study suggests that immune abnormalities in patients with CTD-associated TTP/TMA are located in the acquired immune system. Among the acquired immune systems, only plasmocytes were significantly increased among all cell subsets. The increase in plasmocytes despite the decrease in PBMC cell counts revealed immunological features of increased B cell differentiation and consequent plasmocyte dominance, particularly in CTD-associated TTP/TMA.

Before treatment, plasmocytes were correlated with platelets and LDH, and RTX depleted the B cells and consequently reduced plasmocytes, which may have improved the pathogenesis of connective tissue pathological TTP/TMA. In contrast, the T cells recovered in cell number as a whole, suggesting that the T cells that were mobilized to peripheral tissues may have returned to the peripheral blood in response to treatment. The analysis of each subset did not recover heavily biased toward any particular subset, and it was not possible to determine which T cells were involved in CTD-associated TTP/TMA in this study. In the innate immune system, although the decrease in mDC was restored after treatment, as in the T-cell system, no judgment could be made regarding its significance.

This study has some limitations. First, this was a retrospective, observational study. TMA has recently been classified according to the underlying disease. However, in this study, the cases were examined retrospectively; therefore, the classification range differs from the current diagnostic criteria for TTP and the narrow definition of secondary TMA. In particular, some cases of secondary TMA overlap with the pathology of aHUS [49]; however, in this study, we could not completely rule out the involvement of aHUS pathology. However, none of the patients included in this study showed characteristic findings in C3 or C4. Second, the study involved an extremely rare condition, CTD-associated TTP/TMA, which forced us to analyze a limited number of cases: 15 in the GC + RTX group and 11 in the GC + IS group. Patients with CTD-associated TTP/TMA have a wide range of backgrounds, and to investigate the efficacy of RTX, a prospective study with a larger number of cases and consistent conditions is needed. Third, one patient with a history of RTX treatment was included in the GC + RTX group, which could introduce potential bias. However, this patient had received RTX treatment more than 2 years prior to the study. Furthermore, concurrent flow cytometry demonstrated sufficient detection of CD20-positive B cells, suggesting that the prior RTX treatment had minimal impact on the patient's clinical condition. Fourth, comprehensive immunophenotyping analysis was performed on the peripheral blood of patients, and immune abnormalities in the tissues were not analyzed. Despite the limitations, we report these results here because we found that plasmocytes correlate with platelet counts and LDH in patients with CTD-associated TTP/TMA, and because we believe the results suggest the clinical efficacy and safety of RTX acting on these progenitor cells.

5 | Conclusion

In CTD-associated TTP/TMA, B cells may influence pathology. Therefore, the addition of RTX to plasma exchange and GC therapies should be considered.

Author Contributions

All authors were involved in the drafting and critical revision of the manuscript. All authors approved the final version of the manuscript. N.O., S.N., and Y.T. designed the research study. S.F., Y.I., H.T., and Y.T. analyzed the data. N.O., S.N., and Y.T. wrote the manuscript. Y.T. supervised the research, created the research concept, and supervised the study.

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Conflicts of Interest

Y.M. has received consulting fees, speaking fees, and/or honoraria from Eli Lilly and has received research grants from GlaxoSmithKline. S.N. has received consulting fees, lecture fees, and/or honoraria from Bristol-Myers, AstraZeneca, Pfizer, GlaxoSmithKline, AbbVie, Astellas, Asahi-kasei, Sanofi, Chugai, Eisai, Gilead Sciences, Boehringer Ingelheim and has received research grants from Mitsubishi-Tanabe. Y.T. has received speaking fees and/or honoraria from Gilead, AbbVie, Boehringer-Ingelheim, Eli Lilly, Mitsubishi-Tanabe, Chugai, Amgen, YL Biologics, Eisai, Astellas, Bristol-Myers, and AstraZeneca; received research grants from Asahi-Kasei, AbbVie, Chugai, Mitsubishi-Tanabe, Eisai, Takeda, Corrona, Daiichi-Sankyo, Kowa, and Boehringer-Ingelheim; and received consultant fees from Eli Lilly, Daiichi-Sankyo, Taisho, Ayumi, Sanofi, GSK, and AbbVie. All other authors declare no conflicts of interest.

Data Availability Statement

Data cannot be shared for ethical/privacy reasons.

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ORIGINAL ARTICLE

Clinical Response to Adalimumab Therapy and Its Determinants in Patients With Radiographic Axial Spondyloarthritis: A Prospective Real-World Study in Taiwan

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ABSTRACT

Aim: To investigate the clinical response to adalimumab (ADA) in patients with active radiographic axial spondyloarthritis (r-axSpA) in Taiwan.

Methods: In this real-world study, patients with r-axSpA, starting ADA therapy, were enrolled and followed up every 12 weeks for 48 weeks. Outcome parameters were the proportion of patients with an improvement of 50% in Bath ankylosing spondylitis disease activity index (BASDAI50), inactive disease (ID, <1.3), and low disease activity (LDA, <2.1) per ankylosing spondylitis disease activity score–C-reactive protein (ASDAS-CRP) and ASDAS-erythrocyte sedimentation rate (ASDAS-ESR), and change in peripheral and extra-musculoskeletal manifestations. Determinants of BASDAI50 response to ADA were examined. Treatment-emergent adverse events (TEAEs) were recorded.

Results: Of 88 enrolled patients, 86 were analyzed, and 82 completed the study with all patients receiving 40 mg ADA fortnightly. Patients achieving BASDAI50 increased from 79.1% to 80.5% from weeks 12 to 48. At week 48, ASDAS-CRP and -ESR, ID, and LDA were improved from baseline in 60.8%, 74.7%, 42.1%, and 68.4% of patients, respectively. A decrease in enthesitis,

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peripheral arthritis, dactylitis, and uveitis was noted. Younger age, presence of uveitis, and use of conventional synthetic disease-modifying antirheumatic drugs were the determinants of treatment response. At least one TEAE was reported in 22.7%, serious AEs in 2.3% of patients, and no deaths. The most common TEAEs were upper respiratory tract infection (5.7%) and cough (3.4%).
Conclusions: This real-world, prospective study in Taiwan involving patients with active r-axSpA shows that ADA treatment effectively reduced disease activity and improved physical function. No new safety concerns were noted.

1 | Introduction

Radiographic axial spondyloarthritis (r-axSpA) is a complex, common inflammatory rheumatic disease affecting the axial skeleton, peripheral joints, and entheses [1]. r-axSpA is characterized by axial manifestations: inflammatory chronic back pain, stiffness in the back and waist; peripheral manifestations: dactylitis, enthesitis, arthritis; and extra-musculoskeletal manifestations (EMM): uveitis, psoriasis, and inflammatory bowel disease (IBD) [2–5]. A prevalence of 96.9 per 100000 people and an incidence of 24.4 per 100000 person-years has been reported in Taiwan between 2006 and 2015 [6].

The Taiwan Rheumatology Association consensus recommends treating r-axSpA to the clinical target of reaching clinical remission or at least minimal disease activity [4]. Although the minimal disease activity for r-axSpA has yet to be defined, the consensus recommends achieving ankylosing spondylitis disease activity score (ASDAS) of <2.1 and preferably <1.3 for the management of ankylosing spondylitis (AS) [4]. The Assessment of SpondyloArthritis International Society (ASAS)–European Alliance of Associations for Rheumatology (EULAR)'s 2022 update recommends using a predefined target agreed upon by shared decision between patient and rheumatologist as a guidance for treatment and use of ASDAS with C-reactive protein (CRP) as the preferred index for monitoring [5]. The Bath ankylosing spondylitis disease activity index (BASDAI) <4 with normal acute phase reactants is also a widely accepted indicator of low disease activity [4, 7].

More than 99% of the Taiwan population is covered under the National Health Insurance (NHI) program; therefore, the NHI reimbursement criteria strongly influence the management of patients with r-axSpA [4, 8]. Non-steroidal anti-inflammatory drugs (NSAIDs) remain first-line treatment of r-axSpA in Taiwan [4]. However, in the case of failure of the first-line treatment and after ruling out other causes, biologic therapy is recommended [4]. The NHI has strict reimbursement criteria for biologics: patient must be ≥ 18 years old, be positive for human leukocyte antigen (HLA)-B27, have radiographic evidence of sacroiliitis, and demonstrate at least two out of the following three conditions: limitations in lumbar flexion, limitations in chest expansion, or >3 months of lower back pain and morning stiffness that is not relieved by rest but improves with exercise. Additionally, biologics can be prescribed only if the patient has persistently high disease activity (BASDAI score ≥ 6 and erythrocyte sedimentation rate [ESR] >28 mm/1 h, and CRP >1 mg/dL in two consecutive tests, with at least a 4-week interval in between tests) and fails to respond to extensive treatment with at least two different NSAIDs (must have received continuous treatment at the same clinic or institution for 3 months or more, and must have used each NSAID for at least 4 weeks or more, unless discontinuation due to toxicity or tolerance occurs; patient with peripheral symptoms must have undergone extensive treatment with at least two NSAIDs and sulfasalazine). Furthermore, to continue treatment, patients receiving biologics must demonstrate $>50\%$ improvement or a decrease of at least 2 points in BASDAI after the first 12 weeks of treatment. The BASDAI should be evaluated every 12 weeks to continue the treatment [9].

Because of the endemic presence of tuberculosis (TB) in Taiwan, the TB risk management plan before initiation of biologics commenced in 2012. Every patient undergoes TB screening and preventive treatment as necessary before the start of biologic (tumor necrosis factor α inhibitor [TNFi] and interleukin-17 inhibitor) treatment [10].

Adalimumab, a TNFi, is indicated for active r-axSpA treatment. In a prospective observational study, Kneepkens et al. reported a 50.0% improvement in BASDAI in 42.6% of patients after 24 weeks of adalimumab treatment in 115 patients with r-axSpA, of whom only 30 were from Taiwan [11]. Moreover, active disease in this study was defined as BASDAI ≥ 4 or an ASDAS ≥ 2.1, which contrasts with the Taiwan NHI's definition of active disease (BASDAI ≥ 6) and eligibility criteria for biologic treatment [9, 11]. Furthermore, the Taiwan NHI does not reimburse increased dosing frequency outlined in the treatment protocol in the Kneepkens et al. study [11]. Although this study provided some clinical response data for adalimumab treatment in patients with r-axSpA from Taiwan, the sample size was small, patients enrolled were less severe than the Taiwan NHI criteria, and dose escalation intervention was not carried out. Moreover, the response of peripheral manifestations and EMMs to adalimumab treatment was not recorded.

Overall, real-world data on clinical response to adalimumab in patients with r-axSpA in Taiwan are limited. Assessing the clinical response to adalimumab in patients with r-axSpA is essential because of Taiwan NHI's specific and stringent eligibility criteria. Therefore, the objective of our real-world, prospective, observational study (EAST, NCT03505892) was to investigate the clinical response to adalimumab and its determinants in patients with active r-axSpA in Taiwan.

2 | Materials and Methods

2.1 | Patients

This was a real-world, prospective, observational study. Male or female patients with r-axSpA, aged ≥ 20 years, scheduled to start adalimumab treatment as per the Taiwan NHI criteria and prescribed as per local label, and who provided written informed consent were enrolled from 12 medical centers in Taiwan. Patients who had received treatment with any investigational drug or biologic within a minimum of 30 days or five half-lives

(whichever is longer) of the drug prior to the baseline visit were excluded. Additionally, patients who met any of the contraindications as per the local drug label in Taiwan were also excluded. A majority of patients were biologic-naïve; however, these data were not recorded.

On the basis of the proportion of patients (46.7%) who achieved 50% improvement in BASDAI at 24 weeks of adalimumab treatment from a previous study [11] and considering a dropout rate of 5%, a sample size of 84 was estimated to provide a similar BASDAI improvement with a precision of 10.5%.

2.2 | Study Design

Adalimumab 40 mg, every other week, was prescribed as per the local drug label to all patients. Study assessments were performed at baseline and at follow-up visits. The follow-up visits were aligned with existing clinical practice at each study site (Figure S1) and occurred at weeks 12, 24, 36, and 48 after adalimumab treatment initiation. The visit at week 48 was the final treatment visit. Patients were followed up for the next 70 days or 5 half-lives after the week 48 dosing or after the last dose of the study drug to obtain information on any new or ongoing adverse events (AEs).

The study protocol was approved by an independent ethics committee at each participating site, and written informed consent was obtained from the patients before the commencement of any study procedures.

2.3 | Study Assessments

Data on demographics, clinical history, comorbidities, and concomitant medications were collected at baseline. For the EMM frequency, data on history of uveitis, history or presence of active IBD, and presence of active psoriasis were collected. Clinical response to adalimumab was assessed using the BASDAI, ASDAS questionnaires, serum CRP, and ESR at each visit.

The BASDAI is a patient self-administered questionnaire that assesses six components: fatigue (degree of fatigue/tiredness experienced), spinal pain (r-axSpA-related pain in the neck, back, or hip), peripheral arthritis (pain or swelling in other joints), enthesitis (discomfort from any areas tender to touch), intensity of morning stiffness (pressure and discomfort from the time they wake up), and duration of morning stiffness (how long their morning stiffness lasts from the time they wake up) [12].

Patients filled out the BASDAI questionnaire at each visit on a scale of 0 to 10 (0 being none and 10 being very severe) [12]. ASDAS is a composite score of five components, comprising three questions from BASDAI (spinal pain, duration of morning stiffness, and peripheral pain/swelling), patient global assessment of disease activity, and either CRP or ESR levels [13].

At each visit, peripheral manifestations of disease activity were evaluated through the Maastricht ankylosing spondylitis enthesitis score (MASES) [14], tender joint count (TJC), swollen joint count (SJC), dactylitis count, and the presence of enthesitis of the plantar fascia or Achilles tendon, psoriasis, or IBD. The frequencies of experience of EMMs – acute anterior uveitis, psoriasis, and IBD – were also assessed at each visit.

Adverse events were recorded throughout the study duration and approximately 70 days or five half-lives after the week 48 dosing or after the last administration of adalimumab.

2.4 | Efficacy Outcomes

Efficacy outcomes were defined as the proportion of patients with 50% improvement or absolute improvement of two points in BASDAI (referred to as BASDAI50), clinically important improvement (ΔASDAS ≥ 1.1 and < 2.0 from baseline) and major improvement (ΔASDAS ≥ 2.0 from baseline) in ASDAS at 24 weeks post adalimumab initiation. These parameters were also assessed at every follow-up visit. Other outcome parameters assessed at every follow-up visit were the proportion of patients with inactive disease (ASDAS < 1.3), low disease activity ($1.3 \leq$ ASDAS score < 2.1), change from baseline in peripheral manifestations (enthesitis, dactylitis, peripheral arthritis, and enthesitis of the plantar fascia or Achilles tendon), EMM frequencies (uveitis, psoriasis, and IBD), and MASES score. In patients who had peripheral arthritis (≥ 1 swollen joint) at baseline, the change from baseline in TJC (range: 0–46) and SJC (range: 0–44) scores was also assessed at every follow-up visit.

2.5 | Safety Outcomes

All AEs were coded with the Medical Dictionary for Regulatory Activities (MedDRA version 20.1.) and grouped by system organ class (SOC) and preferred term (PT). A treatment-emergent adverse event (TEAE) was defined as an AE that commences on or after the first dose of adalimumab or worsens in severity during treatment related to the pre-treatment state.

2.6 | Statistical Analysis

The analyzable patient population included all patients who received at least one dose of adalimumab and have BASDAI results at baseline and week 24. No imputation of missing data was performed during this analysis. Continuous data are presented as mean and standard deviation (SD), while categorical data are presented as numbers and proportions.

The outcome parameters were analyzed as number and proportion of patients with 95% confidence intervals (CIs) at every visit. At every visit, the mean and SD of change from baseline in BASDAI score, ASDAS-CRP, ASDAS-ESR, CRP, and ESR were analyzed. The proportion of patients achieving inactive disease (ASDAS < 1.3) and low disease activity ($1.3 <$ ASDAS < 2.1) as per ASDAS-CRP and ASDAS-ESR w analyzed.

Logistic regression analysis was used to examine determinants of response to ADA treatment. The dependent variable

was BASDAI50 response at 24 weeks, while the independent variables were gender, age, BASDAI score, ASDAS-CRP and -ESR (inactive disease vs. low disease activity), TJC (>1 vs. ≤1), SJC (>1 vs. ≤1), presence or absence of dactylitis, uveitis, psoriasis, and conventional synthetic disease modifying antirheumatic drugs (csDMARDs) use. Because the dependent and majority of the independent variables were categorical, age and BASDAI score were converted to categorical variables classifying them above and below median (>38 vs. ≤38 years for age and >65 vs. ≤65 for BASDAI). Logistic regression analysis was also used to examine the determinants of BASDAI50 response at 24 weeks in patient subgroups: 1. non-smoker patients and 2. patients receiving csDMARDs. Odds ratio (OR) and 95% CI for these analyses were presented as a forest plot. All statistical analyses were performed using SAS version 9.4 or higher.

3 | Results

3.1 | Patient Disposition

The study duration was from 4 June 2018 to 30 June 2021. Eighty-eight patients were enrolled and received treatment; 86 were analyzed while 82 patients completed the study. Out of the six patients who discontinued from the study, three patients discontinued because of investigator's decision, two patients withdrew, and one patient discontinued for 'other' reason (Figure S2). At baseline and weeks 12 and 24, 86 patients, at week 36, 83 patients, and at week 48, 82 patients were receiving adalimumab.

3.2 | Demographic and Clinical Characteristics

The mean ± SD age was 40.7 ± 14.0 years (range: 20–72 years), and a mean ± SD disease duration since diagnosis was 6.5 ± 6.0 years (Table 1). BMI ranged from 16.1 kg/m^2 to 39.8 kg/m^2 with a mean ± SD of 25.1 ± 5.2 kg/m^2 with the majority of patients being male (76.1%, Table 1). Of the 88 patients, 65.9% were non-smokers, 18.2% smoked previously, and 15.9% were current smokers. No patient had a history of TB. Study drug adherence was reported to be 100% without any dose modifications. Almost all patients (98.9%) were receiving concomitant medications (Table 1).

TABLE 1 | Baseline characteristics of all patients.

Characteristics	All patients (n = 88)
Age (years)	40.7 ± 14.0
Range (years)	20–72
Gender (male), *n* (%)	67 (76.1)
Height (cm)	166.9 ± 8.1
Weight (kg)	69.7 ± 15.2
Body mass index (kg/m^2)	25.1 ± 5.2
Range (kg/m^2)	16.1–39.8
Serum CRP (mg/L)	28.4 ± 25.2
ESR (mm/h)	40.8 ± 21.8
Duration of r-axSpA (years)	6.5 ± 6.0
History of tuberculosis infection, *n* (%)	0 (0)
HLA-B27 positive	88 (100)
Tobacco use, *n* (%)	
Current smoker	14 (15.9)
Previous smoker	16 (18.2)
Non-smoker	58 (65.9)
Concomitant medications, *n* (%)	
csDMARDs	67 (76.1)
Corticosteroids	21 (23.9)
NSAIDs	87 (98.9)
Most common concomitant medications, *n* (%)	
Sulfasalazine	63 (71.6)
Etoricoxib	52 (59.1)
Celecoxib	46 (52.3)

Note: Data are mean ± SD, unless indicated otherwise.
Abbreviations: CRP, C-reactive protein; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; HLA-B27, human leukocyte antigen B27; NSAIDs, non-steroidal anti-inflammatory drugs; r-axSpA, radiographic axial spondyloarthritis; SD, standard deviation.

3.3 | Efficacy Outcomes

3.3.1 | Changes in BASDAI and ASDAS Scores

The baseline mean ± SD BASDAI score of 5.9 ± 2.2 improved to 2.4 ± 2.0 at week 24 and 2.0 ± 1.9 at week 48 (Table 2). The BASDAI50 was achieved by 79.1%, 75.6%, 80.7%, and 80.5% of patients at weeks 12, 24, 36, and 48, respectively (Figure S3a). After adalimumab initiation, the absolute change in BASDAI ranged from −34.8 ± 20.3 to −38.2 ± 23.4 from week 12 to week 48 (Figure S3b).

Improvements in ASDAS-CRP and ASDAS-ESR were also observed over the study period. ASDAS-CRP improved from a mean ± SD of 3.9 ± 0.9 at baseline to 1.5 ± 1.1 at week 24 and 1.4 ± 1.0 at week 48. The baseline mean ± SD ASDAS-ESR of 3.9 ± 0.9 improved to 1.9 ± 1.0 at week 24 and further to 1.7 ± 0.9 at week 48 (Table 2). The proportion of patients achieving ASDAS-CRP clinically important improvement ranged from 25.3% to 17.7%, and the major improvement ranged from 64.0% to 68.4% from week 12 to 48 (Figure S4a). A similar trend was also observed in ASDAS-ESR categorization (Figure S4b).

Post adalimumab therapy initiation, the proportion of patients with inactive disease and low disease activity as per ASDAS-CRP was 48.0% at week 12% and 50.0% at week 24, improving further to 60.8% at week 48. The proportion of patients with low disease activity at week 24 was 73.6% and in the range of 73.3% to 74.7% from weeks 12 to 48 (Figure 1a). Similar trends were

TABLE 2 | Disease activity at baseline and follow-up visits (analyzable patients).

Variables	Baseline	Week 12	Week 24	Week 36	Week 48
BASDAI, *N*	86	86	86	83	82
Mean ± SD	5.9 ± 2.2	2.4 ± 1.7	2.4 ± 2.0	2.1 ± 1.8	2.0 ± 1.9
ASDAS-CRP, *N*	86	75	72	74	79
Mean ± SD	3.9 ± 0.9	1.5 ± 0.9	1.5 ± 1.1	1.4 ± 1.0	1.4 ± 1.0
ASDAS-ESR, *N*	86	56	55	57	57
Mean ± SD	3.9 ± 0.9	1.9 ± 0.8	1.9 ± 1.0	1.9 ± 0.9	1.7 ± 0.9

Abbreviations: ASDAS, ankylosing spondylitis disease activity score; BASDAI, Bath ankylosing spondylitis disease activity index (range: 0–100 mm); CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; SD, standard deviation.

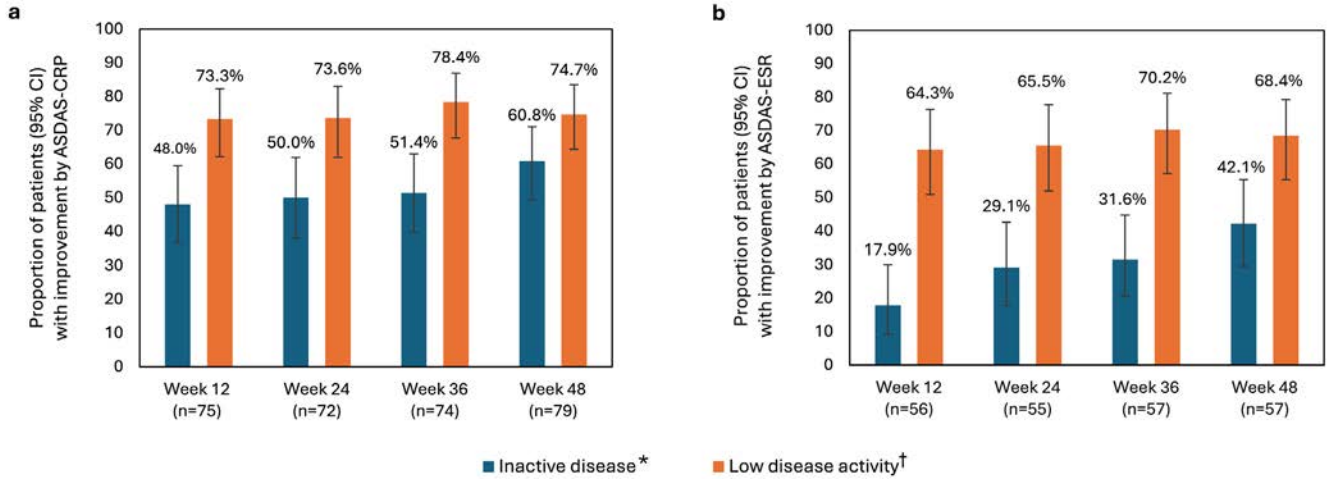

FIGURE 1 | Proportion of patients achieving ASDAS inactive disease and low disease activity (a) ASDAS-CRP (b) ASDAS-ESR. ASDAS, ankylosing spondylitis disease activity score; CI, confidence intervals; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate. *Inactive disease defined as ASDAS < 1.3, †low disease activity defined as ASDAS < 2.1.

seen in the proportions of patients with inactive disease and low disease activity categorized by ASDAS-ESR scores (Figure 1b).

3.3.2 | Determinants of BASDAI50 Response

Regression analysis showed that receiving csDMARDs treatment versus not receiving had the highest odds to achieve BASDAI50 response at week 24 with an OR (95% CI) of 2.72 (0.92–8.01). Patients who were ≤ 38 years of age (OR [95% CI], 1.88 [0.69–5.08]) and had uveitis (OR [95% CI], 1.50 [0.38–5.87]) were also likely to achieve BASDAI50 response at week 24 (Figure S5).

In the subgroup of non-smoker patients, the regression revealed that patients who were ≤ 38 years old (OR [95% CI], 3.00 [0.79–11.46]) and patients receiving csDMARDs (OR [95% CI], 1.33 [0.30–5.96]) were more likely to achieve BASDAI50 response at week 24 (Figure S6). In patients receiving csDMARDs, the likeliness of experiencing BASDAI50 response at week 24 was higher in patients who were aged ≤ 38 years (OR [95% CI], 1.52 [0.45–5.15]), were females (OR [95% CI], 1.20 [0.29–4.99]), had ≤ 1 SJC (OR [95% CI], 1.17 [0.23–5.94]), and had uveitis (OR [95% CI], 1.08 [0.26–4.54]) (Figure S7).

3.3.3 | Changes in Peripheral Manifestations and EMMs

The proportion of patients with enthesitis of the plantar fascia or Achilles tendon at baseline was 25.6% and decreased to 7.0% and 3.7% at weeks 24 and 48, respectively (Table 3). The proportion of patients with SJC decreased from 70.5% at baseline to 52.4% and 48.1% at weeks 24 and 48, respectively. The mean ± SD SJC count decreased from 3.0 ± 5.9 at baseline to 0.3 ± 1.1 at week 24 and 0.1 ± 0.3 at week 48. A similar trend was observed in TJC (Table 3). Post-adalimumab initiation, a notable decrease was observed in dactylitis (baseline: 6.8% patients; weeks 24 and 48: 0.0% patients, Table 3). The baseline mean ± SD MASES was 2.0 ± 2.7, which decreased over time to 0.4 ± 1.1 at week 48 (Table 3). Among the EMMs, a notable decrease was observed in uveitis (baseline: 18.2% patients; week 24: 2.3% patients; week 48: 0.0% of patients).

3.4 | Safety Outcomes

Overall, 20 patients (22.7%) experienced at least one TEAE. Two patients (2.3%) experienced serious AEs requiring hospitalization. One patient had pneumonia, which was ruled as probably

TABLE 3 | Peripheral and extra-musculoskeletal manifestations at baseline and follow-up visits (analyzable patients).

Variables	Baseline	Week 12	Week 24	Week 36	Week 48
Peripheral manifestations					
Enthesitis of the plantar fascia or Achilles tendon, *n*/*N* (%)	22/86 (25.6)	9/86 (10.5)	6/86 (7.0)	5/83 (6.0)	3/82 (3.7)
Peripheral arthritis					
SJC, *n*/*N* (%)	62/88 (70.5)	49/85 (57.6)	44/84 (52.4)	41/81 (50.6)	39/81 (48.1)
Mean ± SD	3.0 ± 5.9	0.6 ± 1.9	0.3 ± 1.1	0.3 ± 1.0	0.1 ± 0.3
TJC, *n*/*N* (%)	62/88 (70.5)	51/86 (59.3)	44/84 (52.4)	43/81 (53.1)	41/81 (50.6)
Mean ± SD	6.9 ± 7.4	3.3 ± 4.2	2.1 ± 4.0	1.5 ± 2.1	1.6 ± 2.1
Dactylitis, *n*/*N* (%)	6/88 (6.8)	3/86 (3.5)	0/86 (0.0)	0/83 (0.0)	0/82 (0.0)
Tender dactylitis count					
Mean ± SD	2.0 ± 1.3	1.0 ± 0.0	—	—	—
MASES, *n*/*N* (%)[a]	48/86 (55.8)	18/86 (20.9)	15/86 (17.4)	11/83 (13.3)	14/82 (17.1)
Mean ± SD	2.0 ± 2.7	0.6 ± 1.5	0.5 ± 1.2	0.3 ± 0.8	0.4 ± 1.1
Extra-musculoskeletal manifestations					
Uveitis, *n*/*N* (%)	16/88 (18.2)	2/86 (2.3)	2/86 (2.3)	0/83 (0.0)	0/82 (0.0)
Acute anterior uveitis episodes/year[b], mean ± SD	1.6 ± 1.4	0.5 ± 0.7	0.5 ± 0.7	—	—
Psoriasis, *n*/*N* (%)	2/88 (2.3)	1/86 (1.2)	2/86 (2.3)	1/83 (1.2)	1/82 (1.2)
Inflammatory bowel disease, *n*/*N* (%)	2/88 (2.3)	1/86 (1.2)	1/86 (1.2)	1/83 (1.2)	1/82 (1.2)

Abbreviations: MASES, Maastricht radiographic axial spondyloarthritis enthesitis score; SD, standard deviation; SJC, swollen joint count (range: 0–44); TJC, tender joint count (range: 0–46).
[a]MASES *n*/*N* (%) calculated as the number of patients with MASES score > 0.
[b]For follow-up visits, episodes of uveitis were reported from the last visit.

related to the study drug, and therefore, the study drug was discontinued. The other patient had abdominal pain, which resolved and was ruled out as probably not treatment related, and therefore, the study drug was continued. Overall, six patients (6.8%) experienced a TEAE that led to adalimumab discontinuation. Among these, two patients (2.3%) discontinued the study because of local reaction at the drug administration site in one patient and swelling at the drug administration site in the other patient. Among the remaining four patients, two patients experienced upper respiratory tract infections, one experienced TB infection, and one experienced pneumonia (same patient stated earlier). All these TEAEs were resolved. All TEAEs were either mild (15 patients, 17.0%) or moderate (8 patients, 9.1%). There were no deaths. The most common TEAEs experienced by SOC were infections and infestations (10 patients, 11.4%) and respiratory, thoracic, and mediastinal disorders (4 patients, 4.5%). The most common TEAEs by PT were upper respiratory tract infection (5 patients, 5.7%) and cough (3 patients each, 3.4%) (Table 4).

4 | Discussion

In this real-world, prospective, observational study, in patients with r-axSpA in Taiwan, treatment with 40 mg of adalimumab every other week for 48 weeks effectively reduced disease activity and improved physical function. Post adalimumab therapy initiation, clinical improvement was observed in patients by both BASDAI50 and ASDAS criteria. A decrease was observed in MASES and in the proportion of patients with enthesitis, peripheral arthritis, dactylitis, and uveitis. No new safety concerns were noted.

A previous multicenter observational study by Opris-Belinski et al. in European patients with r-axSpA reported BASDAI50 response in 78.9% (278/352) patients at 12 months post adalimumab treatment initiation [15]. The authors also observed a decrease from baseline to 12 months in mean ± SD BASDAI scores from 6.3 ± 2.1 to 2.0 ± 1.6 and ASDAS scores from 4.0 ± 1.1 to 1.7 ± 1.0 [15]. Kneepkens et al. reported BASDAI50 response in 42.6% of patients at 24 weeks post adalimumab treatment in patients from the Netherlands ($n = 85$) and Taiwan ($n = 30$) [11]. Furthermore, a real-world r-axSpA trial in Japan ($N = 216$) reported a BASDAI50 response in 42.5% (77/181) patients and 49.0% (70/143) patients at weeks 12 and 48, respectively [16]. A decrease in EMM was also reported in these patients [16]. Chen et al. reported a BASDAI50 response in 60.0% of patients at 24 weeks in a prospective study from China in patients with r-axSpA ($n = 35$) treated with TNFi (TNFi types were not specified) [17]. The baseline mean ± SD BASDAI score of 4.4 ± 1.0 decreased to 1.9 ± 1.3 at week 24, whereas the ASDAS-CRP

TABLE 4 | Summary of treatment-emergent adverse events by system organ class and preferred term occurring in ≥2 patients (all patients).

System organ class, preferred term	All patients ($N=88$), n (%)
At least one TEAE	20 (22.7)
Infections and infestations	10 (11.4)
Upper respiratory tract infection	5 (5.7)
Nasopharyngitis	2 (2.3)
Respiratory, thoracic and mediastinal disorders	4 (4.5)
Cough	3 (3.4)
Rhinorrhea	2 (2.3)
Sneezing	2 (2.3)
Cardiac disorder	2 (2.3)
Palpitations	2 (2.3)
Gastrointestinal disorders	2 (2.3)
General disorders and administration site conditions	2 (2.3)
Injury, poisoning and procedural complications	2 (2.3)
Vascular disorders	2 (2.3)
Hypertension	2 (2.3)

Abbreviation: TEAE, treatment-emergent adverse event.

score decreased from 2.8 ± 0.8 to 1.4 ± 0.8. Notably, we reported a higher proportion of patients achieving BASDAI50 response at week 24 (75.6%) than the abovementioned studies and a similar response at week 48 (80.5%) to the study by Opris-Belinski et al. (78.9%) [11, 15–17].

At baseline, we observed a history of uveitis in 18.2% of patients. In a similar HLA-B27 positive r-axSpA patient population from China, a history of uveitis was noted in 11.2% of patients ($n=3695$) [18]. Active uveitis was observed in 10.4% of patients from Japan ($n=396$, 55.5% HLA-B27 positive), and a history of uveitis was observed in 22.9% of patients from Europe–Latin America ($n=2097$, unknown HLA-B27 status), and 21.7% of patients from Sweden ($n=8517$, unknown HLA-B27 status) [16, 19, 20].

Psoriasis and IBD were observed in 2.3% of patients, each from our study. Psoriasis was observed in 0.7% of patients from China, 5.0% of patients from Taiwan, and 1.3% of patients from Japan, while IBD was observed in 1.5% of patients from all these studies [16, 18, 21].

In Chinese patients with r-axSpA who were HLA-B27 positive, enthesitis was reported in 64.6% of patients, dactylitis in 6.3% of patients, and peripheral arthritis in 27.0% of patients [18]. The proportion of patients with enthesitis from China was higher than in the patients from our study (25.6%), while the proportion of patients with dactylitis (6.8%) was comparable [18]. However, peripheral arthritis was observed in a higher proportion of patients (70.5%) in our study than that in China [18]. Peripheral arthritis was also higher in our patients compared with patients from other regions such as Europe, China, Latin America, Canada, and Arabia (32.8%) [22]. In patients possessing the HLA-B27 gene, a higher proportion of patients with uveitis has been observed than with psoriasis, IBD, and peripheral arthritis [18, 23]. Researchers have reported that HLA-B27 positive status is significantly associated with male sex, earlier age at disease onset and diagnosis, and uveitis [23, 24]. Consistent with this, all our patients were HLA-B27 positive, and the majority were male and were diagnosed before 40 years of age. The HLA-B27 gene positivity is observed in a higher proportion of Asian patients (78.2%–80.3%) than patients from Latin America, North America, Europe, and Africa (57.6%–73.0%) [22, 25]. The types of EMMs experienced by HLA-B27 positive patients with axial spondyloarthritis vary within different populations and between sexes and can be attributed to geographic variation [22, 24, 25].

We observed younger age, presence of uveitis, and receiving csDMARDs to be the determinants of response to treatment. Younger age and use of csDMARDs continued to be the determinants of treatment response even in patients who did not smoke. Furthermore, in patients who were receiving csDMARDs, the determinants were younger age, being female, and having SJC count of ≤1. A systematic review of the literature assessing predictors of r-axSpA remission (where remission is defined either as sustained or point remission) has also reported that younger age and concomitant use of csDMARDs are the most consistently reported determinants of r-axSpA remission [26]. Studies examining EMM as a determinant of response are limited; however, Lindström et al. reported the association of the presence of uveitis with TNFi drug retention in r-axSpA, possibly due to the TNFi's differential effects on uveitis [27]. Additionally, more than 70.0% of our patients were receiving sulfasalazine, which has been shown to improve the frequency and symptoms of peripheral arthritis [28, 29].

Because of the NHI eligibility criteria, all our patients were HLA-B27 positive, which might have contributed to the higher and faster response to adalimumab therapy [30]. Higher response to adalimumab has also been observed in patients with elevated levels of baseline CRP [22, 31, 32]. This could also be one reason for the higher response because our patients' mean baseline CRP levels were elevated (28.4 ± 25.2 mg/L) compared with patients from China (median [Q1, Q3]: 10.0 [3.1, 24.5]; 6.2 [1.9, 21.3]; mean ± SD: 0.63 ± 0.84) [17, 18, 21].

Only one patient from our study reported reactivation of TB, possibly because of the prophylaxis program. The effectiveness and safety of adalimumab in patients with active r-axSpA have been established and confirmed by many clinical trials [33–36]. It has been approved for treatment of active r-axSpA in Taiwan for over 15 years [26]. However, real-world data of clinical response to adalimumab in Taiwan patients with active r-axSpA was limited.

Our study has a few limitations, including that it was a single-arm study with no comparator. We could not report the response in terms of the ASAS criteria for 20% or 40% improvement, as

these data were not collected as part of the local practice. We suggest caution when interpreting the regression analysis results, as age and BASDAI score were converted to categorical variables, and the subgroup regression analyses were conducted on a limited number of patients. Nevertheless, this is the first study of real-world practice in Taiwan to report the clinical response, including EMMs, to adalimumab in patients with active r-axSpA.

5 | Conclusion

This real-world, prospective, observational study in patients with active r-axSpA from Taiwan reaffirmed that adalimumab therapy is effective in reducing the r-axSpA disease activity and improving physical functionality, peripheral manifestations, and EMMs. No new safety concerns were noted with adalimumab therapy.

Author Contributions

All authors conceived and designed the study and contributed to data analysis. All authors interpreted the results and critically reviewed the manuscript. All authors take responsibility for the integrity of the work as a whole and have given their approval for this version to be published.

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Ethics Statement

The study protocol was approved by an independent ethics committee at each participating site and written informed consent was obtained from the patients before the commencement of any study procedures.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

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

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ORIGINAL ARTICLE

Comparative Effectiveness of TNF-α and IL-6 Inhibitors on Bone Health Outcomes and Mortality in Rheumatoid Arthritis Patients: A Retrospective Cohort Study

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Keywords: bone health | fractures | IL-6 inhibitors | mortality | osteoporosis | rheumatoid arthritis | TNF-α inhibitors

ABSTRACT

Background: Rheumatoid arthritis (RA) significantly impacts bone health, leading to osteoporosis and increased fracture risks. This study aims to compare the effects of TNF-α and IL-6 inhibitors on the incidence of fractures, osteoporosis, and mortality among RA patients.

Methods: We conducted a retrospective cohort study using the TriNetX database, spanning from January 1, 2015, to December 31, 2022. The adult patients diagnosed with Rheumatoid Arthritis (RA) were identified and divided into two groups of new users of TNF-α and IL-6 inhibitors. Patients with prior fractures or who switched treatments post-index were excluded. Patients baseline characteristics were adjusted with propensity score matching (PSM). We compared TNF-α and IL-6 inhibitor cohorts in terms of fracture and osteoporosis incidence, and mortality employing Cox proportional hazards models for risk assessment, adjusting for potential confounders.

Results: The study included 2158 RA patients each in the TNF-α and IL-6 cohorts after PSM. Both cohorts had 71 osteoporosis/fractures during a 1-year follow-up. The adjusted HR (95% CI) was 0.987 (0.711–1.372) comparing TNFi versus IL-6is initiators.

Abbreviations: aHR, adjusted hazard ratio; b/ts DMARDs, biologic and targeted synthetic disease-modifying antirheumatic drugs; BMD, bone mineral density; CI, confidence interval; COPD, chronic obstructive pulmonary diseases; DMARDs, disease-modifying antirheumatic drugs; ICD, international classification of diseases; IL-6is, interleukin-6 inhibitors; KM, Kaplan–Meier; PSM, propensity score matching; RA, rheumatoid arthritis; TNFis, TNF inhibitors.

Hong Wang and I-Han Cheng contributed equally as first authors.

Similar results were shown stratified by age, sex, and steroid usage. However, all-cause mortality was significantly lower in the TNF-α cohort with an adjusted HR (95% CI) of 0.247 (0.114–0.536). Subgroup analyses showed the TNF-α cohort was associated with lower all-cause mortality among patients older than 65, male patients, and steroid users.

Conclusions: TNF-α and IL-6 inhibitors exhibit comparable effects on the risk of osteoporosis and fractures among RA patients. Notably, TNF-α inhibitors may offer advantages in reducing all-cause mortality, warranting further investigation.

1 | Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease primarily affecting the joints but can also have systemic impacts throughout the body [1]. Over time, the persistent inflammation may lead to severe joint damage and significant disability. One of the lesser-known but critically important systemic effects of RA is its impact on bone health. Patients with RA face a substantially increased risk of developing osteoporosis—a condition marked by decreased bone mass and density, leading to enhanced bone fragility [2]. This increased susceptibility to osteoporosis significantly heightens the risk of fractures. Studies have shown that individuals with RA have about 1.9 times [3] the incidence of osteoporosis and are 2.25 times [4] more likely to experience bone fractures than those without RA. These risks highlight the importance of considering bone health management as a crucial component of treating rheumatoid arthritis, underscoring the disease's extensive impact beyond the joints.

The treatment of RA has significantly advanced with the development of biologic and targeted synthetic disease-modifying antirheumatic drugs (b/ts DMARDs) [5]. These therapies are designed to specifically target immune pathways that contribute to the inflammatory process in RA. TNF inhibitors (TNFis) [5–8] and interleukin-6 inhibitors (IL-6is) are among the primary biologic options. TNFis, including agents like adalimumab and etanercept, block the inflammatory cytokine tumor necrosis factor and have shown effectiveness in reducing disease symptoms and preventing joint damage. IL-6is, such as tocilizumab and sarilumab, target interleukin-6 and are used especially in patients who do not respond adequately to TNFis. These treatment options are tailored based on disease severity, prior treatment responses, and individual patient needs, aiming to optimize disease management and improve patient outcomes.

Although b/tsDMARDs have revolutionized the treatment of RA, there remains a significant lack of comprehensive data regarding their effects on osteoporosis and the overall risk of fractures. These drugs are highly effective in controlling RA symptoms and disease progression, yet the extent to which they influence bone health remains poorly defined [9, 10]. While some observational studies have observed a reduced incidence of vertebral fractures in RA patients treated with TNFis compared to those treated with methotrexate [11, 12], they generally have not shown significant differences in the risk of other types of fractures when comparing TNFis with non-biologic DMARDs [13], abatacept [14], or tocilizumab [14]. However, these studies often suffer from limitations such as small sample sizes [11, 12] and a generalized approach that groups drugs into broad categories like TNFis and non-biologic DMARDs [13] without assessing the individual effects of each drug. To date, no randomized controlled trials (RCTs) have specifically investigated osteoporosis and general fracture risks as primary outcomes in patients undergoing b/tsDMARD treatment. The existing observational studies offer inconsistent results, constrained by their methodologies, which often involve small cohorts and fail to distinguish between the impacts of different medications. Recent large-scale studies suggest that b/tsDMARDs may not significantly mitigate the risk of osteoporosis or fractures among RA patients [15]. These studies frequently lack essential details such as biochemical data and comprehensive patient medical histories, which are crucial for a thorough assessment of how antirheumatic drugs interact with treatments for osteoporosis. This absence of detailed data underscores the need for more focused research to accurately assess the potential of various b/ts DMARDs to reduce fracture risks and enhance bone mineral density (BMD). Moreover, there is a noticeable shortage of information comparing the risks associated with different b/tsDMARDs concerning osteoporosis and fractures. Previous research has typically concentrated on short-term outcomes and bone turnover markers, which are insufficient for understanding the long-term effects of these treatments on bone health in RA patients. Driven by these deficiencies, our study aims to deliver contemporary insights into the risks of osteoporosis and general fractures in RA patients treated with b/tsDMARDs. The primary objective of this study is to investigate the comparative risks of osteoporosis and general fractures in RA patients who initiate treatment with TNFis or IL-6is. The secondary objective is to assess the impact of these treatments on all-cause mortality among RA patients. To our knowledge, this is also the first study to analyze the protective effects of TNFis and IL-6is on mortality among RA patients.

2 | Methods

2.1 | Study Design and Participants

This retrospective cohort study utilized data sourced from the TriNetX database, covering the period from January 1, 2015, to December 31, 2022. The research focused on adult patients, aged 18 years and older, who had been diagnosed with Rheumatoid Arthritis (RA), as identified by ICD-10 codes M05-M06. The study aimed to evaluate the effects of TNF-α and IL-6 inhibitors on the occurrence of fractures and osteoporosis. To this end, it excluded patients who had sustained any fractures prior to their index date or had switched between these treatments post-index date. A flow chart detailing the selection process is presented in Figure 1.

The TriNetX database serves as the foundation for this study's data collection, characterized by its high integrity and accuracy. This global health research network offers unparalleled access to electronic medical records (EMRs) from millions of patients, underpinned by stringent data governance protocols and best practices in data quality and validation. The platform's use of advanced analytics and sophisticated data

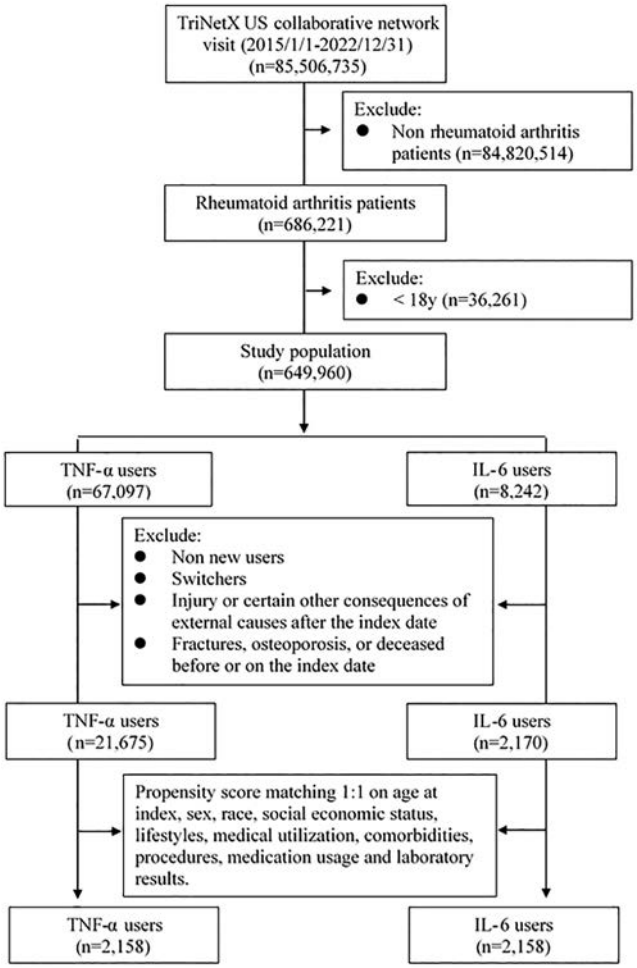

FIGURE 1 | Flowchart of cohort construction.

verification algorithms ensures that the extracted data for research purposes are current, historically accurate, and minimally biased, providing a robust basis for comprehensive and reliable analysis.

2.2 | Cohort Definition and Index Date Selection

Patients were classified into two cohorts based on their prescribed biologic treatment:

1. TNF-α inhibitor cohort:
   - Patients who were prescribed a TNF-α inhibitor at least twice between 2015/01/01 and 2022/12/31.
   - The index date was defined as the date of the first TNF-α prescription.
   - TNF-α inhibitors included: etanercept (Enbrel, 1998), infliximab (Remicade, 1998), adalimumab (Humira, 2002), certolizumab pegol (Cimzia, 2008), and golimumab (Simponi, 2009).
   - Exclusion criteria:
     - Prescribed a TNF-α inhibitor before January 1, 2015 (to ensure a new user cohort).
     - Any recorded fractures before or on the index date.
     - History of injury, poisoning, or other external causes (ICD-10 S00-T88) after the index date.
     - Switching to IL-6 inhibitors after the index date.
     - Deceased before or on the index date.
2. IL-6 Inhibitor Cohort:
   - Patients who were prescribed an IL-6 inhibitor at least twice between 2015/01/01 and 2022/12/31.
   - The index date was defined as the date of the first IL-6 prescription.
   - IL-6 inhibitors included: tocilizumab (Actemra, 2010), siltuximab (Sylvant, 2014), sarilumab (Kevzara, 2017), and satralizumab (Enspryng, 2020).
   - Exclusion criteria:
     - Prescribed an IL-6 inhibitor before January 1, 2015 (to ensure a new user cohort).
     - Any recorded fractures before or on the index date.
     - History of injury, poisoning, or other external causes (ICD-10 S00-T88) after the index date.
     - Switching to TNF-α inhibitors (ATC L04AB) after the index date.
     - Deceased before or on the index date.

2.3 | Addressing Immortal Time Bias

To minimize immortal time bias, follow-up began at prescription initiation for both the TNF-α and IL-6 inhibitor cohorts to ensure fair comparisons. Additionally, a time-dependent Cox model was considered to appropriately adjust for the potential bias introduced by the time between RA diagnosis and treatment initiation. This approach allows for a more accurate estimation of treatment effects while accounting for variations in the timing of drug administration.

2.4 | Outcome Measures

Follow-up began at prescription initiation (1 day–1 year) for both groups to ensure fair comparisons. The primary follow-up period for analysis was 1 year, but long-term outcomes were also assessed.

2.5 | Follow-Up Time

Cohort	Mean follow-up (days)	Standard deviation	Median follow-up (days)	Interquartile range
TNF-α	349.276	60.707	365	0
IL-6	348.196	62.207	365	0

Adherence data was not explicitly available; however, inclusion criteria required patients to have received at least two prescriptions for TNF-α or IL-6 inhibitors, which helps mitigate concerns regarding single-dose non-adherence. We acknowledge that detailed adherence data was unavailable, and this has been included as a limitation in the Discussion section. Follow-up began at prescription initiation (1 day–1 year) for both groups to ensure fair comparisons.

The primary outcomes were fractures and osteoporosis diagnosed after treatment initiation, identified through relevant ICD-10 codes. The secondary outcome was all-cause mortality during the follow-up period.

To minimize confounding, propensity score matching (PSM) was performed to balance baseline characteristics between the TNF-α and IL-6 inhibitor groups. Matching was conducted at a 1:1 ratio using a nearest-neighbor algorithm with a caliper of 0.1. Covariates included in the PSM process encompassed demographic factors (age, sex, race, socioeconomic status), lifestyle factors (tobacco use, alcohol-related disorders, and mobility issues), medical utilization (outpatient services, emergency department visits, and inpatient services), comorbidities (hypertension, cardiovascular diseases, chronic kidney disease, osteoporosis, diabetes, liver diseases, and anemia), and medication usage (corticosteroids, methotrexate, NSAIDs, bisphosphonates, calcium supplements, sex hormones, statins, and diuretics). While PSM adjusted for multiple confounders, RA disease severity markers such as DAS28 and CRP levels were not available in the dataset, which is acknowledged as a limitation in the Discussion section.

2.6 | Statistical Analysis

We employed descriptive statistics to summarize the demographic and clinical characteristics of the cohorts.

TriNetX's built-in service was used to calculate the propensity score and execute the 1: 1 propensity score matching (PSM). To compare the risks of developing fractures or osteoporosis between the two groups, Cox proportional hazards models were used, adjusting for potential confounders such as age, sex, comorbidities, and laboratory results (BMI, Calcium, Calcidiol, and Albumin). Hazard ratios (HRs) with 95% confidence intervals (CIs), and the test for proportionality were computed using R's Survival package v3.2–3.

2.7 | Role of the Funding Source

This work was supported by funding from Chung Shan Medical University Hospital (grant number CSH-2024-E-001-Y2). The funders had no role in the design and conduct of the study, the collection, analysis, interpretation of the data, or approval of the manuscript.

2.8 | Ethical Considerations

The Western Institutional Review Board (WIRB) has granted TriNetX a waiver because it solely aggregates counts and statistical summaries of de-identified information. The study protocol underwent review and approval by the Institutional Review Board (IRB) of Chung Shan Medical University Hospital (CSMUH No: CS2-21176), ensuring compliance with ethical standards. Given the retrospective nature of the study and the use of de-identified patient data, the requirement for informed consent was waived.

3 | Results

3.1 | Study Population and Baseline Characteristics

After propensity score matching, our cohort consisted of 2158 patients treated with TNFis and an equal number treated with IL-6is. The matched groups were comparable in terms of age, sex, and baseline comorbidities, ensuring a balanced comparison between the treatment arms. Detailed baseline characteristics are presented in Table 1.

3.2 | Primary Outcomes

The primary analysis focused on the incidence of fractures and osteoporosis, as well as all-cause mortality within 1 year of treatment initiation. We found no significant difference in the incidence of fractures or osteoporosis between patients treated with either type of inhibitor over a 1-year period, as presented in Table 2. This supports our hypothesis that both treatments have comparable impacts on bone health in RA patients. As illustrated in Figure 2 (Kaplan–Meier curve for any fractures or osteoporosis) and Figure 3 (Kaplan–Meier curve for all-cause mortality), the absolute risk of osteoporosis or fractures was 3.29% in both groups. The adjusted hazard ratio (HR) for any fractures or osteoporosis was 0.987 (0.711–1.372).

For specific outcomes, the incidence risk of any fractures had an HR of 0.657 (0.234–1.846), while the incidence risk of osteoporosis had an HR of 1.003 (1.003 0.714–1.409).

Notably, all-cause mortality was significantly lower in the TNF-α cohort compared to the IL-6 cohort, with an HR of 0.247 (0.114–0.536), suggesting a potential survival advantage associated with TNF-α inhibitors.

3.3 | Advanced Analytical Models

In addition to our primary analyses, we employed several progressively detailed models to assess the robustness of our findings concerning the effects of TNFis and IL-6is on the incidence of fractures, osteoporosis, and all-cause mortality. These models were adjusted for a broad spectrum of confounders, including demographic details, socioeconomic status, lifestyle factors, medical utilization, comorbidities, and treatment specifics. The outcomes of these analyses are summarized in Table 3.

3.4 | Longitudinal Analysis

Long-term outcomes were assessed through extended follow-up periods up to 7 years, revealing persistent non-significant differences in the incidence of fractures and osteoporosis between treatment groups over time (Table 4). This suggests the sustained comparability of TNFis and IL-6is in terms of their impact on bone health. Additionally, the all-cause mortality risk was observed to *increase over time* in both groups, but TNF-α

TABLE 1 | Baseline characteristics of study subjects (before and after matching).

Variables	Before PSM			After PSM		
	TNF-α users ($n = 21\,675$)	IL-6 users ($n = 2175$)	SMD	TNF-α users ($n = 2158$)	IL-6 users ($n = 2158$)	SMD
Age at Index	51.4 ± 14.5	53.0 ± 15.0	**0.110**	52.3 ± 14.7	52.9 ± 15.0	0.039
Mean ± SD	51.4 ± 14.5	53.0 ± 15.0	**0.110**	52.3 ± 14.7	52.9 ± 15.0	0.039
Sex, *n* (%)						
Female	15 239 (70.3)	1666 (76.6)	**0.143**	1700 (78.8)	1649 (76.4)	0.057
Male	5356 (24.7)	451 (20.7)	0.095	404 (18.7)	451 (20.9)	0.055
Race, *n* (%)						
White	14 581 (67.3)	1492 (68.6)	0.028	1490 (69.0)	1481 (68.6)	0.009
Black or African American	2371 (10.9)	284 (13.1)	0.065	254 (11.8)	280 (13.0)	0.037
Other Race	853 (3.9)	85 (3.9)	0.001	82 (3.8)	85 (3.9)	0.007
Asian	511 (2.4)	41 (1.9)	0.033	45 (2.1)	41 (1.9)	0.013
Unknown race	3181 (14.7)	257 (11.8)	0.084	273 (12.7)	255 (11.8)	0.025
Social economic status, *n* (%)						
Persons with potential health hazards related to socioeconomic and psychosocial circumstances	152 (0.7)	13 (0.6)	0.013	13 (0.6)	13 (0.6)	0.000
Lifestyles, *n* (%)						
Nicotine dependence	958 (4.4)	100 (4.6)	0.009	94 (4.4)	99 (4.6)	0.011
Personal history of nicotine dependence	644 (3.0)	82 (3.8)	0.044	59 (2.7)	80 (3.7)	0.055
Tobacco use	316 (1.5)	39 (1.8)	0.027	42 (1.9)	39 (1.8)	0.010
Alcohol related disorders	167 (0.8)	11 (0.5)	0.033	15 (0.7)	11 (0.5)	0.024
Reduced mobility	62 (0.3)	11 (0.5)	0.035	10 (0.5)	10 (0.5)	0.000
Dependence on wheelchair	13 (0.1)	10 (0.5)	0.079	10 (0.5)	10 (0.5)	0.000
Difficulty in walking, not elsewhere classified	79 (0.4)	10 (0.5)	0.015	10 (0.5)	10 (0.5)	0.000
Medical utilization, *n* (%)						
Office or other outpatient services	10 462 (48.3)	1176 (54.1)	**0.116**	1155 (53.5)	1162 (53.8)	0.007
Emergency department services	1362 (6.3)	175 (8.0)	0.068	158 (7.3)	172 (8.0)	0.024

(Continues)

TABLE 1 | (Continued)

Variables	Before PSM			After PSM		
	TNF-α users ($n = 21675$)	IL-6 users ($n = 2175$)	SMD	TNF-α users ($n = 2158$)	IL-6 users ($n = 2158$)	SMD
Preventive medicine services	1188 (5.5)	133 (6.1)	0.027	120 (5.6)	132 (6.1)	0.024
Hospital inpatient and observation care services	511 (2.4)	78 (3.6)	0.072	81 (3.8)	75 (3.5)	0.015
Comorbidities/procedures, *n* (%)						
Hypertensive diseases	3329 (15.4)	434 (20.0)	**0.121**	383 (17.7)	425 (19.7)	0.050
Disorders of lipoprotein metabolism and other lipidemias	2320 (10.7)	333 (15.3)	**0.137**	293 (13.6)	323 (15.0)	0.040
Systemic connective tissue disorders	1348 (6.2)	304 (14.0)	**0.260**	291 (13.5)	288 (13.3)	0.004
Vitamin D deficiency	1664 (7.7)	201 (9.2)	0.056	200 (9.3)	200 (9.3)	0.000
Overweight and obesity	1539 (7.1)	189 (8.7)	0.059	166 (7.7)	188 (8.7)	0.037
Chronic lower respiratory diseases	1318 (6.1)	176 (8.1)	0.078	162 (7.5)	173 (8.0)	0.019
Diabetes mellitus	1431 (6.6)	165 (7.6)	0.038	156 (7.2)	162 (7.5)	0.011
Other disorders of bone density and structure	872 (4.0)	147 (6.8)	**0.121**	135 (6.3)	136 (6.3)	0.002
Aplastic and other anemias and other bone marrow failure syndromes	954 (4.4)	141 (6.5)	0.092	117 (5.4)	135 (6.3)	0.036
Diseases of arteries, arterioles and capillaries	664 (3.1)	132 (6.1)	**0.144**	110 (5.1)	122 (5.7)	0.025
Diseases of liver	589 (2.7)	80 (3.7)	0.055	83 (3.8)	80 (3.7)	0.007
Other disorders of bone	493 (2.3)	70 (3.2)	0.058	62 (2.9)	67 (3.1)	0.014
Ischemic heart diseases	521 (2.4)	74 (3.4)	0.060	60 (2.8)	70 (3.2)	0.027
Chronic kidney disease (CKD)	393 (1.8)	64 (2.9)	0.074	47 (2.2)	61 (2.8)	0.042
Cerebrovascular diseases	239 (1.1)	42 (1.9)	0.068	45 (2.1)	38 (1.8)	0.024
Malnutrition	66 (0.3)	15 (0.7)	0.055	17 (0.8)	13 (0.6)	0.022
Unspecified dementia	18 (0.1)	10 (0.5)	0.072	10 (0.5)	10 (0.5)	0.000
Dual-energy X-ray absorptiometry (DXA), bone density study	406 (1.9)	80 (3.7)	**0.110**	68 (3.2)	77 (3.6)	0.023
Arthroplasty, total hip arthroplasty	17 (0.1)	10 (0.5)	0.074	10 (0.5)	10 (0.5)	0.000
Surgical Procedures on the Femur and Knee Joint	40 (0.2)	10 (0.5)	0.049	10 (0.5)	10 (0.5)	0.000
Comedication, *n* (%)						
Corticosteroids for systemic use	10091 (46.6)	1321 (60.7)	**0.287**	1304 (60.4)	1304 (60.4)	0.000

(Continues)

TABLE 1 | (Continued)

Variables	Before PSM			After PSM		
	TNF-α users ($n = 21\,675$)	IL-6 users ($n = 2175$)	SMD	TNF-α users ($n = 2158$)	IL-6 users ($n = 2158$)	SMD
NSAIDs	6640 (30.6)	697 (32.0)	0.030	734 (34.0)	691 (32.0)	0.042
Methotrexate	7579 (35.0)	657 (30.2)	**0.102**	654 (30.3)	654 (30.3)	0.000
Opioids	3638 (16.8)	513 (23.6)	**0.170**	469 (21.7)	505 (23.4)	0.040
HMG CoA reductase inhibitors	1985 (9.2)	260 (12.0)	0.091	243 (11.3)	251 (11.6)	0.012
Diuretics	1863 (8.6)	286 (13.1)	**0.147**	247 (11.4)	280 (13.0)	0.047
Calcium	1507 (7.0)	214 (9.8)	**0.104**	200 (9.3)	207 (9.6)	0.011
Sex hormones and modulators of the genital system	1281 (5.9)	174 (8.0)	0.082	181 (8.4)	171 (7.9)	0.017
Magnesium	624 (2.9)	103 (4.7)	0.097	91 (4.2)	100 (4.6)	0.020
Bisphosphonates	208 (1.0)	62 (2.9)	**0.139**	56 (2.6)	50 (2.3)	0.018
Denosumab	21 (0.1)	10 (0.5)	0.069	10 (0.5)	10 (0.5)	0.000
Teriparatide	10 (0.0)	10 (0.5)	0.082	10 (0.5)	10 (0.5)	0.000
Laboratories, *n* (%)						
BMI (kg/m^2)						
<30	3677 (17.0)	448 (20.6)	0.093	455 (21.1)	442 (20.5)	0.015
≧30	3162 (14.6)	360 (16.6)	0.054	304 (14.1)	356 (16.5)	0.067
Cholesterol in LDL in serum or plasma (mg/dL)						
<130	2401 (11.1)	354 (16.3)	**0.152**	296 (13.7)	347 (16.1)	0.066
≧130	657 (3.0)	122 (5.6)	**0.127**	86 (4.0)	120 (5.6)	0.074
Cholecalciferol (Vit D3) in serum or plasma (ng/mL)						
<20	53 (0.2)	13 (0.6)	0.055	10 (0.5)	13 (0.6)	0.019
20~<40	124 (0.6)	17 (0.8)	0.026	13 (0.6)	15 (0.7)	0.012
≧40	47 (0.2)	10 (0.5)	0.042	10 (0.5)	10 (0.5)	0.000
Calcidiol in serum or plasma (ng/mL)						
<20	472 (2.2)	36 (1.7)	0.038	35 (1.6)	36 (1.7)	0.004
20~<40	995 (4.6)	106 (4.9)	0.013	115 (5.3)	105 (4.9)	0.021

(Continues)

TABLE 1 | (Continued)

Variables	Before PSM			After PSM		
	TNF-α users ($n=21675$)	IL-6 users ($n=2175$)	SMD	TNF-α users ($n=2158$)	IL-6 users ($n=2158$)	SMD
≧40	430 (2.0)	58 (2.7)	0.045	51 (2.4)	58 (2.7)	0.021
Calcium in serum, plasma or blood (mg/dL)						
<8.5	687 (3.2)	115 (5.3)	**0.105**	123 (5.7)	111 (5.1)	0.025
8.5~<10.5	10410 (48.0)	1214 (55.8)	**0.156**	1166 (54.0)	1199 (55.6)	0.031
≧10.5	257 (1.2)	42 (1.9)	0.060	40 (1.9)	40 (1.9)	0.000
Magnesium in serum, plasma or blood (mg/dL)						
<1.5	95 (0.4)	15 (0.7)	0.034	19 (0.9)	15 (0.7)	0.021
1.5~<2.5	876 (4.0)	116 (5.3)	0.061	137 (6.3)	112 (5.2)	0.050
≧2.5	77 (0.4)	10 (0.5)	0.016	14 (0.6)	10 (0.5)	0.025
Phosphate in serum, plasma or blood (mg/dL)						
<3	315 (1.5)	48 (2.2)	0.056	49 (2.3)	46 (2.1)	0.009
3~<4.5	677 (3.1)	101 (4.6)	0.079	95 (4.4)	97 (4.5)	0.004
≧4.5	110 (0.5)	23 (1.1)	0.062	10 (0.5)	22 (1.0)	0.065
Cobalamin (Vitamin B12) in serum, plasma or blood (pg/mL)						
<200	39 (0.2)	10 (0.5)	0.050	10 (0.5)	10 (0.5)	0.000
200~<900	973 (4.5)	104 (4.8)	0.014	109 (5.1)	102 (4.7)	0.015
≧900	178 (0.8)	31 (1.4)	0.057	27 (1.3)	30 (1.4)	0.012
C reactive protein in serum, plasma or blood (mg/L)						
<3	3561 (16.4)	482 (22.2)	**0.146**	396 (18.4)	477 (22.1)	0.094
3~<5	1783 (8.2)	227 (10.4)	0.076	195 (9.0)	222 (10.3)	0.042
≧5	5040 (23.3)	598 (27.5)	0.098	577 (26.7)	587 (27.2)	0.010
eGFR (mL/min/1.73 m^2)						
<60	2049 (9.5)	302 (13.9)	**0.138**	243 (11.3)	292 (13.5)	0.069
60~<90	7137 (32.9)	852 (39.2)	**0.130**	866 (40.1)	840 (38.9)	0.025
≧90	6731 (31.1)	749 (34.4)	0.072	756 (35.0)	743 (34.4)	0.013

(Continues)

TABLE 1 | (Continued)

Variables	Before PSM			After PSM		
	TNF-α users ($n = 21\,675$)	IL-6 users ($n = 2175$)	SMD	TNF-α users ($n = 2158$)	IL-6 users ($n = 2158$)	SMD
Albumin in serum, plasma or blood (g/dL)						
< 3.5	1791 (8.3)	288 (13.2)	**0.161**	291 (13.5)	279 (12.9)	0.016
3.5 ~ 5.5	10 322 (47.6)	1223 (56.2)	**0.173**	1179 (54.6)	1208 (56.0)	0.027
> 5.5	207 (1.0)	26 (1.2)	0.023	19 (0.9)	25 (1.2)	0.028

Note: Propensity score matching was performed on age at index, sex, race, social economic status (persons with potential health hazards related to socioeconomic and psychosocial circumstances), lifestyles (tobacco use, personal history of nicotine dependence, nicotine dependence, alcohol related disorders, reduced mobility, dependence on wheelchair, difficulty in walking), medical utilization (office or other outpatient services, emergency department services, hospital inpatient and observation care services, preventive medicine services), comorbidities (hypertensive diseases, ischemic heart diseases, cerebrovascular diseases, diseases of arteries, arterioles and capillaries, chronic lower respiratory diseases, diseases of liver, diabetes mellitus, malnutrition, vitamin D deficiency, overweight and obesity, disorders of lipoprotein metabolism and other lipidemias, systemic connective tissue disorders, other disorders of bone density and structure, unspecified dementia, aplastic and other anemias and other bone marrow failure syndromes, chronic kidney disease, Other disorders of bone), procedures (total hip arthroplasty, surgical procedures on the femur and knee joint), medication usage (corticosteroids for systemic use, methotrexate, Bisphosphonates, Calcium, Sex hormones and modulators of the genital system, denosumab, teriparatide), and laboratory results (BMI, Calcium, Calcidiol, and Albumin). Bolded standardized mean differences (SMDs) ≥ 0.1 before matching indicate notable baseline imbalances between groups.
Abbreviations: BMI, body mass index; eGFR, glomerular filtration rate/1.73 sq. M. predicted in serum, plasma or blood by creatinine-based formula; HMG CoA, hydroxy-3-methylglutaryl coenzyme A; IL-6, interleukin-6 inhibitors; NSAIDs, non-steroids anti-inflammatory and anti-rheumatic products; PSM, propensity score matching; SD, standard deviation; SMD, standardized mean difference; TNF-α, tumor necrosis factor alpha inhibitors.

TABLE 2 | Comparative risk of fractures, osteoporosis, and all-cause mortality in RA patients treated with TNF-α versus IL-6 inhibitors over 1 year.

Outcomes	Patients with outcome		Adjusted hazard ratio (95% CI)[a]
	TNF-α users ($n = 2158$)	IL-6 users ($n = 2158$)	
Any fractures or osteoporosis	71	71	0.987 (0.711–1.372)
Any fractures	10	10	0.657 (0.234–1.846)
Osteoporosis	67	66	1.003 (0.714–1.409)
All-cause mortality	10	32	**0.247 (0.114–0.536)**

Note: If the patient is less or equal to 10, results show the count as 10. Bolded adjusted hazard ratios (HRs) indicate statistically significant findings, defined as 95% confidence intervals that do not include 1.0.
Abbreviations: CI, confidence interval; IL-6, interleukin-6 inhibitors; NA, not available; TNF-α, tumor necrosis factor alpha inhibitors.
[a]Propensity score matching was performed on age at index, sex, race, social economic status (persons with potential health hazards related to socioeconomic and psychosocial circumstances), lifestyles (tobacco use, personal history of nicotine dependence, nicotine dependence, alcohol related disorders, reduced mobility, dependence on wheelchair, difficulty in walking), medical utilization (office or other outpatient services, emergency department services, hospital inpatient and observation care services, preventive medicine services), comorbidities (hypertensive diseases, ischemic heart diseases, cerebrovascular diseases, diseases of arteries, arterioles and capillaries, chronic lower respiratory diseases, diseases of liver, diabetes mellitus, malnutrition, vitamin D deficiency, overweight and obesity, disorders of lipoprotein metabolism and other lipidemias, systemic connective tissue disorders, other disorders of bone density and structure, unspecified dementia, aplastic and other anemias and other bone marrow failure syndromes, chronic kidney disease, Other disorders of bone), procedures (total hip arthroplasty, surgical procedures on the femur and knee joint), medication usage (corticosteroids for systemic use, methotrexate, Bisphosphonates, Calcium, Sex hormones and modulators of the genital system, denosumab, teriparatide), and laboratory results (BMI, Calcium, Calcidiol, and Albumin).

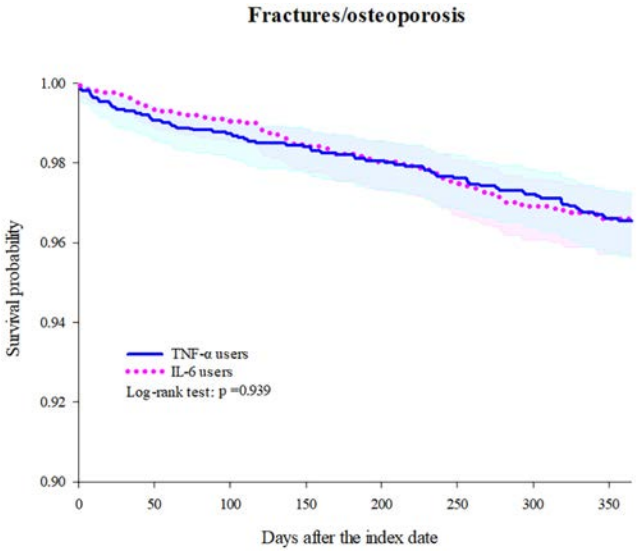

FIGURE 2 | Kaplan–Meier curve for the cumulative probability of any fractures or osteoporosis in patients treated with TNF-α inhibitors and IL-6 inhibitors.

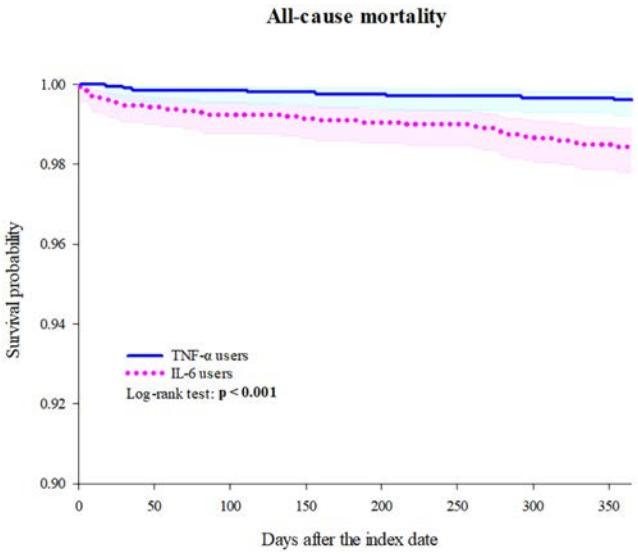

FIGURE 3 | Kaplan–Meier curve for the all-cause mortality in RA patients treated with TNF-α inhibitors and IL-6 inhibitors.

users consistently demonstrated a *lower adjusted hazard ratio* (*aHR*) compared to IL-6 users, with a trend toward a *greater survival advantage* at longer follow-up durations.

3.5 | Subgroup Analyses

Subgroup analyses were conducted to explore differences in outcomes based on age and sex, which provided additional insights into the demographic-specific effects of TNFis and IL-6is. Among younger patients (ages 18–64), there were no significant differences in the risk of fractures or osteoporosis between the two treatment groups. However, in the older cohort (≥65 years), TNF-α users exhibited a significantly lower risk of all-cause mortality with an aHR of 0.349 (0.148–0.825), highlighting a potential benefit in survival for elderly patients treated with TNF-α

TABLE 3 | Risk of outcomes adjusted for different variables (1 day to 1 year).

Outcomes (TNF-α users vs. IL-6 users)	Hazard ratio (95% CI)			
	Model 1[a]	Model 2[b]	Model 3[c]	Model 4[d] (original)
Any fractures or osteoporosis	0.788 (0.618–1.003)	0.842 (0.601–1.178)	0.731 (0.516–1.036)	0.987 (0.711–1.372)
Any fractures	**0.359 (0.178–0.723)**	0.296 (0.082–1.077)	0.296 (0.081–1.075)	0.657 (0.234–1.846)
Osteoporosis	0.816 (0.636–1.048)	0.875 (0.620–1.234)	0.741 (0.517–1.062)	1.003 (0.714–1.409)
All-cause mortality	**0.362 (0.245–0.535)**	**0.371 (0.191–0.721)**	**0.524 (0.291–0.944)**	**0.247 (0.114–0.536)**

Note: Proportionality <0.001. Bolded hazard ratios (HRs) indicate statistically significant findings, defined as 95% confidence intervals that do not include 1.0.

Abbreviations: CI, confidence interval; IL-6, interleukin-6 inhibitors; NA, not available; TNF-α, tumor necrosis factor alpha inhibitors.

[a]Crude, before matching.

[b]Propensity score matching was performed on age at index, sex, and race.

[c]Propensity score matching was performed on age at index, sex, race, socioeconomic status (persons with potential health hazards related to socioeconomic and psychosocial circumstances), lifestyles (tobacco use, personal history of nicotine dependence, nicotine dependence, alcohol related disorders, reduced mobility, dependence on wheelchair, difficulty in walking), and medical utilization (office or other outpatient services, emergency department services, hospital inpatient and observation care services, preventive medicine services).

[d]Propensity score matching was performed on age at index, sex, race, social economic status (persons with potential health hazards related to socioeconomic and psychosocial circumstances), lifestyles (tobacco use, personal history of nicotine dependence, nicotine dependence, alcohol related disorders, reduced mobility, dependence on wheelchair, difficulty in walking), medical utilization (office or other outpatient services, emergency department services, hospital inpatient and observation care services, preventive medicine services), comorbidities (hypertensive diseases, ischemic heart diseases, cerebrovascular diseases, diseases of arteries, arterioles and capillaries, chronic lower respiratory diseases, diseases of liver, diabetes mellitus, malnutrition, vitamin D deficiency, overweight and obesity, disorders of lipoprotein metabolism and other lipidemias, systemic connective tissue disorders, other disorders of bone density and structure, unspecified dementia, aplastic and other anemias and other bone marrow failure syndromes, chronic kidney disease, Other disorders of bone), procedures (total hip arthroplasty, surgical procedures on the femur and knee joint), medication usage (corticosteroids for systemic use, methotrexate, Bisphosphonates, Calcium, Sex hormones and modulators of the genital system, denosumab, teriparatide), and laboratory results (BMI, Calcium, Calcidiol, and Albumin).

TABLE 4 | Risk of outcomes-different follow up duration.

Outcomes (TNF-α users vs. IL-6 users)	Adjusted hazard ratio (95% CI)[a]			
	1 day to 1 year (original)	1 day to 3 years	1 day to 5 years	1 day to 7 years
Any fractures or osteoporosis	0.987 (0.711–1.372)	1.134 (0.891–1.443)	1.113 (0.893–1.388)	1.125 (0.908–1.393)
Any fractures	0.657 (0.234–1.846)	1.032 (0.485–2.197)	1.099 (0.565–2.139)	0.909 (0.481–1.718)
Osteoporosis	1.003 (0.714–1.409)	1.124 (0.878–1.439)	1.106 (0.883–1.385)	1.135 (0.911–1.413)
All-cause mortality	**0.247 (0.114–0.536)**	**0.375 (0.244–0.577)**	**0.508 (0.357–0.723)**	**0.604 (0.440–0.829)**[a]

Note: Proportionality <0.001. Bolded adjusted hazard ratios (HRs) indicate statistically significant findings, defined as 95% confidence intervals that do not include 1.0.

Abbreviations: CI, confidence interval; IL-6, interleukin-6 inhibitors; NA, not available; TNF-α, tumor necrosis factor alpha inhibitors.

[a]Propensity score matching was performed on age at index, sex, race, socioeconomic status (persons with potential health hazards related to socioeconomic and psychosocial circumstances), lifestyles (tobacco use, personal history of nicotine dependence, nicotine dependence, alcohol related disorders, reduced mobility, dependence on wheelchair, difficulty in walking), medical utilization (office or other outpatient services, emergency department services, hospital inpatient and observation care services, preventive medicine services), comorbidities (hypertensive diseases, ischemic heart diseases, cerebrovascular diseases, diseases of arteries, arterioles and capillaries, chronic lower respiratory diseases, diseases of liver, diabetes mellitus, malnutrition, vitamin D deficiency, overweight and obesity, disorders of lipoprotein metabolism and other lipidemias, systemic connective tissue disorders, other disorders of bone density and structure, unspecified dementia, aplastic and other anemias and other bone marrow failure syndromes, chronic kidney disease, Other disorders of bone), procedures (total hip arthroplasty, surgical procedures on the femur and knee joint), medication usage (corticosteroids for systemic use, methotrexate, Bisphosphonates, Calcium, Sex hormones and modulators of the genital system, denosumab, teriparatide), and laboratory results (BMI, Calcium, Calcidiol, and Albumin).

inhibitors (Table 2). This trend persisted across gender stratifications, where no significant differences were observed in bone health outcomes between males and females treated with either TNFis or IL-6is, as shown in Table 5.

This trend persisted across gender stratifications, where no significant differences were observed in bone health outcomes between males and females treated with either TNFis or IL-6is, as shown in Table 3. This consistency across subgroups reinforces the primary findings and suggests that treatment effects are similar regardless of sex, with the noted exception of improved survival rates in male TNF-α users.

Additionally, we performed subgroup analyses to examine the impact of concomitant steroid usage on the outcomes. These analyses revealed nuanced differences in the effects of TNFis and IL-6is on bone health and mortality, contingent upon steroid use. As shown in Table 6, the risk assessments for fractures, osteoporosis, and all-cause mortality among users of corticosteroids did not display significant differences between the two cohorts, suggesting that the influence of these treatments on bone health outcomes is consistent, regardless of corticosteroid use.

3.6 | Sensitivity Analyses

To ensure robustness, sensitivity analyses included patients who switched treatments post-index date. These analyses (Tables 7 and 8) demonstrated that excluding switchers did not significantly alter the hazard ratios, confirming the stability and reliability of our primary findings across different patient management scenarios. Specifically, the all-cause mortality rate remained lower in the TNF-α group, even when treatment switchers were included, reinforcing the potential survival advantage of TNF-α inhibitors.

4 | Discussion

Our retrospective cohort analysis found no significant difference in the incidence of osteoporosis or fractures between RA patients treated with TNFis versus those treated with IL-6is. The results were generally consistent in different subgroup analyses. This suggests comparable effects of both types of b/ts DMARDs on bone health, aligning with existing literature that often yields inconclusive or varied outcomes regarding their specific impacts on bone density and fracture risks. However, a notable finding from our study was a lower rate of all-cause mortality among patients receiving TNFis. This observation highlights a potential systemic advantage of TNFis beyond their anti-inflammatory and joint-protective effects. The reasons for this mortality benefit remain unclear but are likely to involve interactions between drug effects and patient characteristics that influence overall health and longevity.

In RA, a disease characterized by chronic systemic inflammation, the interplay of inflammatory cytokines like TNF-α and IL-6 [16–20] with the pathogenesis of osteoporosis is complex and intriguing [21–24]. TNFis are well recognized for their efficacy in suppressing inflammation and joint destruction, which inadvertently benefits bone health by hindering the

TABLE 5 | Risk of outcomes (1 day to 1 year) stratified by sex.

Outcomes	Male			Female		
	TNF-α users (patients with outcome/ patients in cohort)	IL-6 users (patients with outcome/ patients in cohort)	Adjusted hazard ratio (95% CI)[a]	TNF-α users (patients with outcome/ patients in cohort)	IL-6 users (patients with outcome/ patients in cohort)	Adjusted hazard ratio (95% CI)[a]
Any fractures or osteoporosis	10/443	10/443	1.312 (0.294–5.860)	57/1652	66/1652	0.859 (0.603–1.224)
Any fractures	10/443	10/443	1.964 (0.178–21.65)	10/1652	10/1652	0.498 (0.150–1.654)
Osteoporosis	10/443	10/443	0.983 (0.198–4.872)	56/1652	61/1652	0.914 (0.636–1.314)
All-cause mortality	10/443	14/443	**0.281 (0.093–0.854)**	13/1652	17/1652	0.762 (0.370–1.569)

Note: If the patient is less or equal to 10, results show the count as 10. Bolded adjusted hazard ratios (HRs) indicate statistically significant findings, defined as 95% confidence intervals that do not include 1.0.
Abbreviations: CI, confidence interval; IL-6, interleukin-6 inhibitors; TNF-α, tumor necrosis factor alpha inhibitors.
[a]Propensity score matching was performed on age at index, sex, race, social economic status (persons with potential health hazards related to socioeconomic and psychosocial circumstances), lifestyles (tobacco use, personal history of nicotine dependence, nicotine dependence, alcohol related disorders, reduced mobility, dependence on wheelchair, difficulty in walking), medical utilization (office or other outpatient services, emergency department services, hospital inpatient and observation care services, preventive medicine services), comorbidities (hypertensive diseases, ischemic heart diseases, cerebrovascular diseases, diseases of arteries, arterioles and capillaries, chronic lower respiratory diseases, diseases of liver, diabetes mellitus, malnutrition, vitamin D deficiency, overweight and obesity, disorders of lipoprotein metabolism and other lipidemias, systemic connective tissue disorders, other disorders of bone density and structure, unspecified dementia, aplastic and other anemias and other bone marrow failure syndromes, chronic kidney disease, Other disorders of bone), procedures (total hip arthroplasty, surgical procedures on the femur and knee joint), medication usage (corticosteroids for systemic use, methotrexate, Bisphosphonates, Calcium, Sex hormones and modulators of the genital system, denosumab, teriparatide), and laboratory results (BMI, Calcium, Calcidiol, and Albumin).

TABLE 6 | Risk of outcomes (1 day to 1 year) stratified by steroid usage.

Outcomes	With corticosteroids[a]			Without corticosteroids[b]		
	TNF-α users (patients with outcome/ patients in cohort)	IL-6 users (patients with outcome/ patients in cohort)	Adjusted hazard ratio (95% CI)[c]	TNF-α users (patients with outcome/ patients in cohort)	IL-6 users (patients with outcome/ patients in cohort)	Adjusted hazard ratio (95% CI)[c]
Any fractures or osteoporosis	39/1457	51/1457	0.752 (0.496–1.142)	21/629	21/629	0.993 (0.542–1.818)
Any fractures	10/1457	10/1457	0.329 (0.089–1.216)	0/629	10/629	NA
Osteoporosis	37/1457	46/1457	0.792 (0.514–1.221)	21/629	21/629	0.993 (0.542–1.818)
All-cause mortality	11/1457	28/1457	**0.389 (0.194–0.782)**	10/629	10/629	0.985 (0.246–3.938)

Note: If the patient is less or equal to 10, results show the count as 10. Bolded adjusted hazard ratios (HRs) indicate statistically significant findings, defined as 95% confidence intervals that do not include 1.0.
Abbreviations: CI, confidence interval; IL-6, interleukin-6 inhibitors; NA, not available; TNF-α, tumor necrosis factor alpha inhibitors.
[a]Corticosteroids (ATC code:H02) were prescribed within 1 year before or on the index date.
[b]Corticosteroids (ATC code:H02) were not prescribed within 1 year before or on the index date.
[c]Propensity score matching was performed on age at index, sex, race, social economic status (persons with potential health hazards related to socioeconomic and psychosocial circumstances), lifestyles (tobacco use, personal history of nicotine dependence, nicotine dependence, alcohol related disorders, reduced mobility, dependence on wheelchair, difficulty in walking), medical utilization (office or other outpatient services, emergency department services, hospital inpatient and observation care services, preventive medicine services), comorbidities (hypertensive diseases, ischemic heart diseases, cerebrovascular diseases, diseases of arteries, arterioles and capillaries, chronic lower respiratory diseases, diseases of liver, diabetes mellitus, malnutrition, vitamin D deficiency, overweight and obesity, disorders of lipoprotein metabolism and other lipidemias, systemic connective tissue disorders, other disorders of bone density and structure, unspecified dementia, aplastic and other anemias and other bone marrow failure syndromes, chronic kidney disease, Other disorders of bone), procedures (total hip arthroplasty, surgical procedures on the femur and knee joint), medication usage (corticosteroids for systemic use, methotrexate, Bisphosphonates, Calcium, Sex hormones and modulators of the genital system, denosumab, teriparatide), and laboratory results (BMI, Calcium, Calcidiol, and Albumin).

TABLE 7 | Risk of outcomes (1 day to 1 year) stratified by age at index date.

	18 ~ 64 years			≧ 65 years		
Outcomes	**TNF-α users (patients with outcome/ patients in cohort)**	**IL-6 users (patients with outcome/ patients in cohort)**	**Adjusted hazard ratio (95% CI)[a]**	**TNF-α users (patients with outcome/ patients in cohort)**	**IL-6 users (patients with outcome/ patients in cohort)**	**Adjusted hazard ratio (95% CI)[a]**
Any fractures or osteoporosis	27/1664	38/1664	0.700 (0.427–1.146)	45/556	46/556	0.972 (0.644–1.466)
Any fractures	10/1664	10/1664	0.494 (0.090–2.697)	10/556	10/556	0.166 (0.020–1.380)
Osteoporosis	25/1664	34/1664	0.725 (0.432–1.214)	45/556	45/556	0.994 (0.658–1.502)
All-cause mortality	10/1664	12/1664	0.493 (0.185–1.315)	10/556	20/556	**0.349 (0.148–0.825)**

Note: If the patient is less or equal to 10, results show the count as 10. Bolded adjusted hazard ratios (HRs) indicate statistically significant findings, defined as 95% confidence intervals that do not include 1.0.
Abbreviations: CI, confidence interval; IL-6, interleukin-6 inhibitors; TNF-α, tumor necrosis factor alpha inhibitors.
[a]Propensity score matching was performed on age at index, sex, race, social economic status (persons with potential health hazards related to socioeconomic and psychosocial circumstances), lifestyles (tobacco use, personal history of nicotine dependence, nicotine dependence, alcohol related disorders, reduced mobility, dependence on wheelchair, difficulty in walking), medical utilization (office or other outpatient services, emergency department services, hospital inpatient and observation care services, preventive medicine services), comorbidities (hypertensive diseases, ischemic heart diseases, cerebrovascular diseases, diseases of arteries, arterioles and capillaries, chronic lower respiratory diseases, diseases of liver, diabetes mellitus, malnutrition, vitamin D deficiency, overweight and obesity, disorders of lipoprotein metabolism and other lipidemias, systemic connective tissue disorders, other disorders of bone density and structure, unspecified dementia, aplastic and other anemias and other bone marrow failure syndromes, chronic kidney disease, Other disorders of bone), procedures (total hip arthroplasty, surgical procedures on the femur and knee joint), medication usage (corticosteroids for systemic use, methotrexate, Bisphosphonates, Calcium, Sex hormones and modulators of the genital system, denosumab, teriparatide), and laboratory results (BMI, Calcium, Calcidiol, and Albumin).

TABLE 8 | Risk of outcomes (1 day to 1 year) not excluded switchers.

Outcomes	Patients with outcome		Adjusted hazard ratio (95% CI)[a]
	TNF-α users ($n = 2806$)	IL-6 users ($n = 2806$)	
Any fractures or osteoporosis	75	97	0.766 (0.566–1.035)
Any fractures	10	12	0.496 (0.186–1.322)
Osteoporosis	73	89	0.813 (0.597–1.108)
All-cause mortality	17	36	**0.469 (0.264–0.835)**

Note: If the patient is less or equal to 10, results show the count as 10. Bolded adjusted hazard ratios (HRs) indicate statistically significant findings, defined as 95% confidence intervals that do not include 1.0.
Abbreviations: CI, confidence interval; IL-6, interleukin-6 inhibitors; TNF-α, tumor necrosis factor alpha inhibitors.
[a]Propensity score matching was performed on age at index, sex, race, social economic status (persons with potential health hazards related to socioeconomic and psychosocial circumstances), lifestyles (tobacco use, personal history of nicotine dependence, nicotine dependence, alcohol related disorders, reduced mobility, dependence on wheelchair, difficulty in walking), medical utilization (office or other outpatient services, emergency department services, hospital inpatient and observation care services, preventive medicine services), comorbidities (hypertensive diseases, ischemic heart diseases, cerebrovascular diseases, diseases of arteries, arterioles and capillaries, chronic lower respiratory diseases, diseases of liver, diabetes mellitus, malnutrition, vitamin D deficiency, overweight and obesity, disorders of lipoprotein metabolism and other lipidemias, systemic connective tissue disorders, other disorders of bone density and structure, unspecified dementia, aplastic and other anemias and other bone marrow failure syndromes, chronic kidney disease, Other disorders of bone), procedures (total hip arthroplasty, surgical procedures on the femur and knee joint), medication usage (corticosteroids for systemic use, methotrexate, Bisphosphonates, Calcium, Sex hormones and modulators of the genital system, denosumab, teriparatide), and laboratory results (BMI, Calcium, Calcidiol, and Albumin).

cytokine-driven osteoclastogenesis that accelerates bone resorption [16–18]. Meanwhile, IL-6 inhibitors, like tocilizumab, have been shown to exhibit direct inhibition of osteoclastogenesis while also promoting bone formation [25–27]. The intricate mechanisms by which these biologics exert their influence on bone turnover might be related to their modulatory effects on systemic inflammation and, consequently, on systemic bone loss [24]. Such pharmacological interventions are crucial, especially given that patients with RA exhibit a higher osteoporotic fracture risk than the general population [28, 29].

Several mechanisms may explain the observed reduction in all-cause mortality with TNF-α inhibitors. One potential explanation is the difference in infection risk. TNF-α inhibitors have been associated with a lower risk of opportunistic infections compared to IL-6 inhibitors, which can suppress immune function more broadly and increase susceptibility to severe bacterial and viral infections. Additionally, TNF-α inhibitors have been linked to reduced cardiovascular risk, potentially through their anti-inflammatory effects on the vasculature and endothelial function, thereby lowering the risk of major adverse cardiovascular events (MACE), such as myocardial infarction and stroke. In contrast, IL-6 inhibitors may contribute to a pro-inflammatory state that influences lipid metabolism and increases cardiovascular risk.

Furthermore, TNF-α inhibition may have protective effects against malignancy progression, as chronic inflammation plays a crucial role in cancer development. IL-6, in particular, is involved in tumorigenesis by promoting angiogenesis, proliferation, and survival of malignant cells. This difference in immunomodulatory effects may contribute to a lower long-term mortality risk in patients receiving TNF-α inhibitors.

Our findings align with prior research suggesting a mortality benefit associated with TNFi use in RA. Previous observational studies have shown that TNFis may reduce the risk of cardiovascular disease and overall mortality compared to non-biologic DMARDs [11–13]. While some studies have indicated similar survival rates between TNFis and IL-6 inhibitors, others have reported a modest reduction in all-cause mortality among TNFi users [15]. However, further prospective studies are needed to confirm these findings and to explore whether specific patient subgroups derive greater survival benefits from TNF-α inhibitors.

Our study's robustness stems from its extensive sample size and the utilization of the TriNetX database, facilitating a generalizable and applicable analysis enriched with comprehensive patient data. In our comprehensive study, we meticulously adjusted for factors related to osteoporosis and fractures, implementing extensive adjustments for over 30 covariates using PSM [30]. This approach provided us with four different analytical models, each contributing to a nuanced understanding of treatment impacts. Recognizing RA as a chronic condition, we extended our follow-up period to up to 7 years, allowing for a thorough observation of the long-term risk of outcomes. Notably, our study is the first to highlight the difference in all-cause mortality outcomes between different DMARDs, particularly TNF-α inhibitors and IL-6 inhibitors. This pioneering revelation not only fills a significant gap in the current literature but also suggests a potential advantage of TNFis s in reducing all-cause mortality, warranting further investigation into their systemic effects beyond bone health.

Despite these strengths, several limitations should be acknowledged. IL-6 users were often treated as a second-line therapy after failing TNF-α inhibitors, which may introduce immortal time bias. Additionally, the TriNetX database is not a population-based dataset, which can lead to loss of follow-up and potential misclassification errors. Although propensity score matching was used to minimize confounding, unmeasured variables such as disease severity and prior treatment history could still influence the results. Recognizing RA as a chronic condition, we extended our follow-up period to up to 7 years, allowing for a thorough observation of the long-term risk of outcomes. Notably, our study is the first to highlight the difference in all-cause mortality outcomes between different DMARDs, particularly TNF-α inhibitors and IL-6 inhibitors. This pioneering revelation not only fills a significant gap in the current literature but also suggests a potential advantage of TNFis in reducing all-cause mortality, warranting further investigation into their systemic effects beyond bone health.

Future research should focus on unraveling the distinct impacts of TNFis and IL-6is on all-cause mortality, as well as their long-term effects on bone health. We hypothesize that differences in mortality rates could be influenced by varying infection rates associated with these treatments. This hypothesis was built on a foundation of previous research and clinical observations. Several studies have documented the immunosuppressive effects of TNFis. For example, a systematic review published in the Journal of the American Medical Association highlighted that patients treated with TNFis have an increased risk of serious infections compared to those treated with traditional DMARDs [31]. This is particularly evident in infections such as tuberculosis and bacterial infections, which require a robust cell-mediated immune response that TNFis help coordinate. Further investigations should also delve into more detailed BMD data, rather than solely relying on diagnoses of osteoporosis or fracture. This approach is crucial because some individuals may not exhibit symptoms even when BMD is low. Moreover, recent research suggests that abatacept may have superior BMD-preserving effects in patients with RA [32]. It is imperative to conduct comparative studies on the bone-preserving effects of different DMARDs. The findings from our study underscore the importance of integrating bone health into the comprehensive management of RA. Adapting therapeutic strategies to meet the individual needs of patients is essential for optimizing care outcomes.

5 | Conclusion

In conclusion, our study demonstrates that there is no significant difference in the risk of osteoporosis and fractures between RA patients treated with TNFis and IL-6is, suggesting that both types of biologic agents can be considered for RA management without preferential consideration for bone health impact. Future research should delve deeper into the observed differences in all-cause mortality between the cohorts and explore the long-term effects of these therapies on bone health, ensuring that RA management strategies continue to evolve based on robust evidence.

Author Contributions

All authors were involved in drafting the article or revising it, and all authors approved the final version to be published. Study conception and design: Hong Wang, Yun-Hen Lee, Jingting Ji. Accessed and verified the underlying data: Shiow-Ing Wang, Yun-Hen Lee, Jingting Ji. Analysis and interpretation of data: Hong Wang, I-Han Cheng, Jingting Ji, Yao-Min Hung, Shiow-Ing Wang, Jingting Ji. Writing (original draft preparation): Hong Wang, I-Han Cheng, Shiow-Ing Wang. Writing (review and editing): Yao-Min Hung, Yun-Hen Lee, Jingting Ji.

Acknowledgments

The authors have nothing to report.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that supports the findings of this study are available in the Supporting Information of this article.

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LETTER TO THE EDITOR

Case Report: Successful Treatment of Secukinumab-Induced SAPHO Syndrome With Tofacitinib

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Dear Editor,

SAPHO (synovitis, acne, pustulosis, hyperostosis, osteitis) syndrome is a rare disease with a prevalence of 1/10000. Characterized by synovitis, acne, pustulosis, hyperostosis, and osteitis, its presentation ranges from soft tissue swelling and morning stiffness to cutaneous and osteoarticular manifestations [1]. The etiology of SAPHO syndrome remains enigmatic. The prevailing hypothesis describes a possible role of innate immunity and proinflammatory cytokines in its development [1]. Current medical literature reports effective therapeutics for SAPHO syndrome, employing various interleukin, TNF, JAK, and PDE-4 inhibitors [2, 3].

A 31-year-old female presents with a 5-year history of lumbosacral pain and anterior chest pain with palmoplantar pustulosis for the past 4 weeks while on secukinumab treatment. Sleeping and sitting induce significant pain. The patient also reports 10-min-long morning stiffness and denies previous history of tenosynovitis, uveitis, psoriasis, and chronic diarrhea. One year ago, the patient tested positive for HLA-B27 and was diagnosed with ankylosing spondylitis given inflammation in her sacroiliac joints and positive family history. In July 2022, the patient began treatment with Yisaipu (etanercept biosimilar) 50 mg q. w. for 10 months, providing initial relief with occasional relapses. To provide further symptom relief, the patient was switched to secukinumab (IL-17 inhibitor) 150 mg q. w. However, following 2 weeks of treatment, the patient began to experience anterior chest pain, breathing difficulties, palmoplantar pustulosis, back rashes, and polyarthralgia.

Upon physical examination, rashes were noted on the back. Ruptured pustules were present on the palms and soles, seen in Figures 1a and 2a. Normal temperature was noted over the tender sternoclavicular and sternocostal joints. Spinal curvature was slightly flattened. Bilateral FABER, hip compression, and lateral iliac compression tests were negative. Occiput-wall distance was 0 cm. Schober's test was 3 cm. Thoracic spinal mobility test was 1 cm.

Patient's family history was significant for ankylosing spondylitis in the patient's brother, father, and uncle. Supplementary examinations including routine blood tests, liver function, kidney function, and thyroid function tests were all normal. The patient tested positive for HLA-B27 and exhibited an IgA level of 3.96 g/L, erythrocyte sedimentation rate (ESR) of 44 mm/h, and C-reactive protein (CRP) level of 14.65 mg/L. Additionally,

Man Li and Patrick Wu are co-first authors.

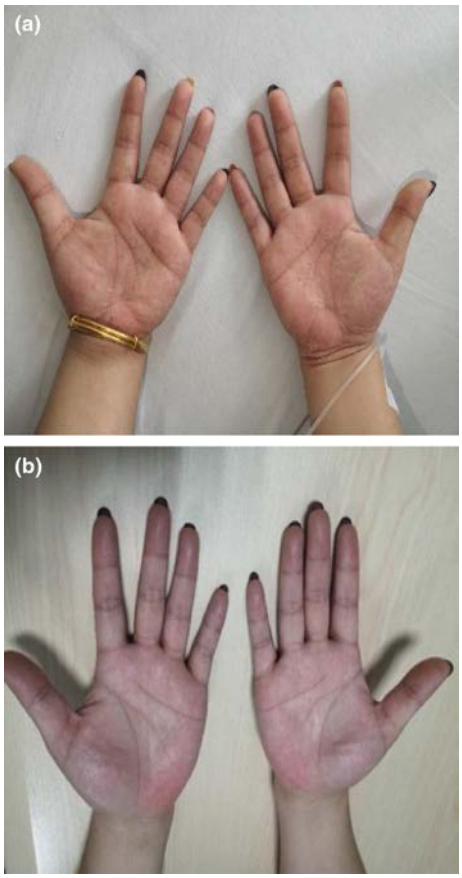

FIGURE 1 | (a, b) Palm Pustules. Prior to versus after 4-week tofacitinib treatment, respectively.

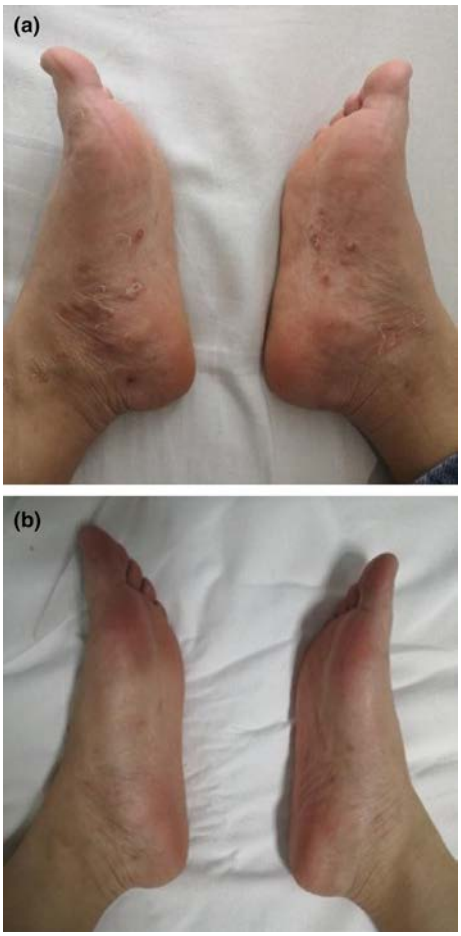

FIGURE 2 | (a, b) Plantar Pustules. Prior to versus after 4-week tofacitinib treatment, respectively.

T-SPOT.*TB* test was negative. Fungal and bacterial cultures of plantar pustular fluid returned negative. Bone imaging revealed imaging-agent accumulation in bilateral sternoclavicular and sacroiliac joints, indicating inflammation. MRI of sacroiliac joints indicated sacroiliitis, with greater severity on the left (see in Figure 3a). The final diagnosis was ankylosing spondylitis with a BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) score of 5.83 and ASDAS-CRP (ankylosing spondylitis disease activity score-CRP) score of 3.87.

The patient was discontinued on secukinumab and switched to tofacitinib (JAK inhibitor) 5 mg b.i.d, without any NSAIDs or topical treatments for cutaneous lesions. After 2 weeks of tofacitinib treatment, there was noticeable improvement of palmoplantar pustulosis. Following 4 weeks, pustules were eradicated, and the patient's anterior chest pain and lower back pain subsided (see Figures 1b and 2b). Additionally, there was decreased inflammation following 4 weeks with CRP and ESR at 4.45 mg/L and 22 mm/H, respectively. Following 6 months of treatment, CRP and ESR further dropped to 1.25 mg/L and 8 mm/H, BASDAI and ASDAS-CRP dropped to 2.76 and 1.56, respectively. No relapses occurred during these 6 months. A follow-up MRI of the sacroiliac joints showed inflammation resolution (see in Figure 3b).

In short, because the medical team was concerned with secukinumab potentially causing paradoxical SAPHO syndrome, the attending physician stopped secukinumab treatment for the

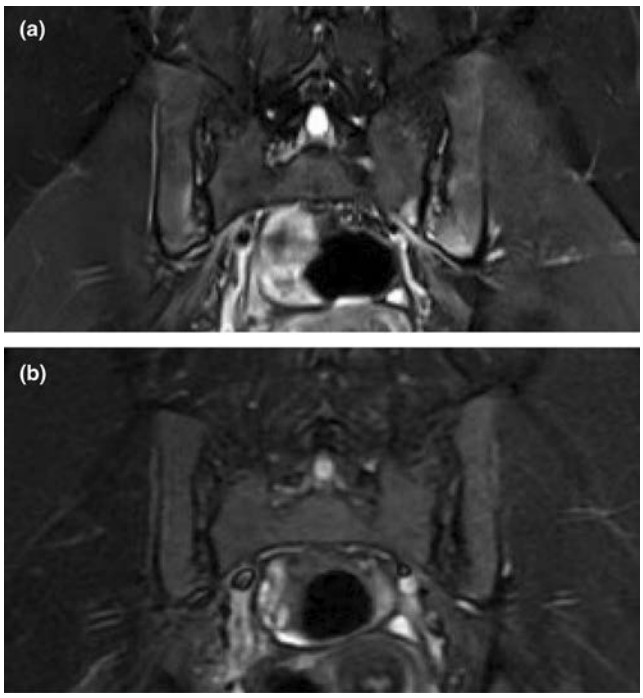

FIGURE 3 | (a, b) MRI of the sacroiliac joint. Prior to versus after 6-month tofacitinib treatment respectively.

patient and switched her over to tofacitinib (JAK inhibitor) 5 mg b.i.d., resulting in a gradual improvement in anterior chest pain, lower back pain, and cutaneous symptoms. Symptom stabilization occurred within 4 weeks (see Figures 1b and 2b), and remission was confirmed after 6 months with imaging (see Figure 3b).

SAPHO syndrome is also known as pustulotic arthro-osteitis (PAO) and is classified as a form of seronegative spondyloarthritis [4]. SAPHO syndrome patients present with cutaneous, bony, and joint diseases, involving the anterior chest wall. Symptoms may involve the spine and include sacroiliitis and peripheral arthritis. Cutaneous lesions manifest as palmoplantar pustulosis and severe acne; however, incomplete clinical manifestations often remain undiagnosed [5].

Given a family history significant for ankylosing spondylitis, previous sacroiliac joint imaging suggested sacroiliitis consistent with ankylosing spondylitis. The patient also denied a past history of palmoplantar pustulosis. Given the patient's family history and history of present illness, secukinumab was suspected to be inducing paradoxical SAPHO syndrome. Because current medical literature lacks reports of paradoxical SAPHO syndrome caused by secukinumab, it is difficult to designate the patient's clinical presentation as part of an adverse drug reaction or an underlying SAPHO syndrome involving the sacroiliac joints.

Paradoxical adverse reactions are side effects of biopharmaceuticals such as inflammation in the skin and various organs, defined as aggravating symptoms and unexpected results that a certain medication did not intend to produce. Adverse reactions are common among TNF-α inhibitors as literature has shown that TNF-α inhibitors can induce SAPHO syndrome and exacerbation of skin lesions [6]. Currently, the etiology of paradoxical adverse reactions remains unclear, but it is theorized that they may be attributed to immunogenicity and target molecules of the drug. Treatment options for such adverse reactions include topical, symptomatic, and hormonal treatments or replacement with new medications. Although previous studies have demonstrated the robust efficacy of TNF inhibitors in SAPHO syndrome [7]. Switching medications to JAK inhibitors such as tofacitinib in this report can produce anti-inflammatory effects mediated by blocking actions of wide-ranging cytokines (e.g., IL-6, IL-17, IL-23, IFN-γ, GM-CSF), regulating Th17 cell differentiation, neutrophil activation, pustulosis, and bone remodeling [8]. Therefore, JAK inhibitors may exhibit stronger anti-inflammatory effects than medications that selectively inhibit one cytokine form. Li et al. [9] examined the treatment response of 13 SAPHO patients with tofacitinib 5 mg b.i.d. over 12 weeks and showed that tofacitinib was successful in relieving pain, inflammation, and rashes without any side effects. Similarly, Yuan et al. [10] reported a case in which a patient with both SAPHO syndrome and ankylosing spondylitis received relief of anterior chest pain, lower back pain, and cutaneous symptoms following tofacitinib treatment. Therefore, according to medical literature, our 31-year-old female patient who was treated with TNF-α and IL-17 inhibitors had a promising prognosis of SAPHO syndrome with tofacitinib. After careful consideration, the JAK inhibitor, tofacitinib, was chosen as the treatment that successfully controlled the patient's pustular rash and lower back pain, confirmed with imaging following 6 months.

1 | Conclusion

This case describes a 31-year-old female with ankylosing spondylitis experiencing lower back pain. Initial treatment with TNF-α and IL-17 inhibitors resulted in unexpected symptoms of anterior chest pain and palmoplantar pustulosis, suggesting paradoxical SAPHO syndrome. Tofacitinib was subsequently administered, effectively managing her symptoms and demonstrating its potential as a treatment option for SAPHO syndrome. This highlights the role of the JAK–STAT pathway in SAPHO syndrome pathophysiology, emphasizing the need for further research to clarify its etiology.

Author Contributions

Dr. Man Li, MD contributed to the writing of the original draft of the paper. Patrick Wu, BS contributed to the writing of the original draft and subsequent revision of the draft. Dr. Su-Boon Yong, MD, PhD and Dr. Pui-Ying Leong, MD contributed to the revision of the draft and serve as published correspondence authors.

Acknowledgments

The authors have nothing to report.

Consent

Written informed consent was obtained from the patient at the Second Hospital of Longyan in Longyan, China on December 7th, 2023, for purposes of authorship and publication of this case report.

Conflicts of Interest

Dr. Su-Boon Yong, MD, PhD serves as an associate editor for the International Journal of Rheumatic Diseases.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Man Li
Patrick Wu
Su-Boon Yong
Pui-Ying Leong

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LETTER TO THE EDITOR

Case Report: Xanthogranulomatous Osteomyelitis of the Femur: A Rare Mimic of Malignant Bone Tumors

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Keywords: bone lytic lesion | osteomyelitis | xanthogranulomatous inflammation

Dear Editor,

A 50-year-old male presented with right thigh pain without any cause for 1 month. Physical examination showed right thigh pain and tenderness without swelling or redness. The patient did not report systemic symptoms such as fever, fatigue, or muscle weakness. Laboratory findings revealed a C-reactive protein level of 2.0 mg/dL, a white blood cell count of $6.1 \times 10^3/\mu L$, and negative results for common tumor markers. Laboratory tests including erythrocyte sedimentation rate, creatine kinase, and antinuclear antibodies were within normal limits. X-ray showed a radiolucent lesion and extra-bone formation of the right proximal femur (Figure 1A). Computed tomography images demonstrated osteolytic bone destruction (Figure 1B,C), whereas magnetic resonance imaging (MRI) revealed an irregularly margined mass extending from the intramedullary region of the bone (Figure 1D,E). A tissue biopsy of the bone lesion in the right thigh was performed, revealing pathological findings of foamy macrophage and inflammatory cell infiltration in both intraosseous and extraosseous lesions, along with bone formation in the thickened periosteum (Figure 1F,G). Bacterial culture results were positive for *Streptococcus intermedius*. A bone tumor or osteomyelitis would be the differential diagnosis; however, the histopathological findings confirmed the lesion as xanthogranulomatous osteomyelitis (XO). Treatment included intravenous cefazolin sodium at 3 g/day for 1 day, followed by oral cefaclor at 750 mg/day for 65 days. Intravenous cefazolin followed by oral cefaclor was chosen based on the susceptibility profile of *Streptococcus intermedius*, in accordance with standard treatment guidelines for streptococcal osteomyelitis [1]. The patient showed a favorable clinical and laboratory response without adverse events. Although the initial CRP level was within the upper normal range (2.0 mg/dL), it gradually decreased to <1.0 mg/dL during treatment, indicating a positive response. His symptoms and bone lesion on X-ray gradually improved (Figure 2A–F). No complications such as pathological fracture, chronic sinus formation, or recurrence were observed during the 6-month follow-up period. However, longer observation may be necessary, as XO is a chronic condition and delayed recurrence has been reported in some cases.

XO is a rare benign but aggressive form of chronic inflammation [2]. This disease is characterized by the accumulation of foamy macrophages interspersed with polynuclear leukocytes, lymphocytes, and activated plasma cells. Although various mechanisms have been implicated, such as immunological disorders, infection caused by low-virulence organisms, and reactions to specific infectious agents, the precise pathogenesis of XO inflammation has not been elucidated [3]. XO is commonly observed in various organs, most notably the gallbladder and kidney; however, its occurrence in the bone, brain, and lungs is rare [4]. XO, a manifestation of this condition in bone, was first described by C. Cozzutto in 1984 [5]. Since it was first reported, there have been only 32 publications and 35 cases of this disease. XO predominantly occurs in males and often arises spontaneously. Although it commonly affects long bones, cases involving flat bones such as ribs, vertebrae, and small bones have also been reported [6]. Various bone lesions, including osteolysis, periosteal reaction, and extraosseous bone formation, are

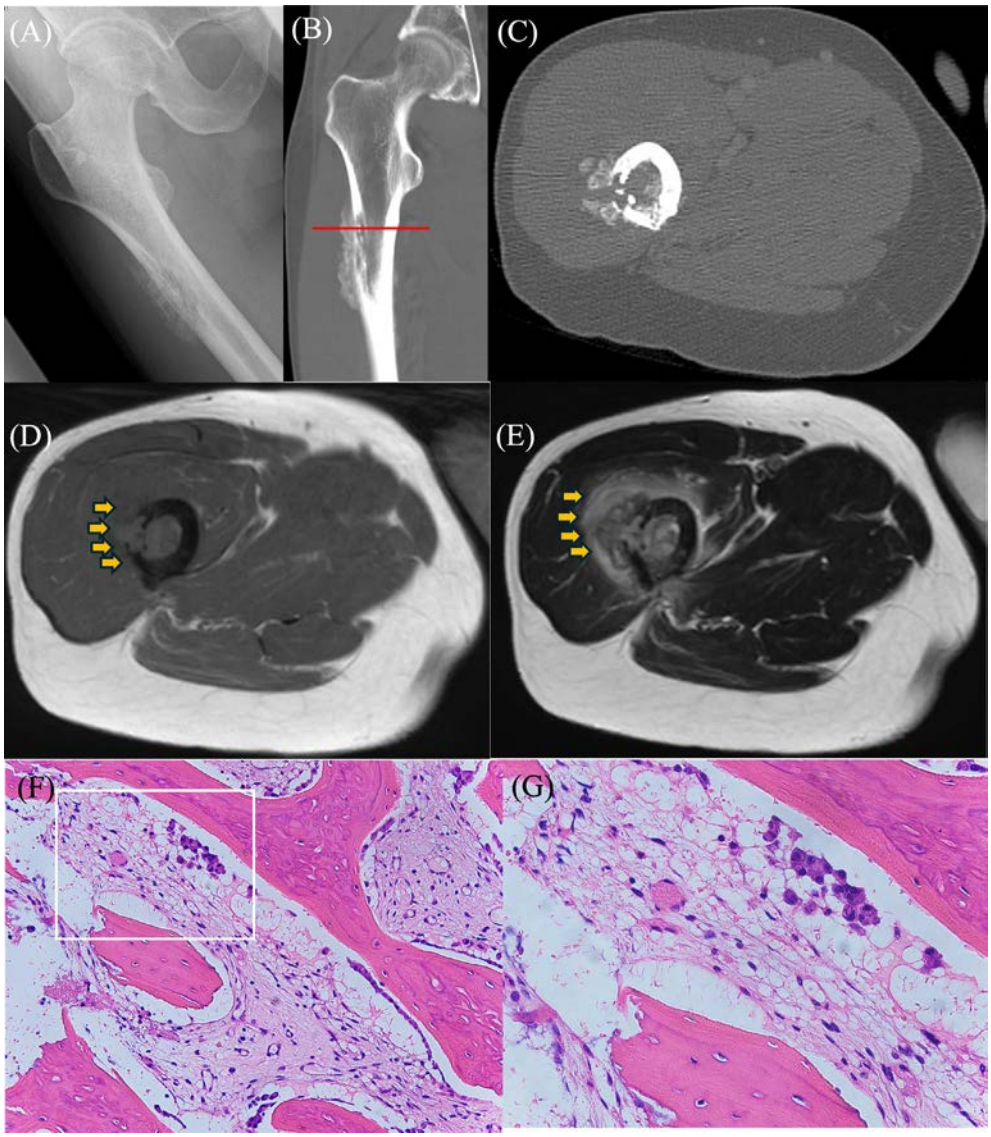

FIGURE 1 | Radiographic and pathological images of the affected region. The lesion measured approximately 38 mm × 28 mm on axial CT images. (A) X-ray images; (B) coronal computed tomography (CT) image; (C) axial CT image; (D) T1-weighted magnetic resonance imaging (MRI) image; (E) T2-weighted MRI image; (F) hematoxylin and eosin (HE) staining of the extraosseous lesion at 200× magnification; (G) HE staining of the extraosseous lesion at 400× magnification. Arrows indicate extramedullary region.

frequently observed in XO, closely resembling the radiographic features of osteosarcoma. Therefore, a definitive diagnosis should be established through histopathological examination of a biopsy specimen [7]. Microbiological culture was occasionally positive, but detected bacteria were diverse (e.g., *Mycobacterium*, *Staphylococcus aureus*, or *Pseudomonas aeruginosa*) [8]. There is no standard treatment, but some papers have reported that curettage of the lesion or antibiotic therapy for culture-positive cases would be effective. Although surgical curettage is often used in previously reported cases of XO, our case demonstrated complete resolution with antibiotic therapy alone. This suggests that in selected patients, particularly those with localized infection and identified pathogens, conservative treatment may be an effective alternative to surgery. Although the radiologic and histologic characteristics of XO are well established, microbiologically confirmed cases involving *Streptococcus intermedius* are extremely rare. *Streptococcus intermedius*, a member of the *Streptococcus anginosus* group, is known for its abscess-forming capability and production of extracellular enzymes such as hyaluronidase and deoxyribonuclease [9]. These virulence factors may contribute to a chronic granulomatous inflammatory response, potentially triggering xanthogranulomatous osteomyelitis in predisposed individuals. This case is notable for the identification of *Streptococcus intermedius* as the causative pathogen and its successful treatment with antibiotics alone, without the need for surgical debridement, providing novel insights into the disease's pathogenesis and therapeutic approach.

XO should be considered as a differential diagnosis for malignant bone tumors due to its bone lesions despite its benign nature. Radiographically, XO may mimic malignant bone tumors such as osteosarcoma; however, features such as diffuse periosteal thickening, absence of aggressive soft tissue extension, and presence of foamy histiocytes on histopathology are useful for differentiation. Histopathological examination is essential to distinguish XO from malignant bone neoplasms.

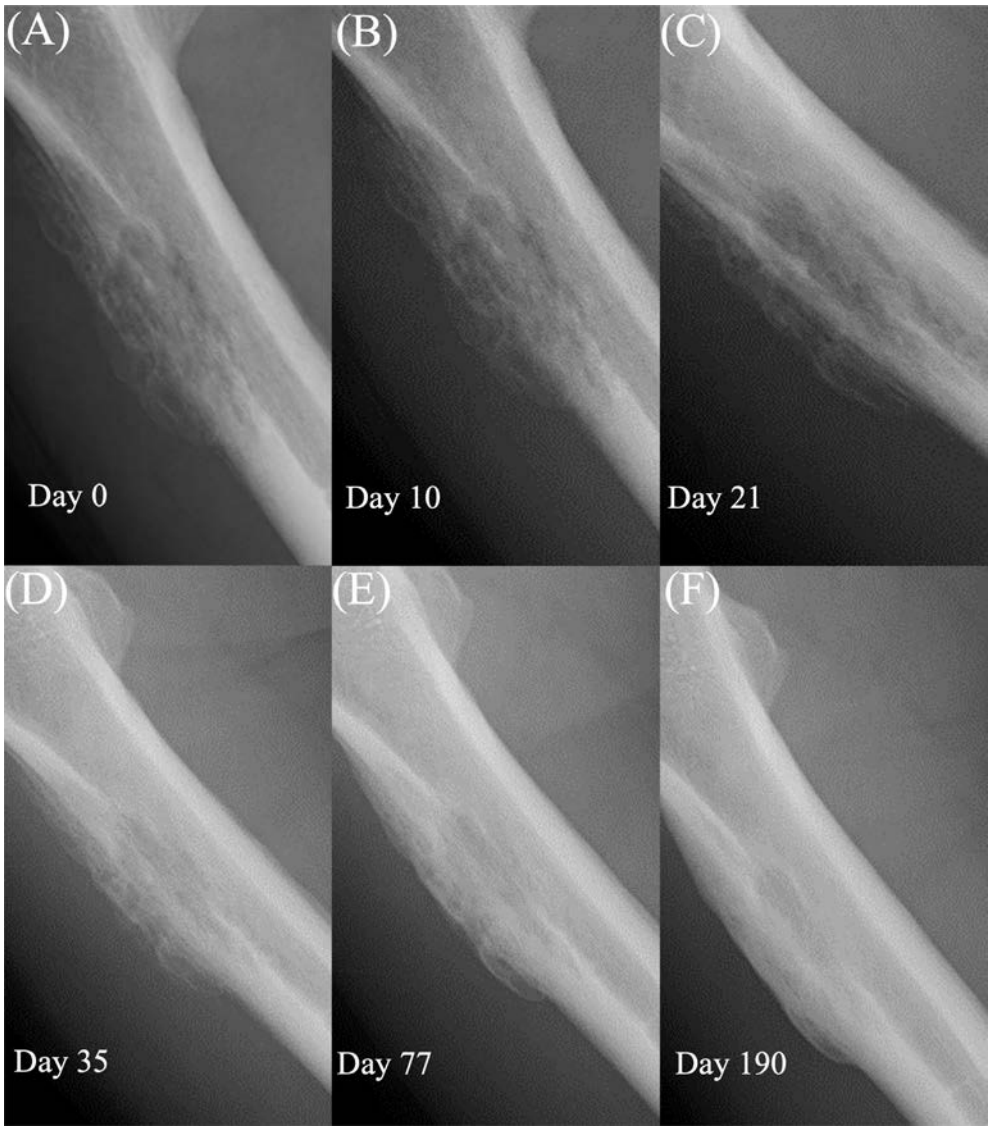

FIGURE 2 | Temporal changes in X-ray images over the course of treatment. (A) Day 0; (B) Day 10; (C) Day 21; (D) Day 35; (E) Day 77; (F) Day 190 of antibiotic treatment.

Author Contributions

H.H. designed the report. H.H., Y.M., S.Y., J.I., H.K., S.H., M.W., and T.A. contributed to the manuscript writing. H.H. handled the data collection responsibilities. H.H., Y.M., S.Y., J.I., H.K., S.H., M.W., and T.A. reviewed and approved the final manuscript.

Acknowledgments

The authors have nothing to report.

Ethics Statement

Informed consent was obtained from the patient for the publication of this report and the accompanying images.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that supports the findings of this study are available in the supporting information of this article.

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EDITORIAL

Advancements in Therapeutic Approaches and Biomarkers: A New Epoch for Sjögren's Syndrome Management

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Primary Sjögren's syndrome (pSS) is a chronic autoimmune disease primarily affecting exocrine glands, characterized by symptoms such as dry mouth and eyes, fatigue, and joint pain. It often accompanies other autoimmune disorders like rheumatoid arthritis and lupus [1]. Despite its widespread occurrence and significant effect on quality of life, treatment strategies for pSS have traditionally been limited. These strategies have often focused on providing symptomatic relief rather than addressing the underlying disease process. pSS poses a complex challenge in the field of autoimmune disorders, particularly in terms of diagnosis and management. Traditionally, diagnosis has been reliant on clinical assessments and invasive biopsies, with therapeutic interventions limited to symptomatic relief. However, with new biomarkers and novel therapeutic strategies emerging, we are entering a new epoch in managing pSS. These advancements promise to revolutionize the field, offering targeted treatment regimens that could significantly enhance patient outcomes and quality of life [2].

PSS is characterized by the infiltration of lymphocytes into exocrine glands, which leads to the destruction of glandular tissue and, consequently, functional impairment. The exact cause of the condition remains unclear; however, it is believed that genetic predisposition, environmental triggers, and abnormal immune responses may contribute to its development. PSS is often underdiagnosed or misdiagnosed due to its nonspecific symptoms and overlap with other autoimmune conditions [3]. Traditional diagnostic methods, including subjective dry eye and dry mouth assessments, serological tests for autoantibodies, and salivary gland biopsy, have limitations in terms of invasiveness, specificity, and sensitivity. This underscores the urgent need for reliable, noninvasive biomarkers to improve early diagnosis, assess disease activity, and monitor therapeutic responses [4].

In pSS, biomarkers play an essential role in early diagnosis, assessment of the severity of the disease, and prediction of the prognosis. A summary of pSS biomarkers is shown in Table 1. The presence of autoantibodies such as SSA (Ro) and SSB (La) is a hallmark of pSS, but newer autoantibodies like ANA, RF, Anti-SP-1, Anti-PSP, Anti-CA-6, Anti-AQP5, and Anti-CarPare are garnering attention for their potential role in the early diagnosis of the disease. Elevated levels of cytokines and chemokines in blood samples, such as CXCL10, IL-6, IL-17A, CXCL13, IL-14a, and BAFF (B-cell activating factor), and decreased levels of CCL28 have been linked to early diagnosis and severe conditions. These not only serve as biomarkers for disease progression but also as potential therapeutic targets. The disease biomarkers are not limited to cytokines and chemokines. Detections of gas, receptors, protein, and RNAs also showed optimum disease prediction ability. The increasing levels of NO, Calprotectin, IFI44, SAMD9L, M3R, sST2, hsa_circ_0045800, and in-DC and decreasing levels of BAFF-R indicated a possible diagnosis of pSS and extended tissue damage. The potential of these biomarkers

Xianfei Gao and Wen Tang contributed equally to this work.

TABLE 1 | Biomarkers in Sjögren's syndrome.

Biomarker	Classification	Sample	Trend	Clinical value	PMID numbers
Anti-Ro/SSA	Autoantibodies	Blood	Positive/elevate	Early diagnosis	30178554
Anti-La/SSB	Autoantibodies	Blood	Positive/elevate	Early diagnosis	30178554
RF	Autoantibodies	Blood	Positive/elevate	Early diagnosis	30178554
ANA	Autoantibodies	Blood	Positive/elevate	Early diagnosis	30178554
TNF-a	Cytokines and chemokines	Saliva/tear	Elevate	Early diagnosis	32791244 37781912
sST2	Receptors	Blood	Elevate	Early diagnosis/High disease activity index	27097949
SAMD9L	Protein	Blood	Elevate	Early diagnosis/High disease activity index	37663755
RANTES	Cytokines and chemokines	Saliva	Elevate	Early diagnosis/Extent of tissue damage	37876509
NO	Gas	Blood/saliva	Elevate	Early diagnosis/Extent of tissue damage	38229348
MIP-1α	Cytokines and chemokines	Saliva	Elevate	Early diagnosis	37876509
MIP-1b	Cytokines and chemokines	Tear	Elevate	Early diagnosis/Extent of tissue damage	31086200
MIG	Cytokines and chemokines	Saliva	Elevate	Early diagnosis	31696913
M3R	Receptors	Blood	Elevate	Early diagnosis	20462524
lnc-DC	RNA	Blood	Elevate	Early diagnosis	33123604
IP-10	Cytokines and chemokines	Saliva/tear	Elevate	Early diagnosis	25524206
IL-8	Cytokines and chemokines	Tear	Elevate	Early diagnosis/Extent of tissue damage	32708341
IL-7	Cytokines and chemokines	Tear	Elevate	Early diagnosis	35405597
IL-6	Cytokines and chemokines	Tear/blood/saliva	Elevate	Early diagnosis/Extent of tissue damage	32708341
IL-4	Cytokines and chemokines	Saliva/tear	Elevate	Early diagnosis/Extent of tissue damage	32708341
IL-23	Cytokines and chemokines	Tear	Degrade	Early diagnosis	32708341
IL-22	Cytokines and chemokines	Tear	Elevate	Early diagnosis	24490899
IL-21	Cytokines and chemokines	Tear	Elevate	Early diagnosis	22226370
IL-2	Cytokines and chemokines	Saliva/tear	Elevate	Early diagnosis/Extent of tissue damage	35526080
IL-1β	Cytokines and chemokines	Tear	Elevate	Early diagnosis	32708341
IL-1α	Cytokines and chemokines	Tear	Elevate	Early diagnosis	32708341

(Continues)

TABLE 1 | (Continued)

Biomarker	Classification	Sample	Trend	Clinical value	PMID numbers
IL-1Ra	Cytokines and chemokines	Tear	Elevate	Early diagnosis/Extent of tissue damage	32708341
IL-17A	Cytokines and chemokines	Blood/saliva/tear	Elevate	Early diagnosis/Extent of tissue damage	25941062
IL-17	Cytokines and chemokines	Saliva/tear	Elevate	Early diagnosis	32708341
IL-14a	Cytokines and chemokines	Blood	Elevate	Early diagnosis/Extent of tissue damage	19038581
IL-12p70	Cytokines and chemokines	Tear	Elevate	Early diagnosis/Extent of tissue damage	39654248
IL-12p40	Cytokines and chemokines	Saliva	Elevate	Early diagnosis	39222420
IL-10	Cytokines and chemokines	Saliva/tear	Elevate	Early diagnosis	39511968 32708341
IL-1	Cytokines and chemokines	Saliva	Elevate	Early diagnosis	32708341
IFN-γ	Cytokines and chemokines	Tear	Elevate	Early diagnosis/Extent of tissue damage	25524206
IFI44	Protein	Blood	Elevate	Early diagnosis/High disease activity index	39219820
hsa_circ_0045800	RNA	Blood	Elevate	Early diagnosis	38866992
CXCL13	Cytokines and chemokines	Blood	Elevate	Early diagnosis/High disease activity index	35309354
CXCL10	Cytokines and chemokines	Blood	Elevate	Early diagnosis	38376769
CCL28	Cytokines and chemokines	Blood	Degrade	Early diagnosis	35048789
Calprotectin	Protein	Blood	Positive/elevate	Early diagnosis/Extent of tissue damage	30178554
BAFF-R	Receptors	Blood	Degrade	Early diagnosis	25740829
BAFF	Cytokines and chemokines	Blood	Elevate	Early diagnosis	25941062
Anti-SP-1	Autoantibodies	Blood	Positive/elevate	Early diagnosis	29292085
Anti-PSP	Autoantibodies	Blood	Positive/elevate	Early diagnosis	31205955
Anti-CarP	Autoantibodies	Blood	Positive/elevate	Early diagnosis/Extent of tissue damage	26350884
Anti-CA6	Autoantibodies	Blood	Positive/elevate	Early diagnosis	31205955
Anti-AQP5	Autoantibodies	Blood	Positive/elevate	Early diagnosis	31684196

to improve early diagnosis and disease monitoring provides reassurance about the future of pSS management [5].

Tear and salivary fluids are easily accessible biofluids, offering a promising biomarker discovery medium. Advances in proteomics have led to the discovery of salivary biomarkers such as IL-1, IL-10, IL-17, TNF-a, IP-10, MIP-1α, IL-12p40, IL-6, MIG, IL-6, IL-17A, IL-4, IL-2, and RANTES. These biomarkers can facilitate noninvasive diagnostic approaches, reducing the need for labial biopsy. Tear fluid is an attractive source for biomarker discovery due to its direct link to ocular surface health and ease of collection. Tears contain a complex mixture of proteins, lipids, electrolytes, and small molecules reflecting local and systemic changes. However, these biomarkers require a large cohort,

extended follow-up, and a more in-depth analysis of their mechanisms to confirm their clinical significance before they can be used in clinical practice. This verification process can be challenging and time-consuming, but it is essential for ensuring the reliability and utility of these biomarkers in a clinical setting [6].

Traditional treatment for pSS is multifaceted. It aims to alleviate symptoms, manage systemic manifestations, and improve overall quality of life. Recent advances in understanding its pathophysiology have catalyzed the development of novel therapeutic strategies. The revolutionary strategy approaches to managing Sjögren's syndrome focus on targeted biologics, small molecules, and innovative symptomatic treatments [7].

1 | Biologic Agents: Target Specific Immune Pathways

Rituximab, a chimeric anti-CD20 monoclonal antibody, depletes B cells, reducing autoantibody production and inflammatory cytokine release. Clinical trials have demonstrated efficacy in improving glandular function and systemic involvement [8]. Belimumab, targeting B-lymphocyte stimulator (BLyS), reduces B-cell survival, improves symptoms, and reduces disease activity scores in patients unresponsive to traditional therapies [8]. Abatacept, by inhibiting T-cell co-stimulation via CTLA-4 Ig, indirectly affects B-cell activity, offering another means of controlling autoimmune activity in pSS [9]. However, the therapeutic approaches of some biological agents were not optimal: thalidomide, oral lozenges of interferon alfa, anakinra, baminercept, and efalizumab were not recommended as their failure outcome in the treatment of pSS [10].

2 | Small Molecule Inhibitors: Orally Available Compounds Offer Convenience and Broader Immunomodulatory Effects

Janus Kinase (JAK) inhibitors, like Tofacitinib and Baricitinib, which impede signaling pathways vital to immune activation and cytokine production, have shown promise in early-phase trials for pSS [11, 12]. Sphingosine-1-Phosphate Receptor Modulators, agents like Fingolimod, modulate lymphocyte trafficking, potentially reducing glandular inflammation [13].

3 | Regenerative Therapies

Stem cell therapy, particularly mesenchymal stem cells (MSCs), may offer reparative benefits by promoting tissue regeneration and modulating immune responses. Initial studies indicate improved glandular function and systemic symptoms in pSS patients receiving MSC infusions [14].

4 | Precision Medicine Approaches

Biomarker discoveries enable more personalized treatment regimens, allowing clinicians to tailor interventions based on genetic, serological, and clinical profiles, optimizing therapeutic efficacy and minimizing adverse effects [15]. Chimeric Antigen Receptor T (CAR-T) cells are genetically engineered T cells designed for immunotherapy. Combined CD19/BCMA-targeted CAR-T cells have been developed and are undergoing evaluation in Sjögren's syndrome (SS) (NCT05085431). In conclusion, the evolving landscape of biomarkers and therapeutic strategies in pSS is reshaping how the disease is diagnosed and managed. The potential for improved patient outcomes is unprecedented, with novel biologics and small molecule inhibitor therapy approaches. As research progresses, a more personalized, targeted approach to pSS management will likely become the standard, significantly enhancing the quality of life for those affected and instilling hope for a brighter future in autoimmune diseases.

Author Contributions

Xianfei Gao wrote the manuscript. Ping Zeng supervised the project and provided advice for the manuscript. Wen Tang participated in writing some parts of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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ORIGINAL ARTICLE

Inflammatory Bowel Disease and Risk of Rheumatoid Arthritis: A UK Biobank Cohort Study

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ABSTRACT

Objectives: Inflammatory bowel disease (IBD) and rheumatoid arthritis (RA) are both prevalent inflammatory conditions within the population. Our objective was to explore the relationship between IBD and RA, while examining the role of inflammatory mediators in the observed association.

Methods: We used data from the UK Biobank, a population-based prospective cohort study that recruited adults aged 37–73 years from 22 centers in England, Scotland, and Wales between 2006 and 2010. We included patients diagnosed with IBD at baseline and excluded those with RA at baseline or missing follow-up information. Cox regression proportional hazard models were employed to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) between patients with IBD (Ulcerative colitis and Crohn's disease) at baseline and the risk of RA. Additionally, we conducted mediation analysis to examine the roles of C-reactive protein (CRP) and several composite inflammatory indices as potential mediators.

Results: After excluding participants with RA at baseline ($N = 6769$), those lacking IBD subtype information ($N = 475$), and those with missing covariate data ($N = 121\,195$), a total of 373 693 individuals were included in the analysis. Compared with individuals without IBD, those with IBD had a significantly higher risk of developing RA (hazard ratio 2.06, 95% confidence interval 1.69–2.51). This association remained robust after adjustment for multiple confounders and across all major subgroups. Notably, the risk of RA associated with IBD was even higher among individuals with a low polygenic risk score for RA. Mediation analysis showed that systemic inflammatory markers, such as CRP, explained only a modest proportion of the association between IBD and RA, with the highest mediation proportion observed being 9.56%.

Conclusion: In the UK Biobank cohort study, individuals with IBD demonstrated an increased risk of developing RA. Future research should aim to gain insight into these underlying mechanisms and explore ways to improve long-term health outcomes in these patients.

Kuangyu He, Yi Xu and Zhengqiang Yuan contributed equally to this paper as co-first authors.

1 | Introduction

Rheumatoid arthritis (RA) and Inflammatory Bowel Disease (IBD) are both chronic, immune-mediated inflammatory disorders that impose substantial burdens on affected individuals and healthcare systems worldwide [1, 2]. RA is primarily characterized by inflammatory synovitis of the peripheral joints, while IBD manifests as chronic inflammation of the gastrointestinal tract, including conditions such as Ulcerative Colitis (UC) and Crohn's Disease (CD). Although these diseases affect different organ systems, growing evidence suggests they may share common immunological and environmental pathways. It is currently believed that RA arises from a complex interplay between genetic and environmental factors, but the precise mechanisms remain unclear [3]. Notably, whether IBD predisposes individuals to an increased risk of developing RA and the underlying mechanisms involved remain to be fully elucidated.

Several studies indicate that patients with IBD are at a heightened risk for developing secondary immune-mediated inflammatory diseases [4–6]. Arthropathy is one of the most common extraintestinal complications of IBD [7, 8], including idiopathic ankylosing spondylitis, reactive arthritis, and psoriatic arthritis [9–11]. Studies exploring the link between IBD and the risk of developing RA have not yet produced definitive results. A retrospective analysis within a Finnish cohort showed that the incidence of RA among individuals with IBD did not differ significantly from that in the general population [12]. Conversely, results from several cross-sectional studies consistently indicated a higher prevalence of RA among individuals with IBD compared to those without it [13–15]. Despite these findings, there remains a significant gap in high-quality prospective research exploring the potential correlation between IBD and RA.

In this prospective cohort study, we investigated whether IBD is associated with an increased risk of developing RA, while rigorously adjusting for a broad set of demographics, lifestyle, clinical, genetic, and environmental factors. We further explored whether this association differed across subgroups and examined the potential mediating role of systemic inflammation—assessed using both an inflammatory biomarker and several composite inflammatory indices—in linking IBD to RA.

2 | Methods

2.1 | Study Design and Participants

UK Biobank [16] (UKBB) is a longitudinal, population-based study that recruited more than 500 000 volunteers aged 37 to 73 years from 2006 to 2010. Participants, who lived within 10 miles of any of the 35 assessment centers, were invited to one of the 22 centers spread across England, Scotland, and Wales for initial assessments. Written informed consent was secured for the collection of the questionnaire and biological data. The UK Biobank received ethical approval from the UK North West Multi Centre Research Ethics Committee (11/NW/0382), and this research was conducted under the UK Biobank application number 141529. Participants included in the study were those who had no history of RA at or before baseline and had complete data on IBD and all covariates at baseline. The directed acyclic graph (DAG) between IBD and RA is provided in the appendix (Figure S2). This research was conducted in accordance with the STROBE guidelines.

2.2 | Exposure and Outcome

We utilized data from UK Biobank participants diagnosed with IBD prior to recruitment. Their disease information was obtained through self-reports (gathered during the verbal interview and translated into International Classification of Diseases, 10th Revision (ICD-10) codes), primary care records (documented and later converted into ICD-10 codes), and hospital inpatient records (directly recorded in ICD-10 format). Baseline IBD was classified as a diagnosis made before recruitment, identified by the specific ICD-10 codes K50 and K51. Participants lacking information on IBD subtypes were excluded from the study. Ultimately, 3867 patients with IBD were included in the primary analyses.

The diagnosis of RA was ascertained through multiple sources including hospital inpatient records (Hospital Episode Statistics for England, Morbidity Records for Scotland, and the Patient Episode Database for Wales), death register data (National Health Services [NHS] Digital, NHS Central Register, and National Records), primary care data, and self-reported medical conditions. To identify participants with RA, we used the ICD-10 codes M05 and M06, along with ICD-9 codes 71 400, 71 401, 71 403, 71 404, 71 405, 71 406, and 71 409. Participants were included if one or more of these codes appeared as a primary or secondary diagnosis in their health records. Additionally, we used a combination of self-reported medical conditions and associated therapeutic drugs, such as steroids, synthetic disease-modifying anti-rheumatic drugs (DMARDs), and biologic DMARDs, as part of the criteria for a self-reported diagnosis of RA. Comprehensive details on the codes utilized to identify RA cases in this study are available in the appendix (Table S1).

2.3 | Covariates

In our analyses, we incorporated the following covariates based on evidence from prior studies [17, 18]: age at baseline, sex, ethnicity, education, income levels, smoking status, alcohol intake, body mass index (BMI), physical activity, hypertension status, diabetes status, and cardiovascular disease (CVD) status. In addition, we also included several psychosocial factors (such as social isolation and loneliness), environmental exposures (including sun exposure and residential pollution indices such as $PM_{2.5}$, PM_{10}, $PM_{2.5-10}$, and NO_2), medication use (NSAIDs), and polygenic risk score (PRS) for RA.

Sex was categorized as male and female. Ethnicity was categorized as White and other. Education was categorized as low, intermediate, or high. The Townsend deprivation index, reflecting area-level socioeconomic status, was derived from participants' residential postcodes at recruitment and categorized into quartiles; higher values signify greater deprivation. Smoking status was classified into current smokers, former smokers, and never smokers. Likewise, alcohol consumption was categorized as heavy, intermediate, moderate,

and never. BMI was measured and categorized according to WHO criteria into normal, overweight, and obese categories. Levels of physical activity were classified as low, moderate, or high. Additionally, the presence of prevalent hypertension, diabetes, and cardiovascular disease was determined through self-reports at baseline and categorized as either present (yes) or absent (no). Social isolation and loneliness were assessed using structured questionnaires. Sunlight exposure was categorized according to average daily exposure time: less than 3 h per day and 3 h or more per day. Residential air pollution indices ($PM_{2.5}$, PM_{10}, $PM_{2.5-10}$, and NO_2) were quantified using land use regression (LUR) models developed by the European Study of Cohorts for Air Pollution Effects (ESCAPE) [19]. NSAIDs use, including aspirin and ibuprofen, was determined based on touchscreen questionnaire responses. The genetic susceptibility (PRS for RA) was generated using a Bayesian approach, and the genetic risk was categorized as low, intermediate, or high according to tertiles of the PRS distribution. More comprehensive details regarding the collection and definitions of covariates can be found in the appendix (Table S1).

2.4 | Statistical Analysis

Summary statistics at baseline are displayed as proportions for categorical variables and as means accompanied by standard deviations (SDs) for continuous variables. We assessed the proportional hazards (PH) assumption for the Cox regression using Schoenfeld residual plots. The global *p*-value exceeded 0.05, suggesting that the PHs assumption held and was therefore considered satisfied (see Figure S1). We used Cox PH models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) to assess the association between baseline IBD and RA risk. For all participants, follow-up began at the date of recruitment and continued until the diagnosis of RA, the date of death, loss to follow-up, or the end of the follow-up period, whichever occurred first.

The associations between IBD and RA were analyzed separately through a series of steps. Initially, we examined the associations by adjusting HRs and 95% CIs for age and sex. To determine if these associations persisted across different subgroups, we performed stratified analyses based not only on sex, age, education, smoking status, and alcohol consumption at baseline, but also on additional clinically relevant factors, including BMI, Townsend deprivation index, physical activity, diabetes, hypertension, CVD, social isolation, loneliness, sun exposure, NSAIDs use, and PRS. These variables were chosen due to their potential as effect modifiers and their use in stratified analyses in earlier UK Biobank studies concerning IBD [20, 21].

Alongside presenting the HRs and 95% CIs in a fully adjusted model, we conducted stepwise regression as well. Specifically, the term "stepwise regression" refers to the sequential construction of a series of Cox PH regression models, each adding additional sets of covariates based on theoretical relevance and evidence from previous literature, rather than automated statistical selection [22]. In model 1, adjustments were made for age, sex, and ethnicity. Model 2 further included education and the Townsend deprivation index to account for socioeconomic factors. Building on this, model 3 additionally adjusted for health behaviors, including smoking status, alcohol intake, BMI, and physical activity. Model 4 extended these adjustments by including chronic diseases (diabetes, hypertension, and cardiovascular disease), genetic susceptibility (PRS), psychosocial factors (social isolation and loneliness), sun exposure, and NSAIDs use. Finally, model 5 further incorporated environmental exposures, specifically air pollution indices such as $PM_{2.5}$, PM_{10}, $PM_{2.5-10}$, and NO_2.

Furthermore, we included C-reactive protein (CRP) as a classical inflammatory biomarker, as well as several composite inflammatory indices as potential mediators in the association between IBD and RA. Specifically, the modified Glasgow Prognostic Score (mGPS) and high-sensitivity mGPS (HS-mGPS) are scores based on serum CRP and albumin levels; the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are calculated as the ratios of neutrophil or platelet counts to lymphocyte count, respectively; the systemic immune-inflammation index (SII) is derived from platelet count multiplied by neutrophil count divided by lymphocyte count; and the neutrophil–platelet score (NPS) is based on predefined thresholds of neutrophil and platelet counts. These measures were selected because they are widely recognized and validated indicators of systemic inflammation, which play a central role in both IBD and RA pathogenesis. Elevated levels of these markers can reflect chronic inflammatory activity and immune dysregulation, providing potential mechanistic links between IBD and the subsequent development of RA. We conducted the mediation analysis using the approach described by Baron and Kenny [23], which involves a series of regression models to assess the extent to which the potential mediator accounts for the effect of IBD on RA risk. Specifically, we first estimated the total effect of IBD on RA. Next, we assessed the association between IBD and the mediator, and finally, the association between the mediator and RA, adjusting for IBD. In all mediation models, we adjusted for the same set of potential confounders as in the fully adjusted main analyses. Additionally, we calculated the attributable risk proportion:

$$\text{Attributable risk proportion} = \frac{\text{HR} - 1}{\text{HR}} \times 100\,\%$$

2.5 | Sensitivity Analysis

To confirm the robustness of our findings, we conducted a series of sensitivity analyses. First, we restricted the analyses to incident RA events occurring at least 3, 5, or 7 years after baseline to minimize the potential for reverse causation and ascertainment bias.

Second, we performed a competing risk analysis by treating death as a competing event. This approach acknowledges that death may preclude the diagnosis of RA and therefore could bias the observed association if not properly accounted for; by using competing risk models, we provide a more accurate estimation of the risk of RA in the presence of the competing risk of death.

In addition, to minimize the potential for misclassification due to the use of multiple data sources, we excluded individuals whose RA diagnosis was based solely on self-reported information and repeated the analysis. By limiting our case

definition to diagnoses verified through hospital inpatient records, primary care data, and death registers, this approach helped to ensure that only clinically validated RA cases were included. As a result, the analysis became less susceptible to diagnostic inaccuracies or misreporting that may arise from self-reported data, thereby enhancing the reliability of our findings.

Lastly, we applied multiple imputation by chained equations (MICE) with 20 imputations, as well as random forest imputation, to address missing covariate data. The proportion of missing data for all variables ranged from 0% to 8.21% (Table S5), which is considered low and appropriate for both imputation methods. MICE offers a flexible and widely accepted approach for handling various types of missing data by creating multiple plausible datasets, while random forest imputation is a robust machine learning technique capable of capturing complex, nonlinear relationships among variables. Using both methods allows us to assess the consistency of our results and ensure that our findings are not sensitive to the specific imputation strategy employed [24].

All data analyses were carried out using R (version 4.3.3). The code used for these analyses is available from the authors upon reasonable request. Statistical significance was indicated by a two-sided *p*-value of 0.05 or lower.

2.6 | Patient and Public Involvement

Neither patients nor the public participated in the design or execution of this study.

2.7 | Role of the Funding Source

The funding sources did not play a role in study design, data interpretation, or writing in this investigation.

3 | Results

3.1 | Baseline Characteristics

After excluding those with RA at baseline ($N = 6769$), those lacking IBD subtype information ($N = 475$), and those with missing covariate data ($N = 121\,195$), we included 373 693 individuals in the analysis (Figure 1). At baseline, the average age of participants was 56.4 years (SD 8.09), with 198 595 (53.1%) being women and 175 098 (46.9%) men. 356 463 (95.4%) were White. 3867 participants had IBD, of which 2701 had UC and 1166 had CD. Over a median follow-up period of 13.6 years (IQR 12.8–14.3), there were 4818 new-onset RA cases (Table 1).

3.2 | IBD and RA Risk

Compared to individuals without IBD, those with IBD had a significantly increased risk of developing RA, with a HR of 2.06 (95% CI 1.69–2.51). This elevated risk remained consistent across most subgroups. Stratified analysis by sex showed HRs

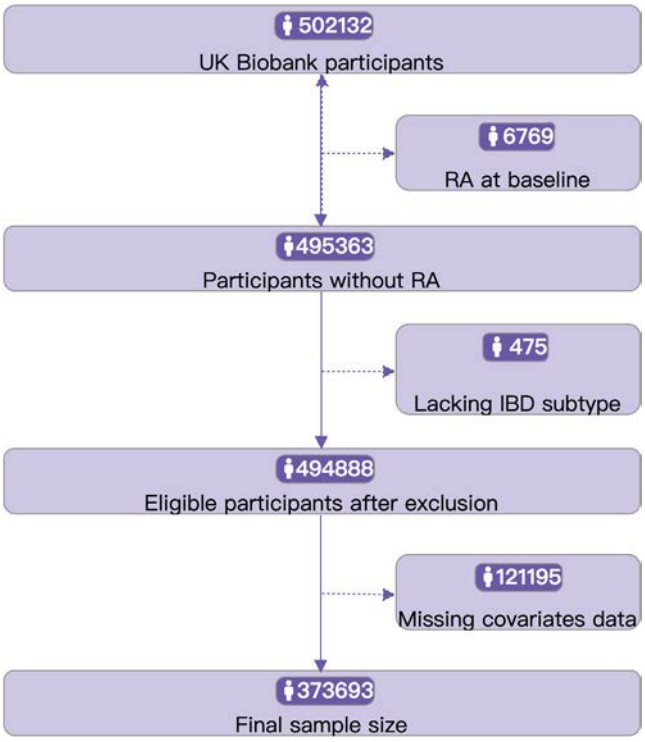

FIGURE 1 | Flow diagram of study participant selection.

of 2.13 (1.66–2.72) for women and 1.96 (1.42–2.72) for men, with a *p*-interaction of 0.72, indicating no significant difference between genders. Similarly, analyses across various demographic, lifestyle, and health-related subgroups showed a consistently increased risk of RA among IBD patients, with no significant interactions, indicating the association was stable across different populations (Figure 2).

Notably, in the subgroup analysis for PRS for RA, the association between IBD and RA risk was stronger in individuals with a low PRS (HR 3.09, 2.23–4.28), compared to those with intermediate (HR 1.47, 0.98–2.20) or high PRS (HR 1.93, 1.41–2.63), with significant *p*-interactions (0.0051 for low, 0.041 for high). This suggests that genetic predisposition may modify the extent of risk conferred by IBD, with the relative impact of IBD being greatest in those at lower genetic risk for RA.

In the stepwise regression, all models consistently indicated an elevated risk of RA among IBD patients. Notably, the HRs gradually stabilized as more covariates were added from Model 1 to Model 5. For instance, the HR for IBD decreased only slightly from 2.07 (95% CI 1.70–2.53) in Model 1 to 1.99 (1.64–2.43) in Model 5 (Figure 3A). Similarly, the HR for UC declined from 1.93 (1.51–2.45) in Model 1 to 1.88 (1.48–2.40) in Model 5 (Figure 3B), and for CD, from 2.40 (1.71–3.36) to 2.22 (1.58–3.11) (Figure 3C). This trend demonstrates that as adjustments for demographic, socioeconomic, health behavior, chronic disease, genetic, and environmental factors were incrementally incorporated, the effect estimates became more robust and reached a plateau, indicating a stable and independent association.

After mediation analysis of potential biochemical markers, it was found that all tested inflammatory markers exhibited

TABLE 1 | Characteristics of the UK Biobank.

		Inflammatory bowel disease	
	Total (*N* = 373 693)	**No (*N* = 369 826)**	**Yes (*N* = 3867)**
Age at baseline, years			
Mean (SD)	56.4 (8.09)	56.4 (8.09)	57.1 (7.91)
Median [min, max]	58.0 [38.0, 73.0]	58.0 [38.0, 73.0]	59.0 [40.0, 70.0]
Age groups, years			
0–49	88 723 (23.7%)	87 908 (23.8%)	815 (21.1%)
50–59	124 686 (33.4%)	123 458 (33.4%)	1228 (31.8%)
60 or older than 60	160 284 (42.9%)	158 460 (42.8%)	1824 (47.2%)
Sex			
Female	198 595 (53.1%)	196 645 (53.2%)	1950 (50.4%)
Male	175 098 (46.9%)	173 181 (46.8%)	1917 (49.6%)
Race			
White	356 463 (95.4%)	352 711 (95.4%)	3752 (97.0%)
Other	17 230 (4.6%)	17 115 (4.6%)	115 (3.0%)
Education			
Low	55 746 (14.9%)	55 059 (14.9%)	687 (17.8%)
Intermediate	190 626 (51.0%)	188 581 (51.0%)	2045 (52.9%)
High	127 321 (34.1%)	126 186 (34.1%)	1135 (29.4%)
Townsend deprivation index quartile			
Mean (SD)	−1.49 (2.96)	−1.49 (2.96)	−1.48 (2.93)
Median [min, max]	−2.29 [−6.26, 10.6]	−2.29 [−6.26, 10.3]	−2.24 [−6.26, 10.6]
Townsend deprivation index quartile group			
Q1	98 035 (26.2%)	97 055 (26.2%)	980 (25.3%)
Q2	97 092 (26.0%)	96 072 (26.0%)	1020 (26.4%)
Q3	94 379 (25.3%)	93 400 (25.3%)	979 (25.3%)
Q4	84 187 (22.5%)	83 299 (22.5%)	888 (23.0%)
BMI, kg/m^2			
Mean (SD)	27.3 (4.69)	27.3 (4.70)	27.0 (4.46)
Median [min, max]	26.6 [12.1, 74.7]	26.6 [12.1, 74.7]	26.5 [14.1, 52.3]
BMI category			
Underweight	124 298 (33.3%)	122 947 (33.2%)	1351 (34.9%)
Normal	87 431 (23.4%)	86 624 (23.4%)	807 (20.9%)
Overweight	160 147 (42.9%)	158 467 (42.8%)	1680 (43.4%)
Obese	1817 (0.5%)	1788 (0.5%)	29 (0.8%)
Smoking status			
Never	205 303 (54.9%)	203 493 (55.0%)	1810 (46.8%)
Previous	131 225 (35.1%)	129 523 (35.0%)	1702 (44.0%)
Current	37 165 (9.9%)	36 810 (10.0%)	355 (9.2%)

(Continues)

TABLE 1 | (Continued)

		Inflammatory bowel disease	
	Total (*N* = 373 693)	**No (*N* = 369 826)**	**Yes (*N* = 3867)**
Alcohol consumption			
Never	26 429 (7.1%)	26 081 (7.1%)	348 (9.0%)
Moderate	80 870 (21.6%)	79 976 (21.6%)	894 (23.1%)
Intermediate	185 847 (49.7%)	183 986 (49.7%)	1861 (48.1%)
Heavy	80 547 (21.6%)	79 783 (21.6%)	764 (19.8%)
Physical activity			
Low	66 370 (17.8%)	65 599 (17.7%)	771 (19.9%)
Moderate	151 360 (40.5%)	149 819 (40.5%)	1541 (39.9%)
High	155 963 (41.7%)	154 408 (41.8%)	1555 (40.2%)
Diabetes			
No	355 402 (95.1%)	351 758 (95.1%)	3644 (94.2%)
Yes	18 291 (4.9%)	18 068 (4.9%)	223 (5.8%)
Hypertension			
No	268 859 (71.9%)	266 158 (72.0%)	2701 (69.8%)
Yes	104 834 (28.1%)	103 668 (28.0%)	1166 (30.2%)
Cardiovascular disease			
No	353 689 (94.6%)	350 079 (94.7%)	3610 (93.4%)
Yes	20 004 (5.4%)	19 747 (5.3%)	257 (6.6%)
Social isolation			
No	341 882 (91.5%)	338 391 (91.5%)	3491 (90.3%)
Yes	31 811 (8.5%)	31 435 (8.5%)	376 (9.7%)
Loneliness			
No	357 771 (95.7%)	354 076 (95.7%)	3695 (95.6%)
Yes	15 922 (4.3%)	15 750 (4.3%)	172 (4.4%)
Sun exposure			
0–3	215 363 (57.6%)	213 170 (57.6%)	2193 (56.7%)
≥ 3	158 330 (42.4%)	156 656 (42.4%)	1674 (43.3%)
NSAIDs use			
No	273 131 (73.1%)	270 175 (73.1%)	2956 (76.4%)
Yes	100 562 (26.9%)	99 651 (26.9%)	911 (23.6%)
PRS			
Mean (SD)	0.129 (0.986)	0.129 (0.986)	0.146 (0.989)
Median [min, max]	0.0844 [−3.74, 5.15]	0.0842 [−3.74, 5.15]	0.116 [−2.66, 3.52]
PRS group			
Low	123 549 (33.1%)	122 299 (33.1%)	1250 (32.3%)
Moderate	127 089 (34.0%)	125 774 (34.0%)	1315 (34.0%)
High	123 055 (32.9%)	121 753 (32.9%)	1302 (33.7%)

(Continues)

TABLE 1 | (Continued)

	Total ($N = 373\,693$)	Inflammatory bowel disease	
		No ($N = 369\,826$)	Yes ($N = 3867$)
PM2.5 exposure, $\mu g/m^3$			
Mean (SD)	9.96 (1.05)	9.96 (1.05)	9.98 (1.03)
Median [min, max]	9.91 [8.17, 21.3]	9.90 [8.17, 21.3]	9.91 [8.17, 17.0]
PM10 exposure, $\mu g/m^3$			
Mean (SD)	22.3 (2.72)	22.3 (2.72)	22.3 (2.68)
Median [min, max]	22.0 [13.8, 36.6]	22.0 [13.8, 36.6]	22.0 [15.5, 33.8]
PM2.5–10 exposure, $\mu g/m^3$			
Mean (SD)	6.42 (0.898)	6.42 (0.898)	6.44 (0.919)
Median [min, max]	6.10 [5.57, 12.8]	6.10 [5.57, 12.8]	6.11 [5.57, 10.0]
NO_2 exposure, $\mu g/m^3$			
Mean (SD)	29.9 (10.2)	29.9 (10.2)	29.7 (9.92)
Median [min, max]	28.3 [7.33, 127]	28.3 [7.33, 127]	28.3 [9.07, 96.8]
Rheumatoid arthritis			
No	368 875 (98.7%)	365 109 (98.7%)	3766 (97.4%)
Yes	4818 (1.3%)	4717 (1.3%)	101 (2.6%)

Note: Summary statistics are presented as proportions (%) for categorical variables and as means with standard deviations (SD) for continuous variables. For each characteristic, data are shown for the total cohort, participants without IBD, and participants with IBD.

statistically significant mediation effects in the association between IBD and RA (Table 2). The proportion of effect mediated by these biomarkers ranged from 0.76% to 9.56% across different pathways. Here, the "mediator proportion" represents the percentage of the total association between IBD and RA that can be explained by the indirect pathway through each inflammatory marker, rather than by a direct link between IBD and RA. In other words, this value quantifies how much of the effect of IBD on RA operates through changes in inflammatory markers. Notably, HS-mGPS consistently showed the highest mediation proportions among all markers, with the maximum observed in the CD → RA pathway (9.56%). In contrast, PLR consistently demonstrated the lowest mediation proportions, generally below 2%. For most pathways, the proportion of the effect mediated by inflammatory markers was modest, with indirect effect sizes ranging from 1.05 to 15.75, all with statistically significant p values ($p < 0.001$). These findings indicate that, while systemic inflammatory markers partially mediate the association between IBD and RA, most of the total effect remains direct.

3.3 | Sensitivity Analysis

The associations observed remained consistent when analyses were restricted to RA events that occurred at least three, five, or seven years post-baseline (Tables S2–S4). Specifically, the risk of RA remained significantly increased among participants with IBD across all lag periods and models: for IBD overall, HRs ranged from 1.85 to 1.94 (95% CI: 1.46–2.52); for UC, HRs ranged from 1.77 to 1.87 (95% CI: 1.28–2.49); and for CD, HRs ranged from 1.94 to 2.24 (95% CI: 1.32–3.52). Consistent results were observed when accounting for the competing risk of death. Using Fine-Gray competing risk models, the associations between IBD and incident RA remained robust: for IBD overall, the subdistribution hazard ratio (SHR) was 1.96 (95% CI: 1.61–2.39); for UC, SHR was 1.87 (95% CI: 1.46–2.38); and for CD, SHR was 2.16 (95% CI: 1.53–3.03). These estimates were like those from the standard Cox models, indicating that the positive associations were not substantially influenced by the competing risk of death (Figure S3).

To further enhance the accuracy of RA diagnosis, we excluded 230 participants with self-reported RA and included only those identified through primary care or hospital admission data. The association between IBD and RA remained robust, with a HR of 2.15 (95% CI: 1.76–2.62) after exclusion. Similar associations were observed across most subgroups, with significant interactions detected only for PRS ($p\_interaction = 0.005$ and 0.036). After multivariable adjustments, the association persisted: for IBD overall, HRs ranged from 2.07 to 2.16 across models; for UC, HRs were 1.94–1.99; and for CD, HRs were 2.33–2.53 (all $p < 0.001$) (Figures S4 and S5).

Additionally, to ensure that missing covariate data did not bias our results, we applied both MICE and random forest imputation. The associations between IBD and RA remained virtually unchanged with either approach: for IBD overall, fully adjusted HRs ranged from 2.12 to 2.20; for UC, from 2.13 to 2.17; and for CD, from 2.05 to 2.25 (all $p < 0.001$), further supporting the robustness of our findings (Figures S6 and S7).

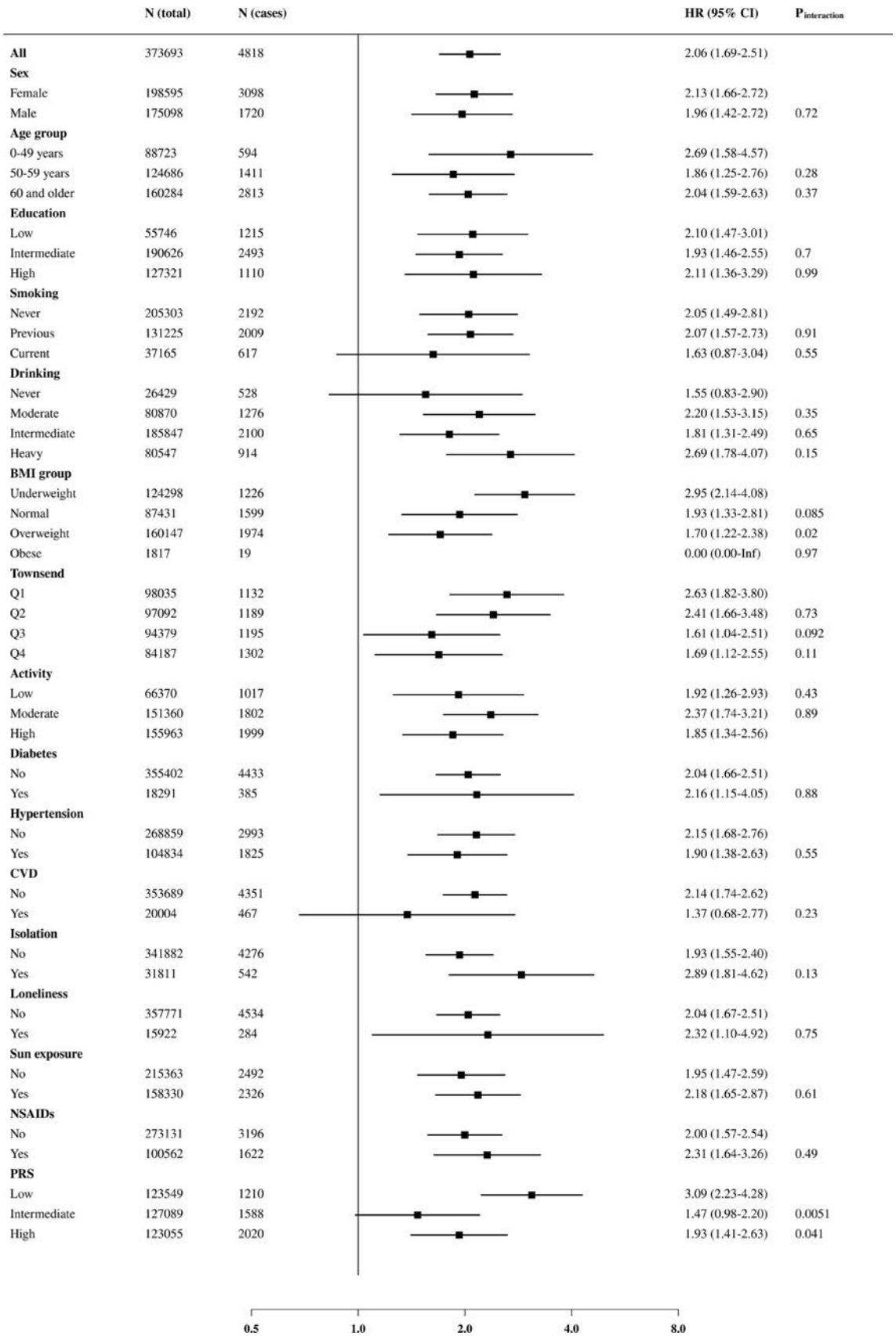

FIGURE 2 | Associations between IBD with RA in different subgroups in the UK Biobank. Subgroup analyses were performed according to key demographic, lifestyle, clinical, psychosocial, environmental, and genetic factors, including sex, age, education, smoking, alcohol consumption, BMI, socioeconomic status (Townsend deprivation index), physical activity, diabetes, hypertension, cardiovascular disease (CVD), social isolation, loneliness, sun exposure, NSAIDs use, and polygenic risk score (PRS) for RA. For each subgroup, the number of participants and RA cases, hazard ratios (HRs) with 95% confidence intervals (CIs), and *p* values for interaction are presented. All models were adjusted for age and sex.

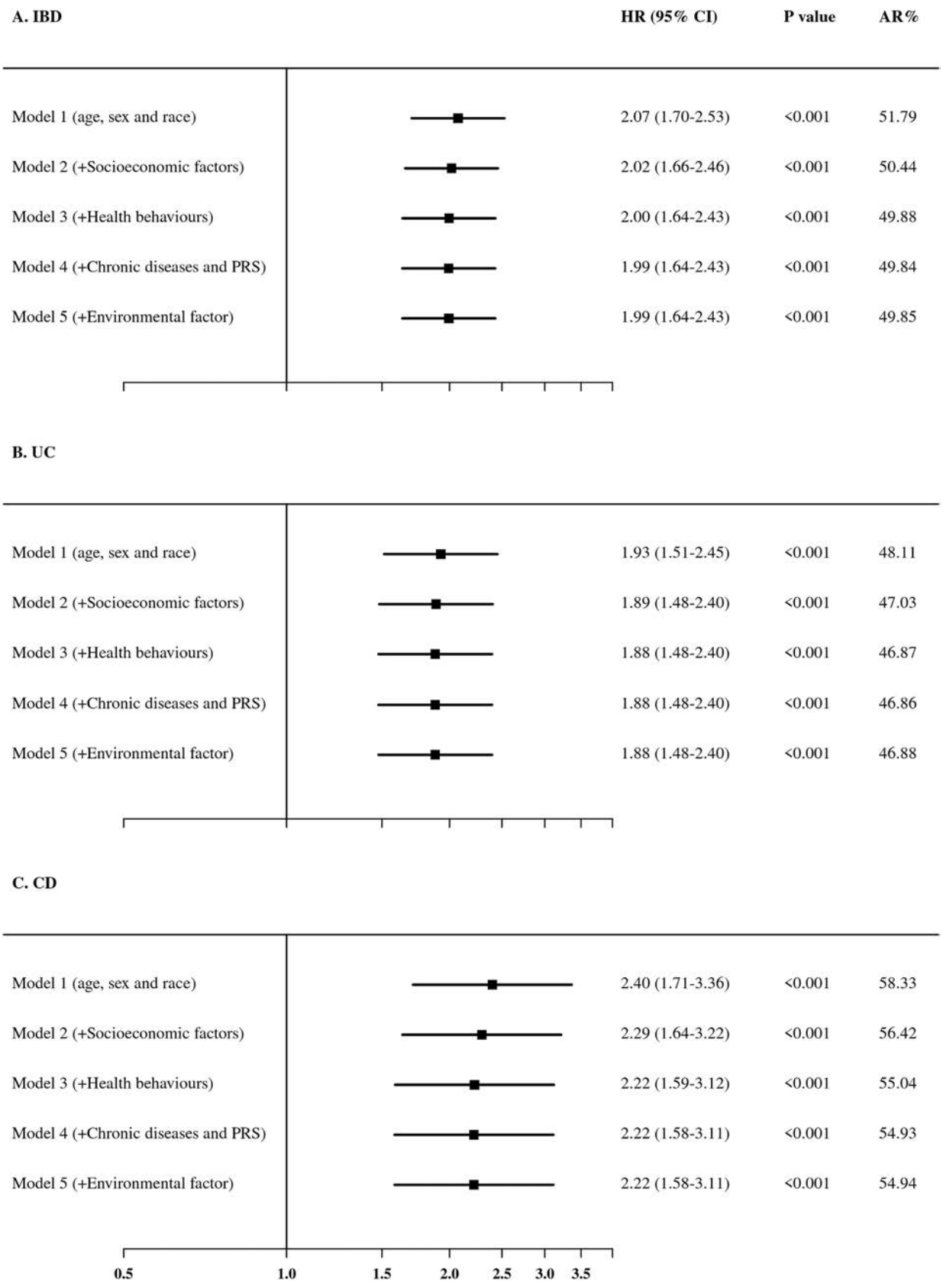

FIGURE 3 | Associations of IBD with RA in the UK Biobank after multivariable adjustments. In model 1, adjustments were made for age, sex, and ethnicity. Model 2 further included education and the Townsend deprivation index to account for socioeconomic factors. Building on this, model 3 additionally adjusted for health behaviors, including smoking status, alcohol intake, BMI, and physical activity. Model 4 extended these adjustments by including chronic diseases (diabetes, hypertension, and cardiovascular disease), genetic susceptibility (polygenic risk score, PRS), psychosocial factors (social isolation and loneliness), sun exposure, and NSAIDs use. Finally, model 5 further incorporated environmental exposures, specifically air pollution indices such as $PM_{2.5}$, PM_{10}, $PM_{2.5-10}$, and NO_2. AR, attributable risk proportion; HR, hazard ratio.

TABLE 2 | Mediation analysis in the association of IBD with RA.

	Total effect		Direct effect		Indirect effect		Proportion mediated (%)
	Size (95% CI)	*p*	Size (95% CI)	*p*	Size (95% CI)	*p*	
IBD → CRP → RA	145.84 (177.14–103.81)	< 0.001	137.50 (167.80–94.64)	< 0.001	8.34 (10.62–6.67)	< 0.001	5.72
IBD → mGPS → RA	139.23 (178.46–94.05)	< 0.001	133.15 (172.51–87.03)	< 0.001	6.08 (8.12–4.26)	< 0.001	4.37
IBD → HS_ mGPS → RA	141.69 (186.86–94.46)	< 0.001	129.55 (174.94–83.47)	< 0.001	12.14 (15.71–9.39)	< 0.001	8.57
IBD → NLR → RA	150.14 (188.97–96.56)	< 0.001	143.94 (183.17–90.13)	< 0.001	6.20 (9.06–5.25)	< 0.001	4.13
IBD → PLR → RA	149.96 (192.74–101.47)	< 0.001	148.51 (189.07–97.98)	< 0.001	1.45 (7.79–0.99)	< 0.001	0.97
IBD → SII → RA	149.76 (206.99–96.37)	< 0.001	143.59 (200.40–87.31)	< 0.001	6.17 (12.87–4.74)	< 0.001	4.12
IBD → NPS → RA	149.36 (202.42–112.46)	< 0.001	144.11 (197.52–107.64)	< 0.001	5.25 (6.54–3.63)	< 0.001	3.51
UC → CRP → RA	129.00 (188.43–56.68)	< 0.001	122.36 (181.80–49.35)	< 0.001	6.64 (8.35–4.79)	< 0.001	5.15
UC → mGPS → RA	125.52 (173.48–39.23)	< 0.001	121.31 (168.24–35.44)	< 0.001	4.21 (6.02–2.81)	< 0.001	3.35
UC → HS_ mGPS → RA	128.18 (176.40–75.16)	< 0.001	117.69 (166.62–64.51)	< 0.001	10.49 (13.51–7.68)	< 0.001	8.19
UC → NLR → RA	138.38 (190.41–82.65)	< 0.001	133.74 (185.51–77.75)	< 0.001	4.64 (6.74–3.40)	< 0.001	3.35
UC → PLR → RA	138.45 (180.63–84.14)	< 0.001	137.39 (178.46–81.81)	< 0.001	1.05 (6.34–0.77)	< 0.001	0.76
UC → SII → RA	138.05 (186.16–83.34)	< 0.001	133.30 (179.68–77.34)	< 0.001	4.75 (9.81–3.78)	< 0.001	3.44
UC → NPS → RA	137.57 (181.33–89.89)	< 0.001	132.23 (176.38–85.74)	< 0.001	5.35 (7.79–3.71)	< 0.001	3.89
CD → CRP → RA	173.66 (220.25–105.47)	< 0.001	161.71 (210.02–93.92)	< 0.001	11.96 (15.15–9.11)	< 0.001	6.88
CD → mGPS → RA	162.49 (216.59–100.79)	< 0.001	152.34 (208.57–87.15)	< 0.001	10.15 (13.81–6.58)	< 0.001	6.25
CD → HS_ mGPS → RA	164.75 (211.76–101.38)	< 0.001	149.00 (198.66–84.43)	< 0.001	15.75 (21.09–11.50)	< 0.001	9.56
CD → NLR → RA	170.38 (221.52–69.60)	< 0.001	160.83 (212.45–58.41)	< 0.001	9.55 (14.41–7.53)	< 0.001	5.60
CD → PLR → RA	169.76 (217.72–76.58)	0.02	167.44 (210.59–67.08)	0.02	2.32 (13.71–1.69)	< 0.001	1.37
CD → SII → RA	169.89 (224.40–84.53)	< 0.001	160.67 (215.16–74.42)	< 0.001	9.22 (18.41–7.19)	< 0.001	5.43
CD → NPS → RA	169.66 (222.89–85.05)	< 0.001	164.61 (217.42–78.44)	< 0.001	5.05 (7.92–2.54)	< 0.001	2.98

Note: For each pathway, the total effect, direct effect, and indirect effect (with 95% confidence intervals and *p* values) are reported. The indirect effect reflects the proportion of the association between IBD and RA that is mediated through the corresponding inflammatory marker. The "Proportion Mediated (%)" indicates the percentage of the total effect explained by the indirect (mediated) pathway. All models were adjusted for all covariates described in the covariates section of the Methods.
Abbreviations: CD, Crohn's disease; CRP, C-reactive protein; HS-mGPS, high-sensitivity mGPS; mGPS, modified Glasgow Prognostic Score; NLR, neutrophil-to-lymphocyte ratio; NPS, neutrophil–platelet score; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; UC, ulcerative colitis.

4 | Discussion

This study represented the first comprehensive assessment utilizing the UKBB prospective cohort to evaluate the association between IBD and the risk of developing RA. Our results showed that IBD, including both UC and CD, was associated with a higher risk compared to the general population. This relationship was consistent across all principal subgroups, including sex (HR: 2.13 in females, 1.96 in males), age (HRs ranging from 1.86 to 2.69), and educational level (HRs: 2.10–2.11), with no significant interactions observed (all p_interac tion >0.05). Notably, the association was strongest among participants with a low polygenic risk score for RA (HR: 3.09), compared to those with high PRS (HR: 1.93), with a significant interaction (p_interaction $=0.041$). Moreover, the robustness of these findings was further substantiated through four sensitivity analyses, reinforcing the credibility of our results.

The stronger association observed in the low PRS group suggests that, for individuals with lower genetic predisposition to RA, environmental or acquired factors such as IBD may play a relatively larger role in increasing RA risk. In contrast, among those with a high genetic risk, the development of RA may be mainly driven by genetic factors, so the additional impact of IBD is less pronounced. This pattern highlights the importance of considering both genetic susceptibility and environmental exposures when assessing disease risk and suggests that individuals with low genetic risk may be more sensitive to environmental triggers like IBD. However, it should be noted that our investigation of this interaction was exploratory and limited to subgroup analyses. Further studies are needed to validate these findings and to elucidate the underlying mechanisms of the gene–environment interaction in RA development.

Research has demonstrated a significant correlation between IBD and the incidence of arthritis, with most arthritis cases related to IBD mirroring the activity of the bowel condition. This often requires treatment for joint disease in a substantial number of patients (97% of type 1 and 95% of type 2) [25]. Prior studies have assessed the likelihood of RA development in individuals with IBD. A cohort study from Denmark reported an incidence rate ratio (IRR) of 2.11 (95% CI 1.66–2.67) for RA in patients with IBD compared to controls without IBD [26]. Similarly, an analysis of the Korean National Health Insurance claims data revealed an association between IBD and an increased risk of RA, with a HR of 4.23 (95% CI 3.25–5.52) [27]. However, these results may lack precision due to the absence of smoking data, a recognized RA risk factor [28, 29]. In our research, we considered subgroups defined by lifestyle factors, such as smoking and drinking habits, and arrived at conclusions that align with these earlier findings.

CRP is elevated in both IBD and RA, reflecting the chronic inflammatory status in these two diseases. In patients with IBD, CRP levels are usually elevated due to persistent intestinal inflammation, and CRP levels can be used as an indicator to assess inflammatory activity and disease severity [30, 31]. In our mediation analysis, we observed that several systemic inflammatory markers, including CRP, contributed modestly to mediating the association between IBD and RA, with the proportion mediated generally below 10%. Notably, HS-mGPS demonstrated the highest mediation proportion among all markers, suggesting it may be a particularly sensitive indicator of inflammation-related risk transmission between IBD and RA, while PLR showed the lowest mediation effect. These findings indicate that while systemic inflammation partly bridges the link between IBD and RA, most of the association remains direct and cannot be fully explained by inflammatory markers alone. Therefore, more research is needed to explore the specific biological pathways and mechanisms underlying this association, including other potential mediators beyond classical inflammatory markers.

The etiology of IBD and RA remains elusive. However, the gut-joint axis has garnered attention for its role in elucidating the complex interactions between the gastrointestinal tract and joint health. This axis highlights the bidirectional impact between the gut and joints, facilitated by mechanisms that include immune modulation, alterations in gut microbiota composition, and the activation of pattern recognition receptors [32–34]. Emerging evidence, as highlighted in a review from Nature Reviews Rheumatology, indicates that disruptions in gut microecology, coupled with intestinal inflammation and compromised barrier integrity, may precipitate the onset of RA [33]. Individuals with IBD demonstrate gut microbiota dysbiosis, marked by decreased levels of Firmicutes and Bacteroidetes, and elevated levels of Proteobacteria and Actinobacteria [35]. Like IBD, in the early, subclinical stages of RA, alterations in the gut microbiome may include an increase in the genus Prevotella and a reduction in the genus Bacteroides [36]. Changes in the microbial landscape may either reflect or influence the development of RA in individuals with IBD. IBD is characterized by chronic intestinal inflammation and heightened intestinal permeability, factors that may increase the risk of RA [37]. Collectively, these findings underscore the interplay between gut health and systemic inflammatory disorders, supporting the notion that targeting the gut microbiota could offer novel therapeutic strategies for the management of RA in individuals with or at risk of IBD.

Our study possessed several strengths. Firstly, it utilized a large prospective cohort, achieving a total follow-up duration of 13 years, which helped to establish a clearer temporal relationship between IBD and RA. Second, we comprehensively explored the mediating role of multiple systemic inflammatory markers—not limited to CRP, but also including HS-mGPS, PLR, and others—in the association between IBD and the risk of RA, thus providing a more nuanced understanding of the inflammatory pathways potentially linking these two diseases. Thirdly, our methodology strengthens the study by including RA events only if they occurred a minimum of 3, 5, or 7 years post-baseline, acknowledging the preclinical phase of RA autoimmunity [38], thereby ensuring a more dependable temporal link between IBD and RA onset. Fourth, to address the issue of missing data, we employed two different imputation methods, which increased the reliability and robustness of our findings. Finally, the study's robustness is further reinforced through the triangulation of self-reported RA diagnoses with pharmaceutical data, including steroid and DMARD usage, and by refining sensitivity analyses to exclude self-reports, which sharpens the accuracy of the observed IBD-RA relationship.

Our study had several limitations. First, although the study may account for numerous recognized confounders, it remains impossible to eliminate the influence of unknown or unmeasured variables. Second, we explored the role of mediators in the association between IBD and RA risk; however, these surrogate markers may not fully reflect the pathological process, which may limit understanding of the underlying mechanisms. Third, although prospective cohort study designs help to reduce reverse causation bias, observational study designs cannot determine causality, only infer associations. Finally, there may have been a "healthy volunteer" selection bias, as the study was conducted based on a voluntary biobank. Participants in the UK Biobank tend to be healthier and have higher socioeconomic status than the general population, which may affect the generalizability of our findings. However, previous research has shown that, despite this bias, the relative associations between risk factors and disease outcomes in the UK Biobank are highly comparable to those observed in more representative population-based cohorts, suggesting that the healthy volunteer bias is unlikely to substantially bias effect estimates for relative risks. Therefore, our findings remain broadly informative and generalizable to other populations [39, 40].

5 | Conclusions

In conclusion, this large prospective cohort study demonstrates that patients with IBD—including UC and CD—face a significantly increased risk of developing RA, regardless of demographic, lifestyle, genetic, or environmental factors. This association is especially strong among those with lower genetic risk for RA, suggesting the important role of acquired factors. While systemic inflammation partly mediates this risk, most of the association remains unexplained by conventional inflammatory markers. These findings highlight the importance of monitoring joint symptoms in IBD patients and call for further research into the underlying mechanisms to inform prevention and management strategies.

Author Contributions

Kuangyu He, Yi Xu, Zhengqiang Yuan: conceptualization; data curation; investigation; methodology; project administration; software; writing – original draft; writing – review and editing. Hao Xiong, Yunhao Zhai, and Juehong Li: software; writing – original draft. Cunyi Fan, Ziyang Sun, Yun Qian: conceptualization; funding acquisition; investigation; methodology; project administration; supervision; writing – original draft; writing – review and editing. All authors contributed to the content and critical revision and approved the final draft of the manuscript.

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Ethics Statement

All the participants provided written informed consent. Ethical clearance for the UK Biobank was approved by the North West Multi-Centre Research Ethics Committee (11/NW/0382).

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Researchers registered with UK Biobank can apply for access to the database by completing an application, which includes a summary of the research plan, data fields required, any new data or variables that will be generated, and payment to cover the incremental costs of servicing an application (https://www.ukbiobank.ac.uk/enable-your-research/applyfor-access).

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Supporting Information

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

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LETTER TO THE EDITOR

Tuberculosis and Gout Risk

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Dear editor,

I read with great interest the study by Kim et al. [1], which provides valuable epidemiological data demonstrating an increased risk of gout among patients with tuberculosis (TB). An additional perspective is raised to enhance the interpretation of these findings.

Although the study suggests that TB is associated with an elevated risk of gout, we propose that this increased risk is largely attributable to the use of specific anti-TB medications rather than TB itself. Pyrazinamide and ethambutol are well-documented for their ability to increase serum uric acid (SUA) levels by inhibiting renal clearance, leading to a higher risk of gout flares [2, 3]. In contrast, isoniazid and rifampin do not significantly impact uric acid metabolism. Given this pharmacological basis, it is crucial to distinguish between the effects of TB itself and the medications used for its treatment. Kim et al.'s [1] study shows that the incidence rate of gout among patients with TB was 2.74 per 1000 person-years, which is only modestly higher than the reported incidence in the general population of South Korea (1.52–1.94 per 1000 person-years) [4]. The incidence rate of gout in TB patients is slightly higher but within a similar range. If TB is an independent risk factor for gout, we would expect a much larger difference in incidence rates. This indirect evidence supports the hypothesis that anti-TB medications, rather than TB itself, are the primary contributors to increased gout risk. Furthermore, a study in South Korea by Ha et al. [5] provides direct evidence that anti-TB medications lead to increased SUA levels. Their findings showed that SUA levels significantly increased at 2 months (8.4 ± 3.1 mg/dL, $p < 0.001$) and remained increased at 6 months (6.5 ± 2.5 mg/dL, $p = 0.028$) after the initiation of TB treatment, compared to baseline levels (5.5 ± 1.9 mg/dL). This study further strengthens the evidence that the increased risk of gout in patients with TB is more likely due to anti-TB drugs rather than TB itself.

To further clarify this issue, we recommend that the authors conduct a subgroup analysis comparing active TB patients currently on anti-TB medications with TB patients who have completed treatment and are no longer taking these medications. Because the study's database already contains both patient groups, this additional analysis would provide critical insights into whether the elevated gout risk persists after TB treatment cessation. If gout risk normalizes post-treatment, it would reinforce the argument that anti-TB drugs, rather than TB itself, drive the association.

This clarification has significant clinical implications. If the increased gout risk is primarily medication-induced, physicians should closely monitor serum uric acid levels in patients with TB during treatment and consider preventive strategies when necessary. The letter aims to discuss medical issues with the authors, not criticize their research. I appreciate the authors' contribution to this important topic and believe that an additional analysis would further enhance the clarity and impact of their findings.

Author Contributions

Shih-Wei Lai initiated the draft of the article and approved the final draft.

Ethics Statement

This article is a letter and informed consent is waived.

Conflicts of Interest

The author declares no conflicts of interest.

Data Availability Statement

The author has nothing to report.

Shih-Wei Lai

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ORIGINAL ARTICLE

Five-Year Delivery Rate and Time to Delivery Among Women With and Without Rheumatoid Arthritis: A Real-World Analysis Using a Nationwide Claims Database in Japan

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Keywords: biological DMARDs | fertility | methotrexate | real-world data | rheumatoid arthritis | time to delivery

ABSTRACT

Introduction: Rheumatoid arthritis (RA) frequently affects women of reproductive age; its treatment requires disease-modifying antirheumatic drugs (DMARDs). Despite the widespread use of biologics and the expected improvement in fertility, real-world studies evaluating reproductive outcomes in women with RA are limited. We aimed to compare reproductive outcomes in women with and without RA using a nationwide claims database in Japan.

Methods: This retrospective cohort study analyzed 231 427 women (aged 20–38 years) from the JMDC Claims Database. After propensity score matching, we compared 262 women with RA (defined by diagnosis and DMARDs prescription) to 1310 matched controls without RA.

Results: During the 5-year follow-up, women with RA showed significantly lower delivery rates than the matched controls (19.0% vs. 28.2%, $p < 0.001$). Kaplan–Meier analysis demonstrated a significantly longer time to delivery in the RA group than in the non-RA group (log-rank $p = 0.0014$). In the subgroup analysis, the mean time to delivery was longer in patients with RA and methotrexate use (38.1 months) than in those without methotrexate use (33.7 months) and in non-RA controls (32.2 months). Despite modern RA treatments, including biologics, women with RA have significantly lower delivery rates and longer delivery times than those without RA. This study was limited by potentially unmeasured confounding factors and the lack of certain data.

Conclusion: These findings highlight the need for proactive reproductive health management in women with RA and emphasize the importance of collaboration between rheumatologists and obstetricians to provide optimal care for these patients.

Summary

- We compared reproductive outcomes in women with and without rheumatoid arthritis (RA) by analyzing the time to delivery and 5-year delivery rates using a nationwide claims database in Japan.
- Despite advancements in RA reatment, fertility in women with RA remains a challenge, with the time to delivery being significantly longer in women with RA than in those without RA.
- The findings highlight the need for proactive reproductive health management in women with RA.

1 | Introduction

Rheumatoid arthritis (RA) frequently develops at childbearing age and affects women's reproductive health and pregnancy planning. With the advancing maternal age in developed countries, RA management during the reproductive period has become increasingly important. In the last decade, RA treatment has dramatically changed; early diagnosis, early administration of disease-modifying antirheumatic drugs (DMARDs), several new drugs, including biologics, and the treat-to-target approach to remission have improved patient outcomes [1, 2]. The European League Against Rheumatism (EULAR) recommends prompt DMARD therapy following RA diagnosis to achieve sustained remission or low disease activity. Improvements in RA treatment have resulted in a growing number of patients expressing a desire to conceive [1]. However, data on the fertility of women with RA, the impact of RA on pregnancy, and the safety of DMARDs during pregnancy are limited [3].

Women with RA often experience prolonged time to pregnancy (TTP)—the period between attempting to conceive and becoming pregnant [4–6]—and are more likely to undergo fertility treatment and have a lower chance of live births than those without RA [6–8]. Reproductive challenges in patients with RA are attributed to multiple factors, with high disease activity being a major factor directly affecting fertility. Another significant concern is medication-related, as women with RA may need to temporarily discontinue certain DMARDs before conception because of potential teratogenic risks, particularly with methotrexate (MTX). Furthermore, comprehensive long-term safety data is lacking for newer biological agents that effectively control disease activity. These concerns often lead women with RA and their healthcare providers to carefully balance disease control and pregnancy planning, sometimes resulting in delayed conception.

Despite advancements in RA treatment with biological DMARDs and improved disease control, the assessment of the current reproductive outcomes in women with RA remains unexplored. Traditional fertility studies tracking women from conception to pregnancy present significant practical challenges in terms of time, resources, and follow-up capabilities. Therefore, new methodological approaches using real-world evidence (RWE), as recently proposed by the US Food and Drug Administration (FDA) [9, 10], are essential for generating evidence in this field. In this study, we aimed to evaluate the time to delivery (TTD) in women with RA as a novel method of assessing reproductive capability using recent real-world data (RWD) from a nationwide claims database in Japan.

2 | Materials and Methods

2.1 | Study Design

This retrospective cohort study used data from the JMDC Claims Database, a comprehensive Japanese claims database from the National Universal Health Insurance System. This study compared the TTD between women with and without RA over a 5-year observation period. The JMDC database contains data from approximately 8.4 million insured subscribers as of 2020, providing linked information on medical institutions, insurers, monthly receipts, diagnoses, drug prescriptions, surgery, and diagnostic tests. Importantly, the database enables tracking of pregnancies and deliveries through family identification codes, allowing for an accurate assessment of reproductive outcomes [11–15]. The study protocol was approved by the Institutional Review Board of the National Centre for Child Health and Development (#2022-092). The need for informed consent was waived due to data anonymity.

2.2 | Participants

From 7 447 761 women in the JMDC database between January 2010 and November 2019, we included women aged 20–38 years. This age range was selected to ensure reasonable observation of gestation and delivery during the 5-year follow-up period based on the age distribution of deliveries in Japan. To enhance the validity of our analysis, we excluded women who had JMDC database subscriptions of < 1 year, were female primary subscribers, or were diagnosed with congenital or chromosomal abnormalities [Q90–Q99]. Female primary subscribers were excluded because infants are presumed to be registered as dependents under the father's insurance in most cases.

RA cases were defined by the presence of at least one concurrent record of an ICD-10-based RA diagnosis [M05, M06, M08] and DMARDs prescription (Table S1) during the first year of JMDC subscription. DMARDs were classified into three categories: conventional synthetic (cs), biological (b), and targeted synthetic (ts).

The control group comprised women without RA diagnosis and without DMARDs prescriptions during the same period.

2.3 | Outcomes

The primary outcome, TTD, was defined as the duration from the index month to the delivery month during the 5-year follow-up period. The index month was set as 1 year after the JMDC subscription to establish baseline RA status and treatment patterns (Figure S1). Delivery was identified on the basis of the birth month and year of a child linked to the women using the same family identification code in the JMDC database. This linkage method has been validated in previous studies and enables the identification of mother–child pairs [13, 14, 16]. Exact birth dates are not available in the database owing to data anonymization policies. The JMDC database contains data on

insured individuals, including not only patients with diseases but also healthy individuals [11, 12]. Thus, it includes births among healthy women that did not involve medical intervention.

The study focused on women aged 20–38 years, an age range selected based on the distribution of deliveries in the JMDC database (Figure S2), to ensure adequate observation of reproductive outcomes during the 5-year follow-up period. This approach allowed us to evaluate both the timing and occurrence of delivery as key reproductive outcomes in women with and without RA.

Subgroup analyses were performed to examine the impact of medication patterns on the TTD. The analysis subjects were categorized into three groups: patients with RA using MTX (MTX use), patients with RA using other DMARDs (without MTX) (no MTX use), and non-RA controls. MTX use was defined as having at least one MTX prescription during the follow-up period, whereas no MTX use was defined as having no MTX prescriptions during the follow-up period.

2.4 | Statistical Analysis

Baseline characteristics were summarized using the mean (standard deviation) for continuous variables and the count (percentage) for categorical variables.

We performed 1:5 propensity score (PS) matching between the RA and non-RA groups, using age and JMDC subscription year as covariates. A greedy-pair algorithm with a 0.2 caliper width was applied.

Time-to-event analysis was conducted using Kaplan–Meier curves with log-rank tests. For subgroup analyses comparing MTX users, nonusers, and controls, we conducted an overall comparison using the log-rank test.

All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

3 | Results

3.1 | Selection and Baseline Characteristics of Patients

From the initial 231 427 eligible women, we identified 262 (0.11%) with RA diagnosis and DMARDs prescription (RA) during their first year of JMDC subscription and 230 718 without RA diagnosis and without DMARD prescriptions (non-RA). After PS matching, 262 women with RA (RA_PSM) were compared with 1310 matched controls (non-RA_PSM) (Figure 1).

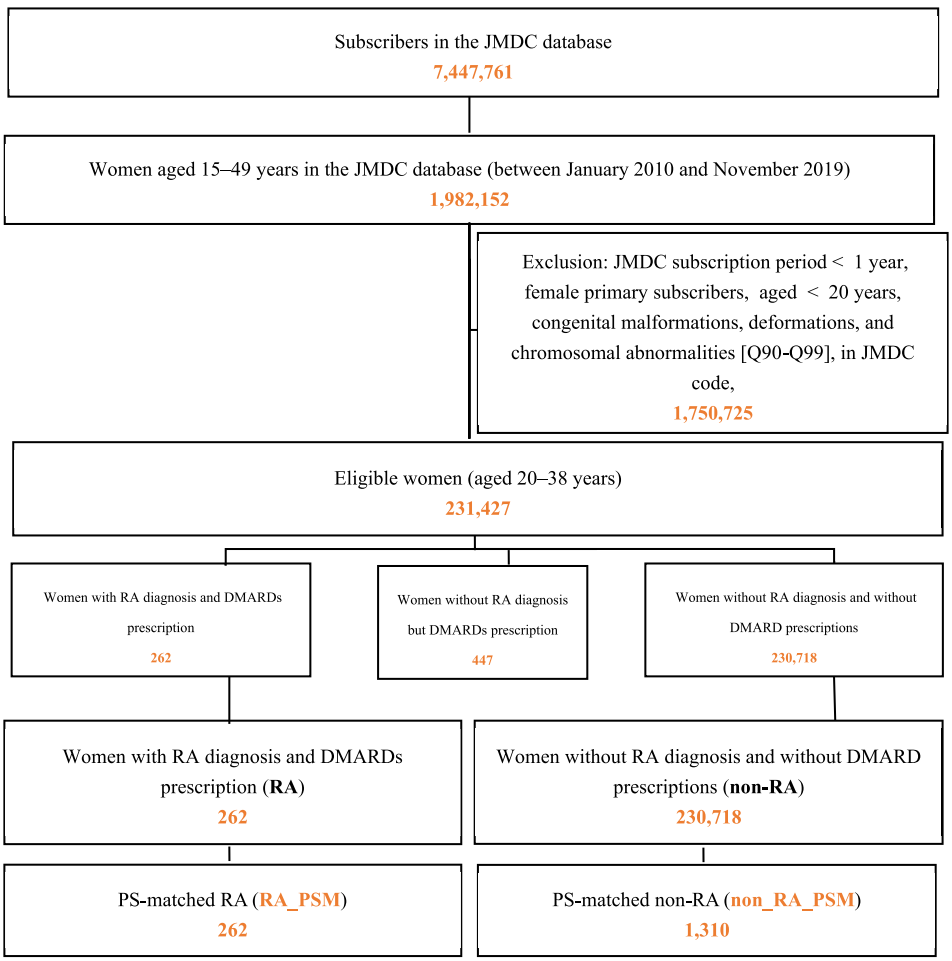

FIGURE 1 | Patient flow. non-RA, women without RA; PSM, propensity score matching; RA, women with rheumatoid arthritis.

Table 1 presents the baseline characteristics of the study population. The mean age was 33.8 (±3.42) years in both the RA_PSM and non-RA_PSM groups. Before PS matching, all comorbidity rates were significantly higher in the RA group than in the non-RA group, partly because of age differences. PS matching successfully eliminated these between-group differences and effectively controlled for potential confounding factors.

The RA treatment prescription patterns are presented in Table S2. During the first year after JMDC subscription, 76.7% of patients with RA received DMARDs, with csDMARDs being the most commonly prescribed (67.6%), followed by bDMARDs (44.3%). The observation period (Table S3) measured from the index month was comparable between the RA and non-RA groups, ensuring a balanced follow-up duration for the outcome assessment.

3.2 | TTD Between Women With and Without RA

Analysis of the 5-year follow-up period revealed significant differences in reproductive outcomes between the groups. In the PS-matched cohort, 50 (19.0%) women in the RA_PSM group delivered, compared with 369 (28.2%) in the non-RA_PSM group (Table 2). Kaplan–Meier analysis demonstrated that women with RA had a significantly longer TTD than those without RA (log-rank $p = 0.0014$) (Figure 2). The separation between the two groups became evident early and remained consistent throughout the follow-up period, with a persistently lower cumulative probability of delivery observed in the RA group than in the non-RA group (Figure 2).

3.3 | Subgroup Analysis According to Medication Use

Among 262 patients with RA, 140 (53.4%) received MTX at least one prescription during the follow-up period. The mean TTD was longer in patients with RA with MTX use (38.1 months) than in those without MTX use (33.7 months) and non-RA controls (32.2 months). Kaplan–Meier analysis demonstrated significant differences in TTD among the three groups (overall log-rank $p = 0.0056$) (Figure S3). Compared with non-RA controls, both RA groups showed significantly lower delivery rates (hazard ratio [95% confidence interval]: 0.54 [0.34–0.86] for MTX users and 0.66 [0.46–0.95] for no MTX users) (Table 3).

4 | Discussion

To our knowledge, this is the first RWD study in Asia to investigate the TTD in women with RA following the widespread adoption of biologics. Over the 5-year period, women with RA had significantly lower delivery rates. Kaplan–Meier analysis further revealed that women with RA experienced significantly longer TTD (log-rank $p = 0.0014$), indicating a substantial impact of RA on reproductive outcomes. These findings have important clinical implications for family planning in women with RA and highlight the need for proactive reproductive health management in this population.

TABLE 1 | Characteristics of the study population.

	Crude			Propensity score-matched		
	RA ($n = 262$)	non-RA ($n = 230718$)	Total ($n = 230980$)	RA ($n = 262$)	non-RA ($n = 1310$)	Total ($n = 1572$)
Age						
Mean (SD)	33.8 (3.42)	32.8 (4.10)	32.8 (4.10)	33.8 (3.42)	33.8 (3.42)	33.8 (3.42)
Median (IQR)	34.0 (32.0, 37.0)	34.0 (30.0, 36.0)	34.0 (30.0, 36.0)	34.0 (32.0, 37.0)	34.0 (32.0, 37.0)	34.0 (32.0, 37.0)
Maternal complications						
HTN, *n* (%)	11 (4.2%)	565 (0.2%)	576 (0.2%)	11 (4.2%)	3 (0.2%)	14 (0.9%)
DL, *n* (%)	12 (4.6%)	384 (0.2%)	396 (0.2%)	12 (4.6%)	2 (0.2%)	14 (0.9%)
DM, *n* (%)	0 (0.0%)	440 (0.2%)	440 (0.2%)	0 (0.0%)	3 (0.2%)	3 (0.2%)
IHD, *n* (%)	5 (1.9%)	44 (0.0%)	49 (0.0%)	5 (1.9%)	0 (0.0%)	5 (0.3%)
CHF, *n* (%)	4 (1.5%)	107 (0.0%)	111 (0.0%)	4 (1.5%)	2 (0.2%)	6 (0.4%)

Note: Data are presented as the mean value (±SD) and chi-square *p* value in crude and after propensity score matching.
Abbreviations: CHF, chronic heart failure; DL, dyslipidemia; DM, diabetes mellitus; HTN, hypertension; IHD, ischemic heart disease; IQR, interquartile range; non-RA, women without RA; OR, Odds ratio; PSM, Propensity score matching; RA, women with rheumatoid arthritis; SD, standard deviation.

TABLE 2 | Number of women who had delivery during the 5-year period from the index month among women with RA or without RA.

	Propensity score-matched (PSM)		
	RA ($n=262$)	**non-RA ($n=1310$)**	**Total ($n=1572$)**
Time to delivery (months)			
Mean (SD)	36.0 (21.42)	32.2 (22.16)	32.8 (22.08)
Median	38.0	29.5	31.0
Delivery rate during 5 years (%)	19.0% (50/262)	28.2% (369/1310)	26.7% (419/1572)
HR (95% CI)	0.62 (0.46–0.84)	Reference	

Note: Log-rank $p=0.0014$. Five-year delivery rate and time to delivery in women with RA compared with women without RA (PS-matched cohort).
Abbreviations: HR, hazard ratio; non-RA, women without RA; RA, women with rheumatoid arthritis; SD, standard deviation.

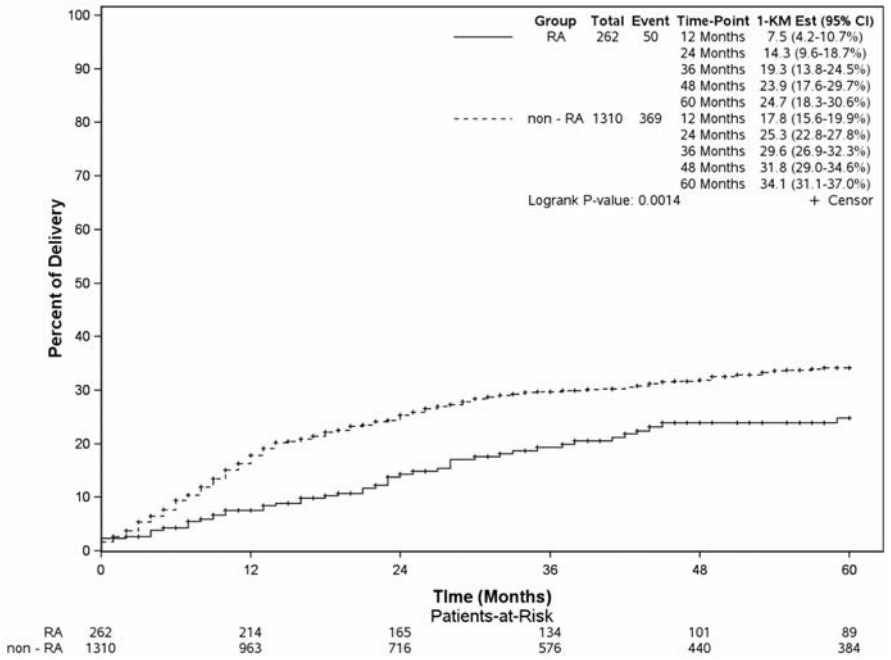

FIGURE 2 | Time to delivery among women with or without RA. Kaplan–Meier curves showing the time to delivery (TTD) in women with rheumatoid arthritis (RA) and without RA (non-RA) over 5 years.

TABLE 3 | Number of women who had delivery during the 5-year period from the index month among women with RA (MTX use), with RA (no MTX use), or without RA (non-RA).

	Propensity score-matched (PSM)			
	RA (MTX use) ($n=140$)	**RA (no MTX use) ($n=122$)**	**non-RA ($n=1310$)**	**Total ($n=1572$)**
Time to delivery (months)				
Mean (SD)	38.1 (21.81)	33.7 (20.81)	32.2 (22.16)	32.8 (22.08)
Median	43.0	31.5	29.5	31.0
Delivery rate during 5 years (%)	20.7% (29/140)	17.2% (21/122)	28.2% (369/1310)	27.9% (419/1572)
HR (95% CI)	0.66 (0.45–0.96)	0.58 (0.37–0.90)	Reference	

Note: Overall log-rank $p=0.0056$. Comparison between patients with RA (MTX use), with RA (no MTX use) (using other DMARDs), and without RA (non-RA controls). MTX use was defined as having at least one prescription during the follow-up period, whereas no MTX use was defined as having no MTX prescriptions during the follow-up period.
Abbreviations: DMARDs, disease-modifying antirheumatic drugs; HR, hazard ratio; MTX, methotrexate; non-RA, women without RA; RA, women with rheumatoid arthritis; SD, standard deviation.

Previous studies [4–6, 17] have reported lower fertility rates in women with RA than in those without RA, based on TTP comparisons. In a prospective cohort study in the Netherlands (PARA study) from 2002 to 2008, 42% of patients with RA did not conceive within 1 year or throughout the follow-up period. TTP was associated with factors such as advanced maternal age, nulliparity, high disease activity, NSAID use, and prednisone doses > 7.5 mg/day [5]. Additionally, Norwegian registry data (2001–2007) indicated that women with RA were more often nulliparous than control women [4]. These findings suggest that maintaining low disease activity could improve fertility, a principle widely recognized in RA management. Biologics may have contributed to improved fertility in patients with RA of childbearing age by effectively controlling disease activity.

Research on fertility in women with RA has been limited, likely due to challenges in recruiting preconception patients actively pursuing pregnancy and maintaining long-term follow-up. TTP has previously been used as a fertility indicator [4, 5]; in the present study, we used TTD, leveraging the mother-baby linkage capabilities of the JMDC database. While pregnancy initiation is important, achieving a live birth holds greater clinical significance, making TTD a suitable fertility metric. Given the timeline of RA treatment approvals in Japan (Table S4), biologics have been widely used since 2010, although few updated studies have been conducted. Our findings suggest that fertility remains a concern for women with RA, despite advances in prognosis with biologics.

Participant age and follow-up periods in the study were based on national data. According to the Ministry of Health, Labour and Welfare, birth rates decline significantly with age [18]. Japan's insurance coverage for infertility treatment is limited to women up to 43 years of age, reflecting the limited efficacy of treatment beyond this age. Delivery data analysis from JMDC also showed a decline in deliveries in women aged 44 years and above (Figure S1), consistent with national trends. Therefore, the participant age range was set at 20–38 years, with a follow-up endpoint at age 43 years, over a 5-year follow-up period.

Two main factors likely contribute to low fertility in women with RA: disease activity control and hesitancy to pursue pregnancy. Preconception treatment to maintain low disease activity could improve pregnancy rates and perinatal outcomes [1]. EULAR guidelines recommend that RA treatment before and during pregnancy should aim to control maternal disease activity while minimizing fetal exposure to risk [19]. Medication management is crucial for patients with RA considering pregnancy. Hesitancy to pursue pregnancy in RA is often related to concerns about medication safety, the need for contraception with teratogenic drugs, financial burdens, and anxiety over potential RA exacerbation, such as postpartum joint pain [4, 20]. MTX use, for instance, may complicate pregnancy planning. Our subgroup analysis showed that the mean TTD was longer in MTX users (38.1 months) than in nonusers (33.7 months) and non-RA controls (32.2 months). The MTX group included women with any MTX prescription during the study period, regardless of timing or duration, because pregnancy intention is not captured in healthcare data. While the analysis was constrained by this limitation, the findings still highlight the importance of careful treatment planning, including MTX discontinuation and DMARDs transitions, for women preparing for pregnancy. Effective perinatal management, including appropriate medication use, is essential for favorable pregnancy outcomes [21]. Healthcare providers should discuss these considerations with patients and offer tailored guidance for pregnancy planning based on individual clinical status.

Research on medication safety and efficacy of medication during pregnancy faces ethical challenges [22, 23]. The FDA has emphasized the value of RWD/RWE studies. As one of Japan's largest insurance claim databases [13, 24, 25], JMDC provides essential data, such as maternal medication prescriptions, congenital anomalies, and relevant covariates, enhancing data reliability [16, 26]. However, gaps remain in optimal RA management for conception, safe medication selection, managing RA exacerbations during pregnancy, timing biologic discontinuation before delivery, and the reciprocal effects of RA and pregnancy [27]. Future studies should address these gaps using diverse methodologies and data sources, including administrative and registry data.

A key strength of this study is the use of a nationwide administrative database in Japan, which enabled the inclusion of a general population of reproductive-age women regardless of disease status. The JMDC database captures data not only on patients with chronic conditions but also on healthy individuals, allowing for robust comparisons between women with and without RA. Additionally, extensive statistical analyses, including PS matching, were conducted to minimize bias. The study outcomes are generalizable because the original data were obtained from a general population of women with RA. Considering many pregnancies are unplanned [28], we included women of reproductive age with and without RA, regardless of whether they wished to conceive, thereby providing a broader perspective than previous studies.

This study has some limitations. First, unmeasured confounding factors may still be present due to the retrospective and observational nature of the study. Second, the JMDC database lacks certain information, including imaging, laboratory data, and clinical symptoms related to RA pathophysiology. Third, DMARDs prescriptions may not directly indicate exposure, as there is no feedback on the quantity and timing of medication use. Additionally, deliveries were identified by linking mother-to-child, meaning miscarriages and stillbirths could not be detected. Finally, the dataset did not include information on pregnancy intentions, partner status, or contraceptive use. However, we believe evaluating delivery rates is valuable regardless of intended pregnancies. Oral contraceptives have been covered by insurance in Japan since 2008, with a usage rate of only 3% as of 2014 [29], making it less relevant to assess oral contraceptive use in this context.

Future studies, including prospective cohort studies and analyses using data from multiple national registries, may help address the limitations of the present study. A prospective design, in particular, would allow for the collection of important clinical and contextual information, such as pregnancy intentions, partner status, and detailed medication use, thereby contributing to a more comprehensive understanding of reproductive outcomes in women with RA.

5 | Conclusion

In conclusion, women with RA have significantly lower delivery rates and longer TTD than those without RA. Despite advancements in RA treatments, reproductive challenges remain clinically significant. Although the lower fertility of women with RA has been observed in Europe and the United States, similar trends have also been reported in Asia. Our findings highlight the importance of considering reproductive outcomes in RA and the need for further research to optimize RA treatment strategies before, during, and after pregnancy. This study provides valuable insights for rheumatologists and obstetricians managing reproductive-age women with RA.

Author Contributions

H.O., I.F., K.S., and A.M. conceptualized the study. H.O., I.F., and K.S. designed the methodology, and H.O. and K.S. performed the formal analysis. H.O., N.Y., and K.S. collected and curated the data. H.O. and I.F. drafted the original manuscript, and all authors contributed to reviewing and editing. K.S. and A.M. provided supervision.

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Ethics Statement

The study protocol was approved by the Institutional Review Board of the National Centre for Child Health and Development (#2022-092).

Consent

The authors have nothing to report.

Conflicts of Interest

H.O. received a consultant fee from EPS International. N.Y. is an employee and shareholder of Pfizer. K.S. has received lecture fees from Daiichi Sankyo, Novartis, Pfizer, and Bristol-Myers Squibb. A.M. has been offered lecture fees, a scholarship from Chugai Pharmaceutical Co. Ltd and UCB Japan, and lecture fees from Asahi Kasei Pharma. These conflicts do not impact the conduct or results of the submitted study. The other authors have no conflicts of interest to declare.

Data Availability Statement

Data are not publicly available and may be made available through the JMDC (www.jmdc.co.jp/en/jmdc-claims-database/).

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Supporting Information

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

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LETTER TO THE EDITOR

Tacrolimus Induced Abnormal Uterine Bleeding in a Patient With Systemic Lupus Erythematosus: A Case Report

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Keywords: abnormal uterine bleeding | systemic lupus erythematosus | tacrolimus

Dear Editor,

A 20-year-old female patient was admitted due to "fever and polyarthralgia for one month." One month prior, she experienced recurrent fever without an identifiable cause, with a maximum temperature of 38.9°C, accompanied by migratory joint pain primarily involving the bilateral wrists, elbows, shoulders, and knees. She denied alopecia, photosensitivity, and oral ulcers. Physical examination revealed periungual erythema and tenderness in the bilateral wrists, elbows, shoulders, and knees, with no obvious swelling. The remainder of the physical examination was unremarkable. Menstrual history: The patient had menarche at the age of 13, with regular cycles (28 ± 7 days), a duration of approximately 5–7 days, and a normal menstrual flow (about 10–15 mL/day). She had no family history of hemophilia and no history of using oral contraceptives, sex hormones, or anticoagulants. Laboratory test results are shown in Table 1. She met the 2019 EULAR/ACR diagnostic criteria for systemic lupus erythematosus (SLE), with a total score of 18, and her SLEDAI score was 14. She was treated with intravenous methylprednisolone 40 mg once daily, and her fever resolved on the second day of treatment. By the fourth day, she reported significant improvement in joint pain. On the sixth day, she began taking oral tacrolimus (TAC) 1 mg twice daily (manufactured by Hangzhou Zhongmei Huazhong Pharmaceutical Co. Ltd., approval number: Guoyao Zhunzi H20094027). She was discharged on the seventh day with a prescription of oral prednisolone 40 mg once daily, TAC 1 mg twice daily, and hydroxychloroquine 200 mg twice daily. Four days after starting TAC, the patient developed persistent vaginal bleeding, with an estimated daily blood loss of 10–15 mL. These symptoms persisted for over 20 days, prompting a visit to a gynecologist. Blood HCG, Vaginal ultrasonography, Hysteroscopy, Vaginal discharge. Reproductive hormone 6: All within normal limits. Endometrial biopsy: endometrial hyperplasia without atypia, and with stromal breakdown and bleeding. The gynecologist assessed the abnormal uterine bleeding (AUB) as potentially related to SLE or medication and referred the patient to a rheumatologist. The rheumatologist reviewed the TAC package insert, which indicated that abnormal uterine bleeding is an infrequent adverse event associated with TAC. Therefore, TAC was discontinued while other medications were maintained at their original doses. The vaginal bleeding ceased 4 days after stopping TAC, and no new medications were introduced during this period. After 5 days of attempted reexposure, the patient redeveloped similar symptoms, which led us to confirm that it was an infrequent adverse event associated with the use of tacrolimus.

Cases of AUB caused by TAC have not been reported previously. In 2018, the International Federation of Gynecology and Obstetrics (FIGO) updated its classification system for the etiology of AUB, known as PALM-COEIN [1–3]. The patient's diagnostic process, based on this classification, is shown in Figure 1. The precise mechanism underlying TAC-induced AUB remains unclear but may involve the following factors: First, TAC might indirectly

TABLE 1 | Changes in laboratory indicators before and after.

Items	Before treatment	After treatment	
Time	**2024.4.21**	**2024.11.18**	**Reference range**
WBC (×109/L)	3.47	6.79	3.5–9.5
HB (g/L)	100	109	130–175
PLT (×109/L)	248	261	100–300
ALT (U/L)	30	11	7–40
AST (U/L)	50	22	13–35
Alb(g/L)	32.6	38.2	40–55
ESR (mm/h)	84	94	<21
CRP (mg/L)	9.01	0.149	0.068–8.2
Immunoglobulin G (g/L)	28.6	16.1	7.51–15.6
Complement C3 (g/L)	0.95	1.03	0.79–1.52
Complement C4 (g/L)	0.11	0.12	0.16–0.38 g/L
Rheumatoid factor (IU/mL)	239	49	<20
24-h urinary proteinquantity (g/24 h)	0.72	0.23	0–0.15
Anti-double-stranded DNA antibody	++	+	–
anti-Sm antibodies	++	++	–
anti-SSA antibody	+++	+++	–
anti-RO52	+++	+++	–
anti-ribosomal P antibody	+++	+	–
Anti-nucleosome antibody	+++	++	–
anti-ANA antibodies	1:1000	1:1000	–

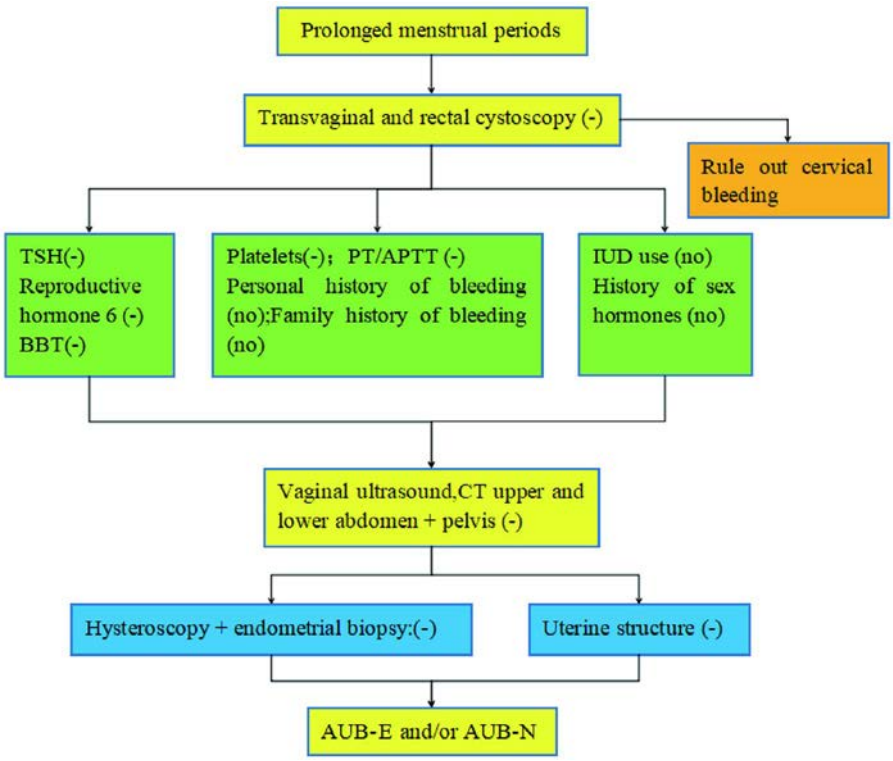

FIGURE 1 | Diagnostic flowchart for prolonged menstrual periods. –, Indicates no abnormality; AUB, abnormal uterine bleeding; AUB-E, AUB due to local abnormality of the uterine endothelium; AUB-N, AUB due to other etiologies; BBT, basal body temperature measurement; IUD, intrauterine device; NO, not available.

disrupt the endocrine system balance by inhibiting T-cell activation and cytokine production. For instance, it could interfere with the hypothalamic–pituitary–ovarian axis, resulting in hormonal imbalances that trigger abnormal endometrial hyperplasia or bleeding [4, 5]. Second, the drug may have direct or indirect effects on the endometrium, potentially causing abnormal endometrial hyperplasia or bleeding by influencing endometrial cell metabolism or angiogenesis [6]. Third, drug metabolism and hormonal fluctuations: Tacrolimus metabolism in the body can be affected by other medications or underlying conditions, leading to variations in drug blood levels, which may indirectly impact hormone levels and cause uterine bleeding [7]. Fourth, other potential mechanisms include thrombosis and bleeding tendencies [8, 9]. Given the normal reproductive hormone levels and endometrial pathology results in this case, it is hypothesized that the abnormal endometrial hyperplasia is most likely due to factor 2.

Author Contributions

Yuren Wang, ShiYu Cui, YuZhuo Luo and Xuejiao Lou collected the patient data. Chunyan Li and Yu Wang are responsible for the specific writing of the manuscript, including data organization, description of experimental results, and the drafting of the discussion section. Meanwhile, Mei Tian is responsible for revising and reviewing the manuscript. All authors contributed to the article and approved the submitted version.

Disclosure

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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