ISSN 1756-1841 VOLUME 28 NUMBER 11 2025

International Journal of Rheumatic Diseases

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

WILEY

International Journal of Rheumatic Diseases

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LETTER TO THE EDITOR

From Silicone to Synovitis: Autoimmune/Inflammatory Syndrome Induced by Adjuvants (ASIA) in Behçet's Disease

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Received: 31 August 2025 | **Revised:** 7 October 2025 | **Accepted:** 22 October 2025

Funding: The authors received no specific funding for this work.

Keywords: arthritis | immunity | prosthesis | tenosynovitis | ultrasound

Dear Editor,

A 39-year-old female patient presented with severe pain and swelling in the proximal interphalangeal joint of the left 3rd finger. She also reported bilateral significant pain in the 1st metatarsophalangeal joints. The patient stated that these complaints had been present for several years but had become more pronounced over the past year, particularly following a silicone breast implant procedure. Her medical history was notable for Behçet's disease, diagnosed 5 years prior, for which she was receiving azathioprine and colchicine.

On physical examination, tenderness and pain were elicited upon palpation of the affected joints. Ultrasound examination (using a 6- to 24-MHz hockey stick probe) revealed tenosynovitis involving the flexor digitorum superficialis and profundus tendons, accompanied by marked effusion in the left 3rd proximal interphalangeal joint (Figure 1). Additionally, effusion and active synovitis were observed in the 1st metatarsophalangeal joints bilaterally (Figure 2). Given the temporal relationship between the breast implant procedure and symptom worsening, the aforementioned rheumatic involvement was diagnosed as Autoimmune/Inflammatory Syndrome-Induced by Adjuvants (ASIA). Methylprednisolone (16 mg/day) was added to her current treatment regimen. At the one-week follow-up, the patient's condition had significantly improved, with complete resolution of the symptoms, and the follow-up has remained uneventful.

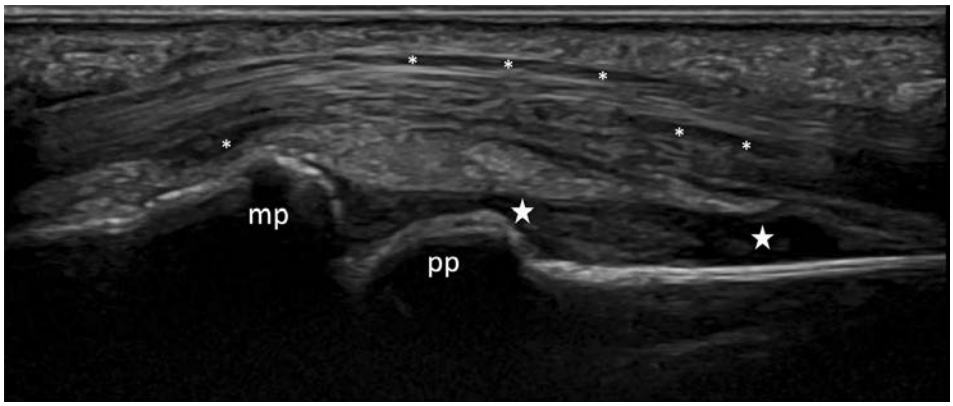

FIGURE 1 | Long-axis ultrasound image illustrates flexor tenosynovitis (*asterisks*) and significant effusion (*stars*) in the left third proximal interphalangeal joint. mp, middle phalanx; pp., proximal phalanx.

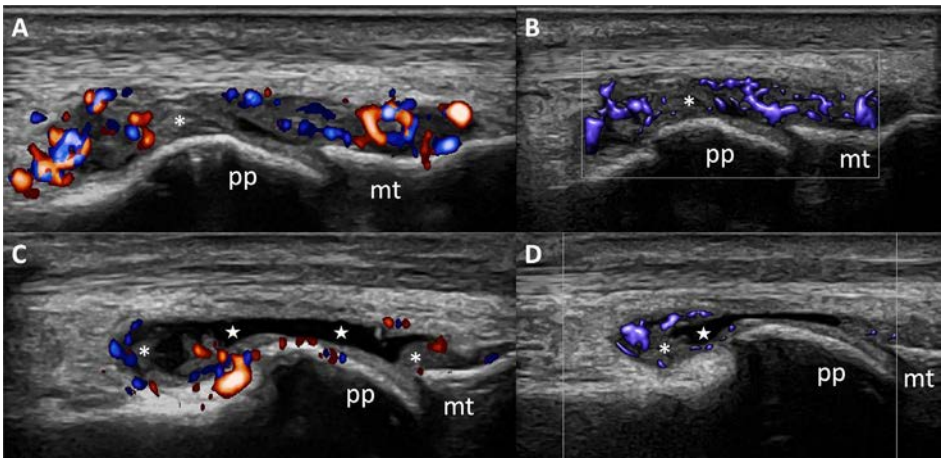

FIGURE 2 | Long-axis ultrasound images of the right (A, B) and left (C, D) 1st metatarsophalangeal joints demonstrate synovitis (*asterisks*) and marked effusion (*stars*). Power Doppler (A, C) and superb microvascular imaging (B, D) findings are observed to be worse on the right side. pp., proximal phalanx; mt, metatarsal bone.

Also known as Shoenfeld's syndrome, ASIA is a clinical condition that may present with features resembling various autoimmune diseases [1]. Exposure to foreign materials with adjuvant activity is believed to ensue via a T-cell-mediated, antigen-driven immune response [2]. Notably, its incidence is increasing, particularly due to the rise in cosmetic silicone implant surgeries. Clinical manifestations may vary and include myalgia, arthralgia, sicca symptoms, localized or systemic granulomatous disease, and irritable bowel syndrome. ASIA has also been reported to present with various types of vasculitis, cutaneous sarcoidosis, and even type 1 diabetes mellitus [3]. Herewith, ASIA may trigger disease flares in patients with pre-existing rheumatic conditions (e.g., systemic lupus erythematosus) as well [4]. To the best of our knowledge, there are no prior reports of "rheumatoid-like" Behçet's disease flares associated with ASIA syndrome. It should also be noted that Behçet's disease is associated with a predisposition to inflammatory arthritis and various autoimmune diseases [5]. As such, describing this rare scenario, we, once again, exemplify the role of ultrasound in better understanding and prompt management of relevant patients [6, 7].

Author Contributions

H.B.A., A.F.Ç., and B.Y. wrote the main manuscript and conducted the literature review. L.Ö. edited and supervised the text.

Acknowledgments

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The authors have nothing to report.

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LETTER TO THE EDITOR

Letter to the Editor: Cervical Facet Joint Ankylosis in Patients With Axial Spondyloarthritis Serves as a Surrogate Radiographic Indicator of Propensity for Bone Formation

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Received: 6 September 2025 | **Revised:** 6 September 2025 | **Accepted:** 31 October 2025

Funding: The authors received no specific funding for this work.

Dear Editor,

We read with great interest the article by Baek et al., "Cervical Facet Joint Ankylosis in Patients With Axial Spondyloarthritis Serves as a Surrogate Radiographic Indicator of Propensity for Bone Formation," recently published in the *International Journal of Rheumatic Diseases* [1]. The authors are to be commended for addressing an underrecognized but clinically relevant aspect of axial spondyloarthritis, highlighting the role of cervical facet joint ankylosis as a marker of structural progression and its association with treatment needs. Their meticulous analysis of a large cohort and emphasis on radiographic evaluation provide an important contribution to the literature. However, this study carries the following limitations that warrant consideration.

First, the study was conducted exclusively in a single Korean center, which limits the generalizability of its findings to broader, multi-ethnic populations. Radiographic progression in axial spondyloarthritis (axSpA) is known to be influenced by both genetic and environmental factors, such as HLA-B27 prevalence, smoking habits, and even microbiome variations. These determinants vary substantially across different populations, meaning the associations reported may not fully apply elsewhere. Previous work has highlighted how ethnic and geographic differences contribute to variability in radiographic outcomes [2]. This suggests that the conclusions drawn may be partly specific to the studied population. Second, the study did not adequately control for treatment exposure, especially the use of TNF inhibitors and NSAIDs, which themselves influence radiographic outcomes. Since patients with more severe disease are simultaneously more likely to develop facet fusion and to initiate biologic therapy, the observed link between fusion and TNF inhibitor initiation may be partly circular. Without detailed adjustment for longitudinal treatment exposure, disease activity and therapy effects become confounded. TNF inhibitors reduce symptoms but show inconsistent effects on radiographic progression, underscoring the importance of disentangling drug exposure from disease-related structural outcomes [3]. This reduces confidence in the causal interpretation of results. Third, the study relied on a binary classification of facet joints as fused or not fused, oversimplifying the disease spectrum. Ankylosis represents an end-stage lesion, but earlier changes such as erosion, capsular ossification, sclerosis, or partial fusion were not captured. This may underestimate the clinical and prognostic significance of early facet joint involvement. A study states that using overly simplistic scoring systems leads to information loss and misrepresentation of disease burden [4]. Consequently, the study may miss important stages of pathological progression that could precede ankylosis. Fourth, the absence of MRI assessment is another major limitation, as radiographs alone cannot distinguish between fusion due to active inflammation and changes caused by mechanical degeneration. MRI can reveal active bone marrow edema, capsulitis, and early inflammatory changes that precede structural damage. By not incorporating MRI data, the study cannot establish whether facet fusion is truly a marker of inflammatory osteoproliferation or a byproduct of chronic degeneration. MRI provides essential insight into the relationship between inflammation and structural progression, which plain radiographs often miss [5]. Thus, the mechanistic interpretation of findings is weakened. Fifth, the authors noted incomplete retrieval of BASFI and BASMI; the deeper

issue lies in the retrospective design, which precluded systematic functional data collection alongside imaging. Without standardized and prospective measures of function and mobility, the true clinical impact of facet fusion cannot be confidently assessed. Radiographic findings may not directly translate into disability unless validated against objective functional scores. A study highlighted the importance of integrating mobility indices, which strongly correlate with imaging outcomes [6]. Thus, the current study may have underestimated the functional burden of cervical facet ankylosis.

To strengthen future research on cervical facet joint ankylosis in axial spondyloarthritis, studies should first validate findings in multi-center, multinational cohorts representing diverse ethnic groups to ensure external generalizability. Next, they should incorporate time-dependent treatment covariates and stratify by therapy duration to account for confounding from biologic and NSAID exposure. Radiographic assessments ought to be expanded by adopting graded scoring systems for facet joint pathology and using advanced imaging modalities such as CT or MRI to capture early-to-late disease changes. Importantly, integrating MRI with radiographs would help clarify whether ankylosis reflects inflammatory osteoproliferation or degenerative processes. Finally, research should synchronize imaging with standardized functional outcome measures such as BASFI, BASMI, and ASDAS, ensuring that structural findings are directly linked to clinically meaningful impairment.

In conclusion, while Baek et al. provide valuable insights into the clinical significance of cervical facet joint ankylosis in axSpA, important methodological considerations remain unaddressed. Broader validation across diverse populations, refined imaging and scoring approaches, careful adjustment for treatment effects, and integration of functional outcomes will be essential to fully establish the role of facet joint pathology as a surrogate marker of bone formation and disease progression.

Author Contributions

All the authors meet the ICMJE authorship criteria and have made significant and equal contributions to this manuscript. All authors approved the final version and agree to be accountable for all aspects of the work, ensuring the accuracy and integrity of the data and interpretation.

Acknowledgments

The authors have nothing to report.

Ethics Statement

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing does not apply to this article as no datasets were generated during the current study; all data were sourced from published literature.

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Zaib Un Nisa

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ORIGINAL ARTICLE

An Efficient Machine Learning Pipeline for Distinguishing Cancer and Non-Cancer Patients in Systemic Lupus Erythematosus

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Received: 25 August 2025 | **Revised:** 14 October 2025 | **Accepted:** 24 October 2025

Funding: This work was supported by grants from Luzhou Municipal People's Government–Southwest Medical University Science and Technology Strategic Cooperation Project Fund (2023LZXNYDJ021).

Keywords: cancer | machine learning | systemic lupus erythematosus

ABSTRACT

Background: The objective is to develop a machine learning model that is capable of effectively distinguishing between cancer and non-cancer patients among systemic lupus erythematosus (SLE).

Methods: A total of 2811 patients with SLE were included in this study, among which 208 had concurrent cancers. Age, gender, and 95 clinical and laboratory indicators were included. Initially, data preprocessing and feature transformation were conducted. After evaluating feature importance, selected features were included in the subsequent steps for establishing the machine learning model. The optimal model chosen was assessed using a series of metrics to obtain a comprehensive performance evaluation of the model.

Results: Through integrated feature selection, features such as Age, C4, WBC (urine), BASO_R, ALP, AST, and C3 were screened out for model construction. Among the various machine learning (ML) models established after parameter optimization, the logistic regression model performed the best. Furthermore, the logistic regression model still showed the best predictive capability by evaluating metrics such as receiver operating characteristic (ROC) curves, precision-recall curve (PRC) plots, as well as model prediction accuracy, F1 score, and recall.

Conclusion: We have developed a convenient and straightforward machine learning model for SLE patients, which can easily and usefully distinguish cancer from non-cancer patients within the SLE patients.

1 | Introduction

Systemic lupus erythematosus (SLE) is a complex chronic autoimmune disease characterized by the immune system being attacked by its own tissues; this disease has a similar pathogenesis to other autoimmune diseases [1]. Skin, joints, kidneys, blood system and nervous system are commonly involved [2]. It is recognized that the disease is repeatedly recurrent, and the active state of the disease and the remission state appear alternately. This brings the patients both physical and psychological torture [3]. Current studies showed that genetic factors and environmental factors can affect the development of the disease [4]. In addition, the disease tends to occur in women, and the ratio of men to women in the affected population is about 1:9 [5], suggesting that estrogen may also affect the occurrence of the disease.

Compared to the healthy population, SLE patients exhibit a significantly increased susceptibility to cancers [6]. Recent studies have demonstrated that SLE patients exhibit an elevated risk of developing various malignancies, such as non-Hodgkin lymphoma, Hodgkin lymphoma, leukemia, multiple myeloma, as well as cancers of the cervix, vagina/vulva, kidney, bladder, esophagus, stomach, hepatobiliary system, lung, oropharynx, larynx, non-melanoma skin, and thyroid. The overall cancer risk in this population is significantly higher compared to the general population [7]. Female SLE patients have a higher cancer risk than males, and long-term use of immunosuppressants in SLE patients may further increase this risk [8]. To date, some studies have employed machine learning to predict long-term disease activity in SLE, the risk of patients' hospitalization, complications (such as lupus nephritis, herpes, and secondary macrophage activation syndrome) [9–15]. Interestingly, some studies have applied machine learning to the field of cancer, evaluating the risk of hepatocellular carcinoma in hepatitis B patients and diagnosing chronic lymphocytic leukemia [16, 17]. Although there is limited study directly using machine learning (ML) to diagnose cancer in SLE patients, studies have already utilized ML to explore the complex relationships between autoimmunity, immunosuppression, and cancer risk. For example, artificial intelligence has been applied in the diagnosis or biomarker identification of thyroid cancer and autoimmune thyroid diseases, machine learning has been used to identify SLE-related prognostic genes for breast cancer, and ML has been employed to distinguish autoimmune pancreatitis and pancreatic ductal adenocarcinoma [18–22]. Therefore, we conduct this study by ML pipeline, which will help to find SLE patients with cancers, thereby reducing the disease burden on patients and their families in the future.

2 | Methods

2.1 | Objectives

The overall workflow of this research is illustrated in Figure 1. A total of 2811 SLE patients were recruited from the Affiliated Hospital of Southwest Medical University from 2018 to 2024. All patients with SLE included in the study met the European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) revised 2019 criteria for SLE. Of these 2811 patients, 208 patients were diagnosed with cancers and 2603 patients were not diagnosed with cancers. These cancers include lung cancer, breast cancer, colon cancer, cervical cancer, thyroid cancer, lymphoma, uterine leiomyoma, rectal cancer, liver cancer, ovarian cancer, and so on. The specific case numbers for each type of cancer, their respective proportions among all cancers, and the corresponding diagnostic criteria are detailed in Table S1. Different cancers were diagnosed by the gold standard including the corresponding pathology. We collected demographic variables such as age and gender, as well as 95 clinical and laboratory indicators from the SLE patients. This study was approved by the Ethics Committee of the Affiliated Hospital of Southwest Medical University and was in accordance with the Declaration of Helsinki. Clinical Trial Number was not applicable. All participants provided written informed consent.

2.2 | Data Preprocessing and Feature Transformation

In this study, we included patients who did not have missing any of the 97 variables discussed above. We then performed one-way

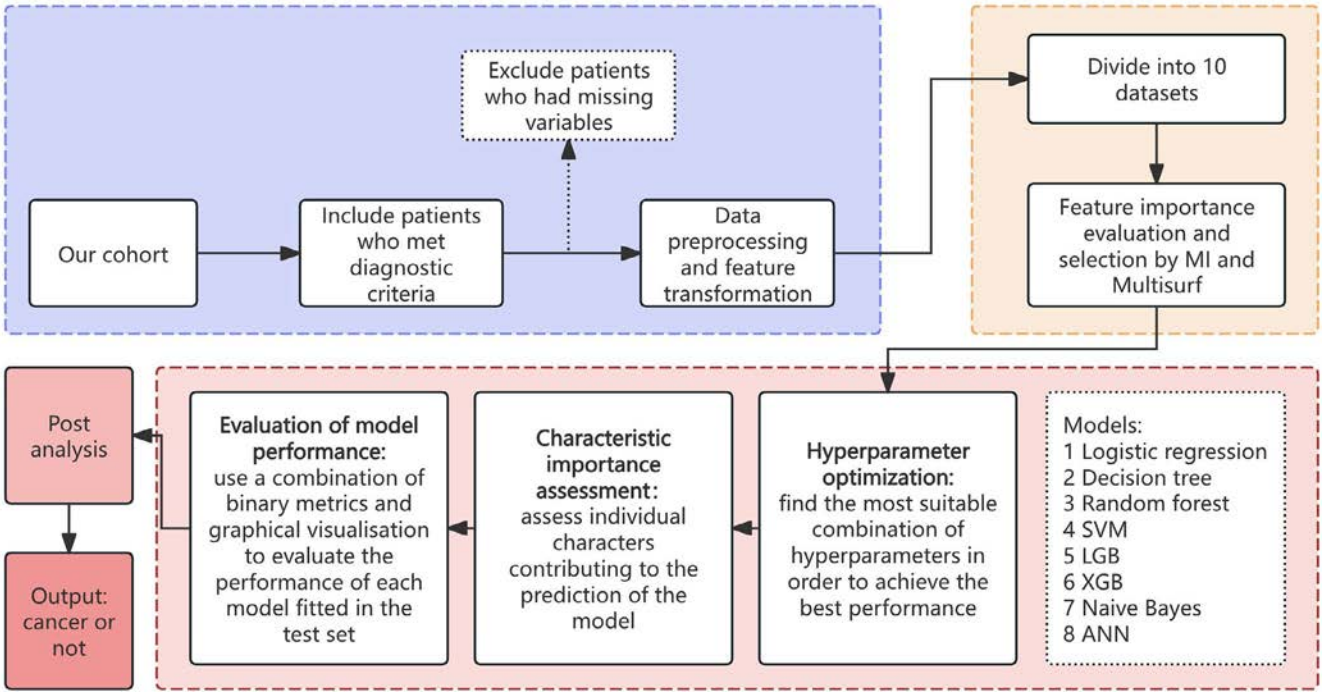

FIGURE 1 | Flowchart of the machine learning pipeline for distinguishing cancer patients among patients with SLE.

analysis of variance for each variable to explore the relationship between the individual variable and the outcome variable with respect to having cancers or not. Moreover, 10-fold cross-validation was used to divide our data into 10 parts. The process is repeated by rotating nine of the ten subsets as the training set and one subset as the testing set for ten iterations of model training and evaluation, which obtained more stable performance metrics. Finally, we chose a standard scalar method for feature selection and normalization, scaling the standard independently for each variable. This helps to eliminate the gap between the mean and the scaling unit, which in turn was applied to the corresponding testing set.

2.3 | Feature Importance Evaluation and Selection

Before ML model building, we selected the variables. We evaluated the feature importance for various ML model algorithms to derive a ranking of feature importance, preventing the inclusion of unnecessary variables in the ensuing model building process. We chose Mutual Information (MI) and multisurf (a relief-based feature selection algorithm) as methods for batch feature selection to determine whether a particular feature should be retained or deleted. MI is the best for evaluating the variables and outcome variables, whereas multisurf not only evaluates single-factor associations but is also sensitive to heterogeneity across variables. The evaluation of feature importance in this section is performed independently in the ten training sets. Thus, the feature selection method combining MI and multisurf generates ten different feature importance order lists. Finally, we used the average feature importance scores calculated from the ten feature importance order lists to determine the combination of features that can fit the ML model with better performance.

2.4 | Model Building

2.4.1 | Hyperparameter Optimization

The primary step in ML model is hyperparameter optimization scanning. Hyperparameters need to be set before the learning process begins and can not be automatically learned through training. They have a significant impact on model performance. This step aims to find the optimal combination of hyperparameters to achieve the best performance on the data at the right time. By adjusting hyperparameters, metrics such as accuracy and speed of the model can be optimized, making it more suitable for specific tasks and datasets.

Typically, ML algorithms use default hyperparameters, but this can lead to unfair comparisons between algorithms. Hyperparameters are critical settings in an algorithm that directly influence its performance and outcomes. Since different datasets and tasks may require different hyperparameter configurations, the default settings may not be optimal. To address this, we set a goal of balancing accuracy and conducted different combinations of hyperparameters in the training set to compare their impact on model performance and identify the best configuration for training the final model.

The naive bayes model adopted the default hyperparameter settings in Scikit-learn (v1.2): GaussianNB (priors = None, var_smoothing = 10^{-9}) was used for continuous variables, and BernoulliNB (alpha = 1.0, binarize = 0.0, fit_prior = True) was applied for categorical variables. This model served as a baseline comparator and did not undergo hyperparameter optimization, as it is inherently less sensitive to parameter adjustments and already provides stable and reliable benchmark performance under default settings. Furthermore, we discussed hyperparameter optimization for the other seven algorithms, conducting various combinations and selecting the configurations that best enhanced model performance. This optimization process improved the accuracy and generalization ability of these algorithms across different datasets and tasks.

2.4.2 | Feature Importance Assessment

We examined feature importance in each training set from the perspective of various ML models, providing strong explanations for subsequent model predictions. In ML, feature importance refers to how much an individual feature contributes to a model's prediction.

Decision tree and random forest algorithms inherently evaluate feature importance during training, eliminating the need for additional calculations afterward. Decision tree recursively selects optimal features to split datasets, forming a tree structure. Random forest enhances model accuracy and robustness by aggregating predictions from multiple decision trees. Each tree in random forest randomly selects features for splitting, enabling natural assessment of feature importance. For other algorithms, we employed the leave-one-out (LOO) method to estimate feature importance. LOO, a cross-validation technique, leaves one sample out as a validation set, trains the model on the remaining samples, and evaluates performance on the validation set. By repeating this process, we calculated importance scores for each feature, reflecting their contribution to model prediction. Although computationally intensive, LOO provides more accurate estimates of feature importance.

2.4.3 | Evaluation of Model Performance

We used a combination of binary metrics and graphical visualization to evaluate the performance of each model fitted in the testing set. Metrics include: Accuracy, F1 score, Recall, Specificity, Precision, Area Under the Curve (AUC), True Positive Count (TP), True Negative Count (TN), False Positive Count (FP), False Negative Count (FN), Precision-Recall Curve (PRC), Average Precision Score (APS). In addition, we visualized all the ML algorithms in this study with receiver operating characteristic (ROC) and PRC plots, and evaluated the performance of the models by AUC and APS. The ROC curve demonstrates the relationship between true positive rate (TPR) and false positive rate (FPR) at different thresholds, while the PRC curve demonstrates the precision rate under different recall levels. AUC and APS, as quantitative metrics of these two curves, provide us with an objective basis for evaluating the performance of the model.

2.4.4 | Post Analysis

We summarized the average performance and feature importance of each ML algorithm. The average ROC curve and average PRC of all ML algorithms were first compared. These two metrics are important measures of the performance of binary classification models. By comparing them, we can get a preliminary idea of how different algorithms perform on classification tasks. We then summarized the performance metrics for all models and performed a Kruskal-Wallis one-way analysis of variance (ANOVA) statistical analysis of the average model performance for each metric. The Kruskal-Wallis test is a nonparametric test used to compare the median of multiple independent samples. Here, we used it to determine whether any ML algorithm performs better or worse for a given evaluation metric. Finally, we generated four composite feature importance bar plots (CFIBPs) to demonstrate and summarize the consistency of feature importance across all ML algorithms. The first CFIBP was generated by normalizing each algorithm's feature importance score. Then, a second CFIBP was generated by normalizing each algorithm's feature importance score and summarizing the algorithm's score, which ensured that each algorithm had the same weight in the CFIBP. The third CFIBP was generated by weighting the normalized score with the average balanced accuracy of each algorithm. The fourth CFIBP was generated by dividing the normalized score by the sum of the score and weight to further adjust the results of the feature importance assessment.

2.4.5 | Statistical Analysis

One-way ANOVA was performed during the initial exploration of the data, with the chi-square test for categorical variables and the Mann–Whitney test for quantitative variables. Kruskal–Wallis one-way ANOVA was used for post hoc analysis to assess the performance of each ML algorithm. R (1.4.1), Python (3.10.14), and Anaconda (2.3.1) were used to complete the data analysis and picture plotting in this study. $p < 0.05$ was considered statistically significant.

3 | Results

3.1 | Exploratory Analysis

In this step, we compared the baseline features, laboratory and clinical indicators between SLE patients with and without cancers. Results showed that there were significant differences such as gender, age, and WBC (urine) (Table S2).

3.2 | Data Preprocessing and Feature Transformation

Figure 2A,B show the results of average feature importance scores for MI and multisurf, respectively. We found that the two feature selection algorithms share age, C4, WBC (urine), BASO_R, ALP, AST, and C3. The average feature selection scores of the two algorithms were shown in Tables S3 and S4.

3.3 | ML Modeling

3.3.1 | Model Hyperparameter Optimization

For each model, we evaluated the optimal hyperparameters. Figure S1A–G displayed the hyperparameter optimization results for models excluding naive Bayes. For logistic regression, the best performance was achieved when the hyperparameter was set to "saga". Therefore, we finally chose "saga" as the optimal hyperparameter for logistic regression and applied it to model building (Figure S1A). For the decision tree, the model had the best performance when we set the hyperparameter to "random" (Figure S1B). Figure S1C visualized the hyperparameter optimization results of the random forest algorithm. The model performed better when the hyperparameter was set to "true". Interestingly, the model performed the best when the hyperparameter of LGB was set to "−1" (Figure S1D). The model was optimal when the hyperparameter of ANN was set to "sgd" (Figure S1E). The model was optimal when the hyperparameter of XGB was set to "0" (Figure S1F). For SVM, the model was optimal when the hyperparameter was set to "rbf" (Figure S1G). Due to the feature independence assumption, the probability-based classification and the easy implementation of the algorithm, we omitted the hyperparameter optimization step of the algorithm in this study.

3.3.2 | Logistic Regression

Figures S2–S4 discussed feature importance scores, PRC and ROC curves for the different algorithms and models. Figures S3A–H and S4A–H showed the PRC and ROC curves for the eight models in this study. In the logistic regression model, the PRC and ROC of the ten training sets were shown in Figures S3A and S4A, respectively. The average AUC of PRC was 0.27 ± 0.07 and the average AUC of ROC was 0.81 ± 0.05. The feature importance scores of the algorithm were obtained by the LOO method (Figure S2A).

3.3.3 | Decision Tree

For this algorithm, the PRC and ROC of the model were shown in Figures S3B and S4B. As we found, the model had an average AUC of 0.35 ± 0.11 for PRC and 0.78 ± 0.04 for ROC. The decision tree algorithm had a mechanism for feature estimation, and therefore automatically evaluated the significance of each incorporated feature (Figure S2B).

3.3.4 | Random Forest

The PRC and ROC of the random forest algorithm were shown in Figures S3C and S4C. The average AUC of PRC was 0.35 ± 0.09, and the average AUC of ROC was 0.83 ± 0.06. Like the decision tree, the random forest algorithm automatically evaluated feature importance. The results of feature importance assessed by this algorithm were shown in Figure S2C.

3.3.5 | SVM

The PRC of SVM algorithm was shown in Figure S3D, with an average AUC of 0.27 ± 0.07. The ROC curve was shown in

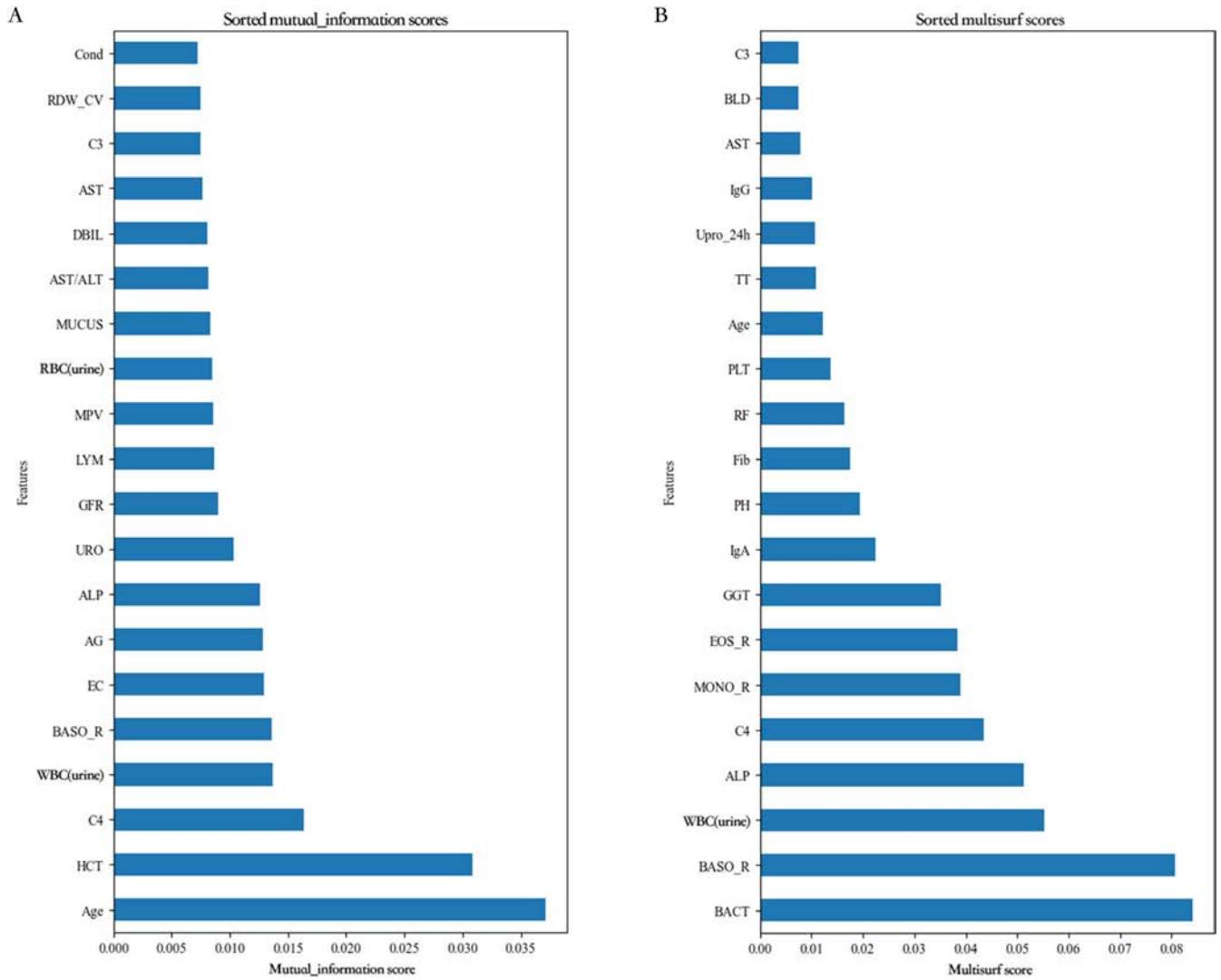

FIGURE 2 | The plot of average feature importance scores for MI and multisurf. MI is the best for evaluating the variables and outcome variables, whereas multisurf not only evaluates single-factor associations but is also sensitive to heterogeneity across variables.

Figure S4D, with an average AUC of 0.81 ± 0.05. The result of feature importance assessment by SVM through the "leave-one-out" method was shown in Figure S2D.

3.3.6 | ANN

The mean AUC of PRC and ROC for the ANN algorithm was 0.28 ± 0.07 (Figure S3E) and 0.76 ± 0.05 (Figure S4E), respectively. The algorithm also evaluated the importance of features by the "leave-one-out" method, and the results were shown in Figure S2E.

3.3.7 | Naive Bayes

The mean AUC of the PRC and ROC curves for this algorithm was 0.38 ± 0.10 (Figure S3F) and 0.67 ± 0.08 (Figure S4F), respectively. Results of the algorithm's "leave-one-out" feature importance assessment were shown in Figure S2F.

3.3.8 | LGB

The average AUC of PRC and ROC for the LGB algorithm was 0.34 ± 0.09 (Figure S3G) and 0.83 ± 0.05 (Figure S4G). Results of the feature importance assessment calculated by the algorithm through the "leave-one-out" method were shown in Figure S2G.

3.3.9 | XGB

The average AUC of PRC and ROC of the XGB algorithm was 0.30 ± 0.05 (Figure S3H) and 0.82 ± 0.04 (Figure S4H). Results of the feature importance assessment analyzed by the algorithm through the "leave-one-out" method were shown in Figure S2H.

3.3.10 | Post Analysis

The XGBoost model is excluded from the discussion of the final optimal model due to its poor performance on this specific task, indicating a lack of fundamental predictive capability.

We discussed all the algorithms and various evaluation metrics (Table S5). As shown in Figures 3 and 4, logistic regression performed the best among the eight algorithms in terms of PRC and ROC, while the ANN model had the worst fit. The four CFIBPs were shown in Figure 5A–D. After summarizing the feature importance of all the ML algorithms, the importance of the conforming features of HCT was significantly greater than the others, followed by age.

4 | Discussion

It is known that SLE patients exhibited a higher susceptibility to cancers than healthy individuals [23]. Therefore, this study developed a ML model to predict having cancer risk in SLE patients. This predictive tool will assist clinicians in identifying cancer cases among the SLE population, thereby enhancing diagnostic efficiency and optimizing clinical decision-making in routine practice.

There are some studies discussing the application of machine learning to clinical diagnosis and treatment of SLE [21, 24]. However, there is no study about the establishment of multiple models to predict cancer occurrence in SLE patients. In this study, we used the real-world data from the year 2018 to 2024, which made the results of this study more authentic and credible. In addition, because SLE itself can bring a huge psychological and financial burden to patients, and if cancer develops at this time, it is undoubtedly worse for patients and their families. Thus, our study focused on cancer patients in the SLE population. In our opinion, our study has strong practical significance. Moreover, the common clinical and laboratory indicators were used to fit the machine learning model, which further enhanced the practicability of this algorithm for clinical usage.

In this study, we assessed the importance of all features in the dataset. It is worth pointing out that we used LOO to accurately evaluate the importance of each feature and visualize the contribution of each feature to the predictive ability of each model, which is different from other machine learning prediction models. In addition, we also used accuracy, F1 score and binary indexes as well as ROC, PCR and other abundant indexes to evaluate the performance of each model, which can help us understand the pros and cons of each model from various aspects and help us make subsequent decisions. A post hoc analysis of the eight machine learning models showed that the logistic regression algorithm performed the best and the ANN algorithm fitted the worst. We selected the logistic regression model as the ML model for the final prediction of having cancers in SLE patients.

It is notable that an intriguing finding emerged from our analysis. In the four post hoc CFIBP figures, the index HCT showed substantially greater feature importance than all other variables,

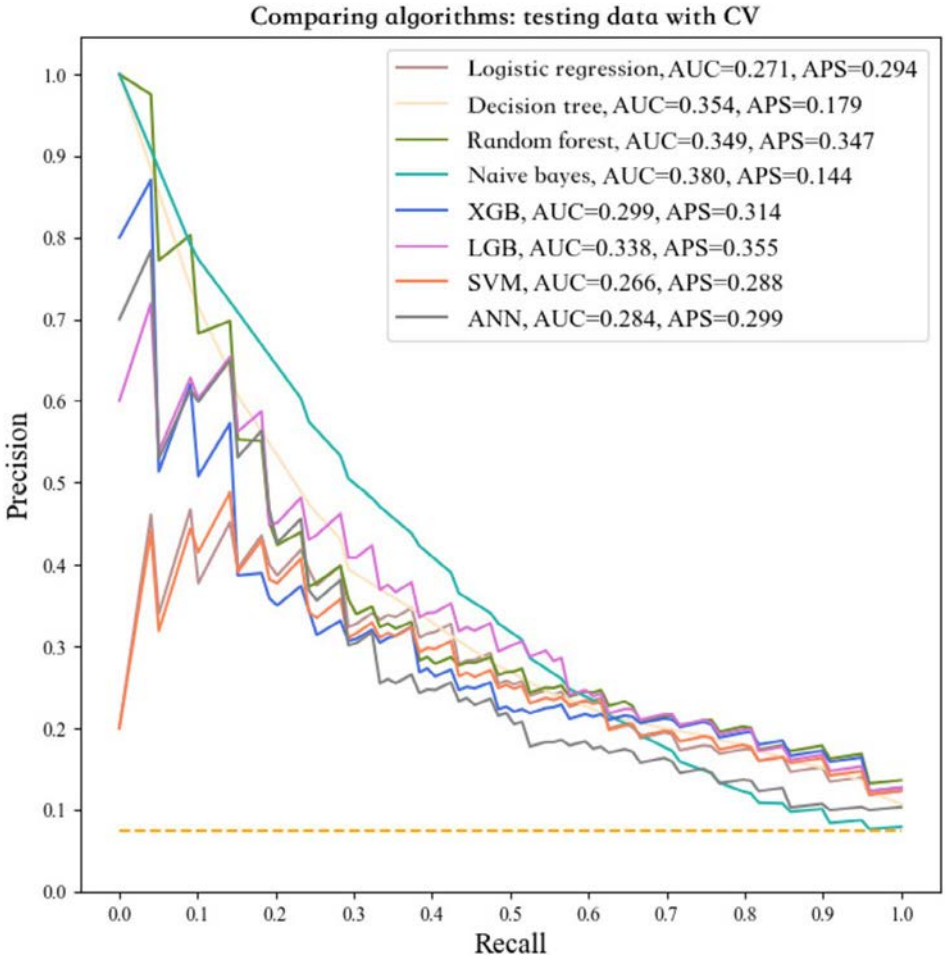

FIGURE 3 | Precision-recall curve integrating the eight algorithms.

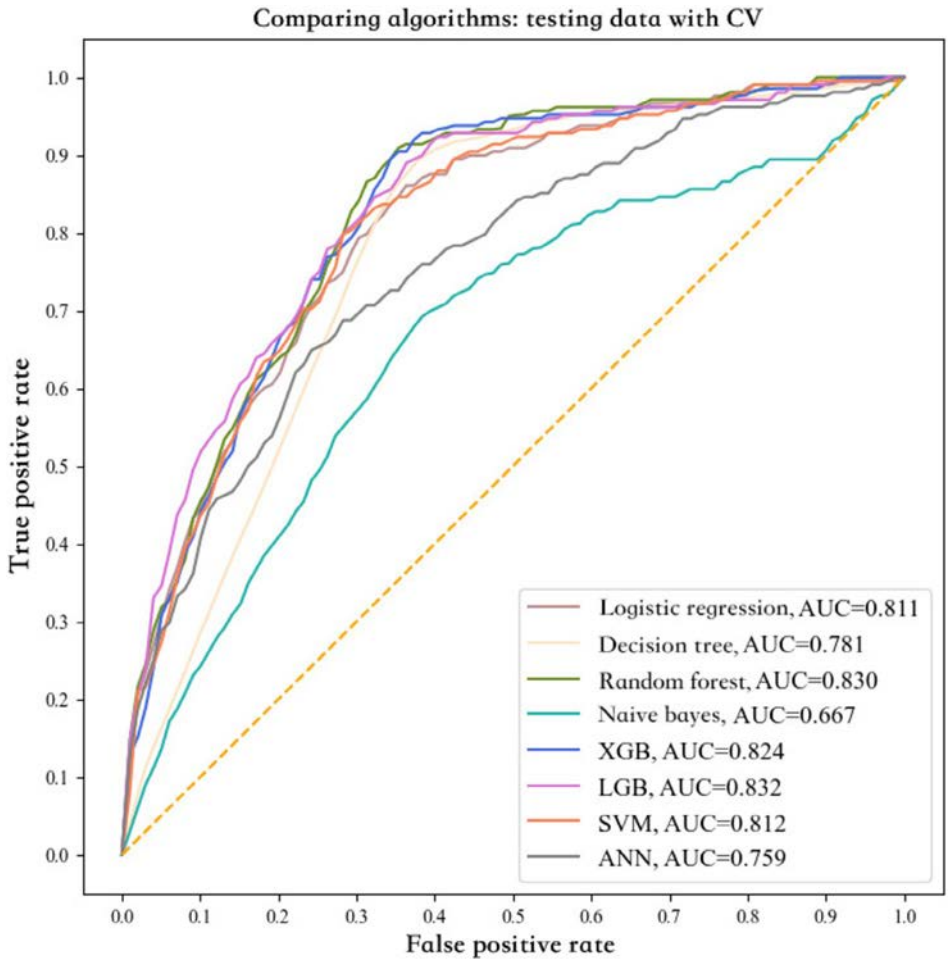

FIGURE 4 | Receiver operating characteristic integrating the eight algorithms.

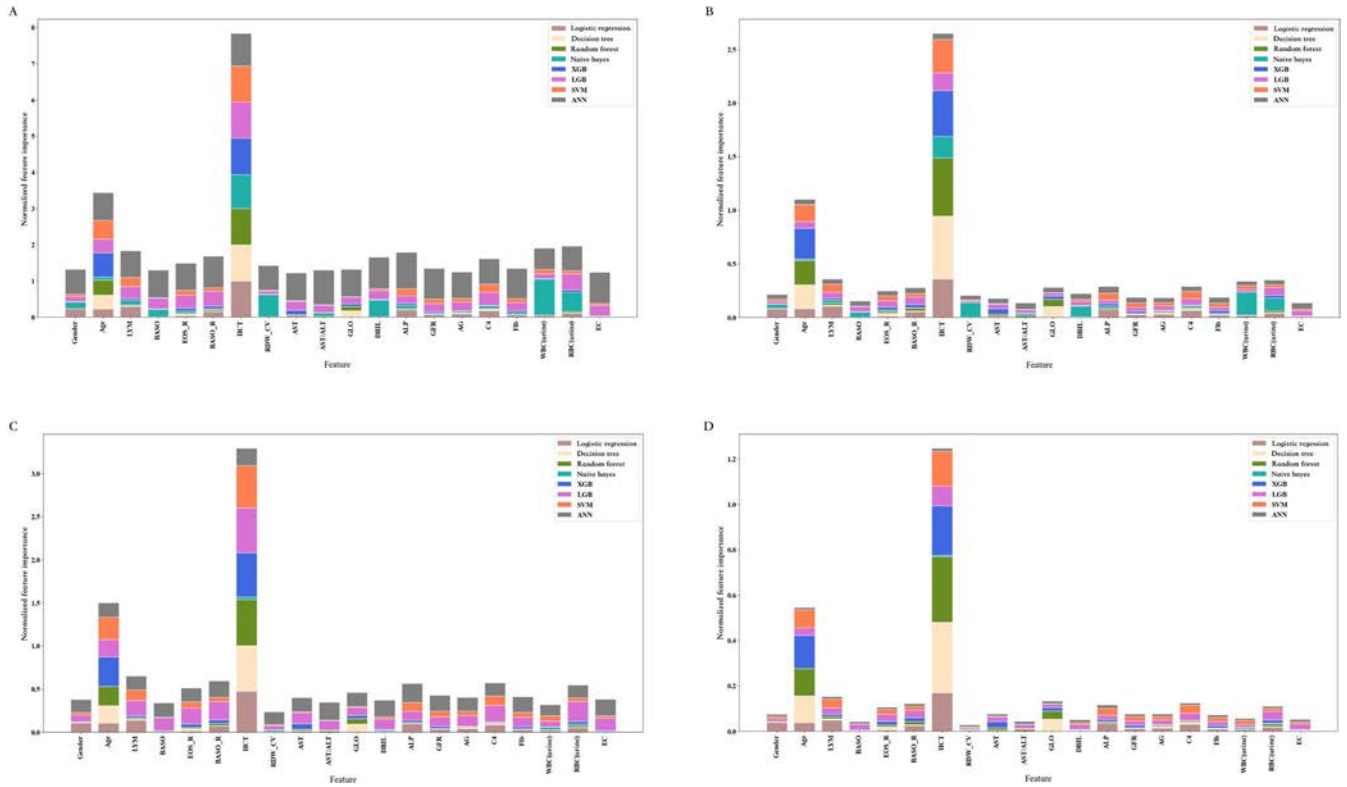

FIGURE 5 | Four composite feature importance bar plots analysis.

with age ranking as the second most influential factor. SLE is often accompanied by anemia [19–21], showing a significantly lower HCT level compared to healthy individuals [25]. In this study, SLE patients with concomitant cancer exhibited lower HCT values than those without cancer. Tumor-secreted TGF-β has been demonstrated to inhibit erythropoiesis through organ-specific mechanisms [26, 27], while cancer can also induce anemia by reducing EPO production [28], causing extramedullary hematopoiesis [29], and increasing erythrocyte destruction [30]. Additionally, cancer is a catabolic disease; the growth and proliferation of tumor cells require substantial nutrients, which can result in malnutrition in patients. Nutrient deficiencies can affect red blood cell metabolism, causing anemia and lowering HCT values [31]. Chronic inflammatory responses are present in SLE patients [32]. Such as high expression of interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), which in turn inhibit bone marrow hematopoietic function for red blood cell production [33]. Cancer itself also induces inflammatory responses [34]. Exacerbating the suppression of bone marrow hematopoietic function, and promoting the development of anemia and decreased HCT values [35].

Age is an important feature in predicting SLE with cancers. This may correlate with several reasons. It is accepted that increased age, T cell function declines and immune surveillance dysregulation are related to reduced ability to remove cancerous cells, and the risk of having cancers will increase [2, 36]. Compared with the young population, clinicians will pay more attention to whether the elderly suffer from cancers, and all sectors of society will also conduct more detailed cancer screening for the elderly. More kinds of cancers and the number of cancer patients were detected in the SLE population at an older age than those without cancers. SLE patients are in a state of chronic inflammation for a long time, which may lead to the occurrence of continuous interferon signal, DNA damage, and promote tumorigenesis [31].

This study has some limitations. We utilized only single-center real-world data and did not perform external validation of the model, which prevents us from confirming its generalizability. The performance of the model may vary due to differences in regions, ethnic populations, healthcare systems, and diagnostic protocols. Moreover, this study is a preliminary exploratory investigation, with its primary aim to validate the existence of signals within complex data from SLE patients that can be used for cancer risk prediction, rather than to develop a diagnostic tool ready for immediate clinical application. Therefore, rigorous localized validation and multicenter external validation are essential before it can be directly applied to other clinical settings. Additionally, our data consist of retrospective records that did not establish the chronological sequence of SLE onset and cancer development. Therefore, we can not definitively conclude whether SLE contributes to cancer occurrence or if cancer increases the risk of developing SLE. Consequently, further validation through multicenter prospective cohort studies is warranted. Furthermore, an important limitation of this study lies in the fact that the model we developed aims to predict "overall cancer risk". However, cancer is a group of highly heterogeneous diseases, and the distribution of its subtypes (such as lung cancer, breast cancer, lymphoma) varies across regions, ethnicities, and populations. Since our training data were sourced from a single center, the specific distribution of cancer types in this dataset may not be representative of populations in other regions. This discrepancy could lead to fluctuations in the model's predictive performance when applied to populations with different cancer profiles. The model's predictive capability may be more focused on identifying risks for cancer types that are overrepresented in the training data, while being less sensitive to underrepresented cancer types. Future research should aim to validate this model in larger, multi-regional, and multi-ethnic cohorts to assess its generalizability. Ideally, sufficient cases should be collected to develop models capable of predicting risks for specific cancer types simultaneously, which would hold greater clinical translational value. Finally, the APS in our model was relatively low and did not reach ideal values. This phenomenon can be attributed to the extreme class imbalance (the proportion of cancer patients among the overall SLE population remains low) and the high-noise nature of the data (significant overlap exists between the clinical manifestations and laboratory indicators of SLE and cancer-related symptoms). Therefore, constructing high-accuracy cancer diagnosis models within the SLE population requires more specific biomarkers or more sophisticated multimodal models, which represent an important direction for future research.

In conclusion, we have established an effective ML model for distinguishing cancer patients in SLE patients. Screening cancer patients in the SLE population will reduce the burden of diagnosis and treatment for clinicians and reduce the psychological and economic burden for patients in the future. Moreover, this model may be used for other autoimmune diseases, and help other autoimmune diseases with cancer prediction [37–40].

Author Contributions

Study conception and design: Y.-Y.C., A.-F.H., J.Y., L.F., W.-D.X. Acquisition of data, analysis and interpretation of data: Y.-Y.C., A.-F.H., J.Y., L.F., W.-D.X. Drafting the article: Y.-Y.C., W.-D.X. Final approval of the version of the article to be published: all authors, and that all authors agree to be accountable for all aspects of the work.

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. **Figure S1:** The plot of hyperparameter optimization results for each model. **Figure S2:** The feature importance scores of the eight algorithms. **Figure S3:** Precision-recall curve for the eight models. **Figure S4:** Receiver operating characteristic curves for the eight models. **Table S1:** The proportion of each tumor. **Table S2:** Univariate analysis of clinical, laboratory data between SLE patients without cancers and SLE patients with cancers. **Table S3:** The multisurf scores of all features in 10 training sets. **Table S4:** The mutual information scores of all features in 10 training sets. **Table S5:** Various evaluation metrics for all the 8 algorithms.

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EDITORIAL

Editorial: The Essential Role of Emulated Clinical Trial Designs in TriNetX Studies: Avoiding Confounding by Indication

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Received: 8 July 2025 | **Revised:** 8 September 2025 | **Accepted:** 8 October 2025

Funding: The authors received no specific funding for this work.

Keywords: emulated clinical trial designs | observational research | rheumatology | TriNetX

The growing availability of real-world data (RWD) through large-scale networks such as TriNetX has revolutionized observational research, offering unprecedented opportunities to explore potential treatment effects, disease outcomes, and healthcare utilization patterns in diverse and representative patient populations [1]. TriNetX, a global health research network providing access to real-time, de-identified electronic medical records from multiple healthcare organizations, has become an invaluable tool in generating real-world evidence (RWE) for clinical decision-making [2]. However, many investigations fail to adopt emulated clinical trial (ECT) designs, raising significant concerns about the risk of confounding by indication and the overall validity of pharmaco-epidemiological study findings.

1 | Understanding Confounding by Indication in Observational Research

Confounding by indication refers to a type of bias that arises in observational studies when the reason for prescribing a treatment is related to the outcome of interest. This is particularly problematic in settings where patient characteristics influencing the choice of therapy are also associated with prognosis [3]. For example, in studies comparing biologic therapies for autoimmune diseases such as rheumatoid arthritis or systemic lupus erythematosus, patients receiving newer or more aggressive treatments may inherently differ from those on standard therapies in terms of disease severity, comorbidities, and previous treatment failures. Without appropriate methodological safeguards, these differences can distort effect estimates, leading to misleading conclusions.

2 | The Importance of Emulated Clinical Trial Designs

Emulated clinical trial designs, also known as target trial emulations, have emerged as a methodological gold standard for reducing bias in observational research [4]. By explicitly defining eligibility criteria, treatment strategies, assignment procedures, follow-up periods, and outcome definitions prior to analysis, ECTs attempt to replicate the design and rigor of randomized controlled trials (RCTs) using observational data [5]. The adoption of such frameworks is crucial when utilizing platforms like TriNetX to mitigate immortal time bias, selection bias, and confounding by indication.

Abbreviations: bDMARDs, biologic disease-modifying antirheumatic drugs; ECT, emulated clinical trial; IPW, inverse probability weighting; PSM, propensity score matching; RCTs, randomized controlled trials; RWD, real-world data.

For example, a rheumatology study emulating a trial of methotrexate versus TNF inhibitors in new-onset rheumatoid arthritis could: (1) define eligibility as patients aged 18–75 without prior biologic disease-modifying antirheumatic drugs (bDMARD) use; (2) assign treatments based on the first prescription; (3) set time zero as treatment initiation; (4) follow-up for 12 months; and (5) assess outcomes such as The Disease Activity Score-28 (DAS28) improvement or adverse events. These components can be implemented in TriNetX using index events, inclusion criteria, and time-to-event tools.

3 | Current Limitations in TriNetX Studies

Unfortunately, a considerable number of published studies leveraging TriNetX data do not adhere to ECT principles. Instead, they often employ simple cohort designs or unmatched comparisons, relying heavily on propensity score matching (PSM) or inverse probability weighting (IPW) as post hoc statistical corrections [2]. While these methods help balance measured covariates, they fall short of addressing the underlying clinical reasoning that drives treatment choices [6, 7]. The absence of clear temporal alignment between treatment initiation and outcome assessment further exacerbates these issues, particularly in complex chronic diseases where treatment decisions evolve over time. Strategies for handling treatment switching and adherence are often underused. Time zero should be defined as the date of treatment initiation to ensure proper temporal alignment. Switching can be addressed by setting rules (e.g., adding a second bDMARD within 90 days) and applying censoring or stratification. Adherence may be assessed using metrics such as medication possession ratio or refill gaps. TriNetX supports these strategies through prescription tracking and time-to-event analysis.

4 | Consequences of Methodological Shortcomings

The consequences of failing to emulate clinical trial conditions in TriNetX studies are far-reaching. First, such studies may generate biased or spurious findings, potentially leading to erroneous clinical recommendations. Second, they may undermine the credibility of RWE as a reliable complement to traditional RCTs, especially in the context of regulatory decision-making and guideline development. Finally, the reproducibility and transparency of research conducted on real-world platforms remain compromised without standardized design frameworks [8].

5 | Opportunities and Benefits for Rheumatology Research

The rheumatology community stands to gain substantially from the proper utilization of RWD platforms like TriNetX. Autoimmune and inflammatory diseases often present with heterogeneity in clinical presentation, treatment response, and disease trajectory, making them prime candidates for RWE studies. Yet, to maximize the value of these data, methodological rigor must be prioritized. This involves not only adopting ECT frameworks but also pre-specifying study protocols, employing advanced causal inference techniques, and conducting sensitivity analyses to evaluate the robustness of findings [2, 9].

Confounding by indication is especially problematic in rheumatology, where treatment choices are shaped by multiple factors, including disease severity, organ involvement, patient preferences, and clinician judgment. For instance, studies assessing the comparative effectiveness of bDMARDs without adequately emulating clinical trials risk conflating the effects of treatment with the underlying risk profiles of patients selected for those treatments. This can result in over- or under-estimation of treatment benefits and harms (Table 1).

6 | Methodological Tools and Collaborative Efforts

TriNetX and similar platforms support ECT by enabling index event selection, eligibility criteria, and time-to-event analysis.

TABLE 1 | Cohort study vs. emulated clinical trial feature traditional cohort study emulated clinical trial design rheumatology example.

Feature	Traditional cohort study	Emulated clinical trial design	Rheumatology example
Definition of Eligibility Criteria	Often broad or retrospective	Pre-defined and explicit	New-onset RA with no prior bDMARD use, age 18–75
Treatment Assignment	Observational, based on real use	Defined to mimic random assignment	First-line methotrexate vs. TNF inhibitor
Follow-up Start	Variable or unclear	Uniform, linked to treatment initiation	Day of first prescription
Handling of Time-related Bias	Limited or absent	Explicit alignment to avoid immortal time bias	Ensure consistent index date to avoid misattribution of events
Confounding Control	Propensity score methods	Target trial framework + causal inference methods	Adjust for DAS28, CRP, prior flares, steroid use
Transparency and Reproducibility	Variable	High with protocol specification	Publicly shared emulation protocol on GitHub

Still, rigorous study design and clearly defined target trial protocols are essential to reduce bias and enhance interpretability.

7 | The Role of Multidisciplinary Collaboration and Methodological Innovation

Closer collaboration among clinicians, epidemiologists, and biostatisticians is essential to ensure that TriNetX studies follow best practices. Training, methodological guidelines, and peer review should highlight the importance of trial emulation and common pitfalls in observational analysis.

To further safeguard against confounding by indication, triangulation with other data sources, use of instrumental variable analysis, and application of negative control outcomes and exposures can be employed [10]. While no method can fully eliminate bias in non-randomized studies, combining multiple analytical strategies can significantly strengthen causal inference. Still, important limitations remain, such as incomplete records, missing variables like cognitive or socioeconomic factors, and the challenge of replicating trial conditions in real-world settings. Clear reporting and sensitivity analyses are essential to ensure valid and transparent interpretation.

8 | Advancing Real-World Evidence in Rheumatology

In conclusion, TriNetX offers powerful opportunities to advance rheumatology research through real-world evidence. However, neglecting ECT design risks introducing confounding by indication and undermines study validity. To ensure RWE meaningfully informs clinical care, the rheumatology community must adopt rigorous methodological standards, including trial emulation, transparent reporting, and ongoing innovation in study design.

Author Contributions

H.-Y.C. and S.-B.Y.: Writing original draft. Review and editing: S.-B.Y. and R.C.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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CLINICAL IMAGE

Pigmented Villonodular Synovitis in a Patient With Gout

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Received: 13 January 2025 | **Accepted:** 29 October 2025

Funding: This work was supported by grants from Hainan Provincial Natural Science Foundation of China (824MS172) and Hainan Province Joint Program on Health Science & Technology Innovation (WSJK2025QN007).

Keywords: gout | magnetic resonance imaging | pigmented villonodular synovitis

A 33-year-old male with an 11-year history of gout presents with recurrent episodes of inflammation, particularly in the right first metatarsophalangeal joint. Despite uric acid-lowering treatment, he has experienced soft tissue swelling and pain in the right knee and lower femur over the past year, which has limited his mobility. Magnetic resonance imaging (MRI) indicates diffuse thickening of the synovial membrane with villous (Figure 1A) and nodular hyperplasia (Figure 1B), as well as bone erosion. Ultrasound examination reveals a linear strong echo on the surface of the right femoral trochlear cartilage, exhibiting a "double contour sign" (Figure 1C). Additionally, an echogenic mass is observed within the suprapatellar capsule of the right knee, with visible crystal signals inside (Figure 1D). Pathological findings confirm the presence of hemosiderin deposition and infiltration of multinucleated giant cells (Figure 1E). The patient was subsequently referred to the orthopedics department for further management.

Pigmented villonodular synovitis (PVNS) is a rare benign invasive condition characterized by synovial tissue hyperplasia [1]. It is preferentially diagnosed using MRI and synovial biopsy [2]. The concurrent presence of gout and pigmented villonodular synovitis (PVNS) is infrequent, and the similar joint swelling associated with both conditions can complicate the diagnosis of PVNS. It is thus essential for clinicians to exercise caution and thoroughness in the diagnostic process to prevent potential misdiagnoses.

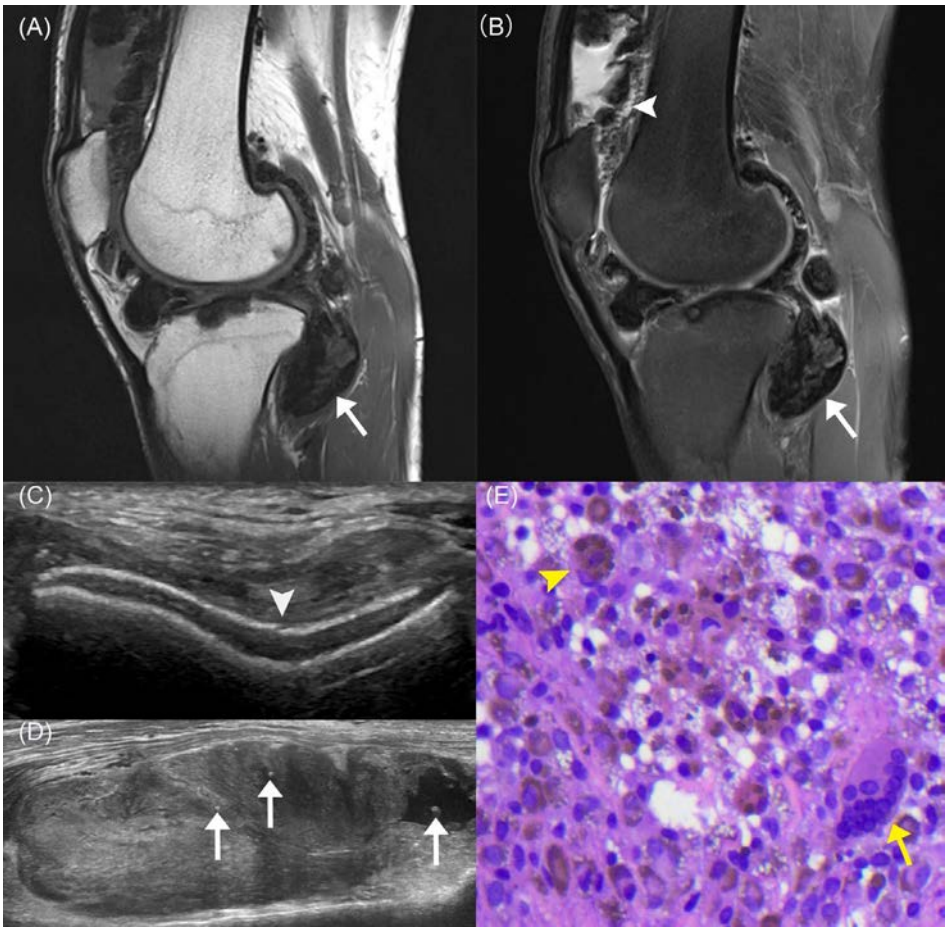

FIGURE 1 | T1-weighted imaging (A) and proton density weighted imaging (B) reveal suprapatellar synovitis (white arrowhead), nodules (white arrow), and bone erosion in PVNS. Ultrasound detects a "double contour sign" on the surface of the right femoral trochlear cartilage (white arrowhead) (C) and an isoechoic mass containing crystals in the suprapatellar pouch (white arrow) (D). Pathological examination (E) of synovial tissue indicates extensive hemosiderin deposition (yellow arrowhead) and multinucleated giant cells (yellow arrow).

Author Contributions

X.L. collected the data; X.C. and X.L. co-drafted the initial manuscript.

Ethics Statement

The authors have nothing to report.

Consent

Informed consent for publication was obtained from the patient.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

All data relevant to the study are included in the article.

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EDITORIAL

APLAR Young Rheumatology's Vision for Holistic Professional Development in Rheumatology

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Received: 14 October 2025 | **Revised:** 14 October 2025 | **Accepted:** 23 October 2025

Funding: The authors received no specific funding for this work.

Keywords: digital health | mentorship | professional development | rheumatology education | soft skills

ABSTRACT

The Asia-Pacific League of Associations for Rheumatology (APLAR) Young Rheumatologists (AYR) initiative addresses critical gaps in professional development through innovative soft skills training and comprehensive mentorship models. This editorial examines holistic approaches to developing emotional intelligence, leadership capabilities, and adaptive competencies essential for contemporary rheumatology practice.

1 | Introduction

The Asia-Pacific region presents unique challenges for rheumatology education. Geographic isolation, resource disparities, and cultural differences create barriers that traditional training models struggle to address. The Asia Pacific League of Associations in Rheumatology (APLAR) Young Rheumatologists (AYR) initiative addresses these educational gaps.

Professional success requires psychological wellness, intellectual growth, and emotional competence as foundational elements. When educational systems neglect these developmental needs, practitioners experience predictable consequences: emotional exhaustion compromises clinical judgment, professional isolation limits advancement, and inadequate support contributes to specialty attrition. Healthcare organizations report higher turnover, decreased engagement, and measurable negative impact on patient care when comprehensive development is absent.

AYR's vision addresses this gap by developing holistic professional competencies essential for contemporary rheumatology practice.

2 | The Soft Skills Imperative in Rheumatology

The unique nature of rheumatology requires specialized soft skills that extend beyond generic medical communication training, as clinicians increasingly coordinate multidisciplinary care teams including nurses, pharmacists, physiotherapists, and mental health professionals [1]. Soft skills, including leadership, self-confidence, teamwork, time management, empathy, stress management, problem-solving, and cultural competence, form the foundation of professional excellence [2]. Time management and organizational competencies become critical given rheumatology's complex caseloads requiring extended consultation periods, comprehensive care planning, and frequent follow-up coordination [3]. Effective programs combine experiential

learning opportunities with structured reflection, peer feedback mechanisms, and mentorship support.

AYR's mentorship approach recognizes that traditional hierarchical models inadequately serve diverse, globally distributed learners. The framework emphasizes peer collaboration, expert networks, and technology-mediated guidance rather than single mentor–mentee relationships.

The challenge of retaining specialists in rheumatology requires mentors who nurture the next generation through creative, personalized strategies. These mentors focus on building diverse career pathways tailored to individual interests and strengths, while fostering a strong sense of community and professional value. A supportive and inclusive mentorship environment with egalitarian engagement between mentors and mentees can have a far-reaching influence on confidence-building strategies to help mentees enhance their skills and accelerate their growth as future leaders in healthcare [4].

Alongside conventional curriculum elements, AYR leverages modern platforms to enhance accessibility and engagement; for instance, using dedicated online platforms to teach MRI interpretation in axial spondyloarthritis. In parallel, mentorship programs address critical non-clinical skills such as leadership and productivity among other soft skills, acknowledging that career advancement is a multidimensional journey.

The Asia-Pacific region's diversity requires educational approaches that acknowledge and celebrate cultural differences while building bridges across these differences. AYR's programming intentionally incorporates perspectives from different healthcare systems, cultural contexts, and economic environments.

Global perspective development extends beyond cultural awareness to include understanding of health equity issues, resource-appropriate care models, and diverse patient populations. Participants develop skills in adapting evidence-based practices to local contexts while maintaining quality standards.

3 | Program Components

The implementation of comprehensive professional development requires systematic attention to multiple competency domains. A matrix approach can help map academic leadership attributes and expertise across diverse areas including research capabilities, clinical skills, technological competencies, and personal well-being factors.

Successful programs combine flexible learning structures that accommodate diverse learning styles and career stages. Virtual and in-person opportunities should be integrated to ensure accessibility and relevance for all participants. The framework must serve as both a developmental tool and evaluation mechanism.

Key components of effective programs include pre-course preparation modules focusing on essential skill areas, intensive workshops with expert faculty, peer-to-peer learning opportunities, and structured post-course mentorship extending over several months.

Educational programming includes career narrative sessions, methodology workshops, and journal clubs designed to build technical expertise and professional confidence. Clinical excellence can be achieved through specialized training programs and experiential learning opportunities. These must be enhanced by professional support mechanisms, including cultural competence, well-being workshops, and productivity science guidance.

Career enhancement programs should extend beyond knowledge and skills maintenance to focus on personal capabilities and requirements throughout practitioners' career lifespans [4]. Through structured mentorship and cross-cultural interdisciplinary learning environments, practitioners develop both professional competence and personal resilience—essential qualities for sustained career satisfaction in healthcare.

Notable examples of successful structured career development include specialty fellowship programs and early-career investigator initiatives [5]. Innovative programs demonstrate how structured career development can strengthen the research workforce through cross-pollination of successful strategies.

4 | Digital Transformation and Professional Growth

The digital revolution has fundamentally altered how rheumatologists engage with knowledge, collaborate with colleagues, and deliver patient care. While there is strong interest in digital skill acquisition and telemedicine practice, actual competency remains limited, particularly regarding artificial intelligence (AI) applications and professional networking through social media [6].

A recent survey of young rheumatologists found that 79% agreed that large language model knowledge will become essential for practice. However, only 7% had received formal training, revealing a critical knowledge-to-practice gap that directly impacts diagnostic support, patient education, research efficiency, and clinical decision-making [7].

Interestingly, many young rheumatologists lack structured guidance on leveraging these platforms for career advancement, knowledge dissemination, and professional networking [8]. The potential for digital tools to bridge inequities in access to mentorship and professional development opportunities remains largely untapped.

5 | Sustainability

Network effects amplify impact beyond direct participants as program alumni become ambassadors for innovative educational approaches in their home institutions. Strategic partnerships with academic institutions, professional societies, and healthcare organizations help embed AYR's innovations into broader educational systems.

6 | Future Directions

The framework we propose emphasizes integrated development through multiple complementary pathways. The future of rheumatology depends on our ability to nurture young professionals who possess not only clinical and research expertise but also the leadership capabilities, digital competencies, and personal resilience necessary to thrive in an evolving healthcare landscape [9]. AYR's commitment to comprehensive professional development represents holistic approaches that address the complete spectrum of professional needs.

Through systematic implementation of comprehensive support frameworks, we can ensure that the next generation of rheumatologists is equipped not only with clinical competence but also with the broader skill set necessary to lead meaningful change in global healthcare delivery.

Author Contributions

Latika Gupta: conceptualization, writing – original draft, writing – review and editing. **Kosar Ansa Ashari:** writing – original draft, writing – review and editing. **Ghita Harifi:** writing – original draft, writing – review and editing.

Conflicts of Interest

The views and opinions expressed are solely those of the author and do not represent or reflect those of any affiliated institution. G.H. currently serves as the convenor for The Asia-Pacific League of Associations for Rheumatology (APLAR) Young Rheumatologists (AYR). K.A.A. is a member of the AYR partnerships committee. L.G. leads the AYR partnerships committee.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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LETTER TO THE EDITOR

Chronic Spontaneous Urticaria in Patients With Sjögren's Disease

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Received: 25 July 2025 | **Revised:** 13 October 2025 | **Accepted:** 23 October 2025

Dear Editor,

Chronic spontaneous urticaria (CSU) is a condition characterized by episodic eruptions of urticaria (hives) with or without angioedema that lasts for 6 weeks or longer, with no clear precipitating cause [1]. The prevalence of CSU in the general population is between 0.5% and 5%, affecting women more than men, and commonly arises in the third to fifth decades of life [1]. There is a well-recognized association between CSU and other autoimmune disorders; however, occurrence in rheumatology, including Sjögren's disease (SjD) is rare but of high relevance.

SjD is a chronic autoimmune disorder with lymphocytic infiltration of the salivary and lacrimal glands, manifesting as keratoconjunctivitis sicca and xerostomia [2]. Similar to CSU, primary SjD also has a female predilection, with mean age of onset between the fourth and fifth decades, and a rarer estimated prevalence between 0.01% and 0.05% [3]. Given the similar timeline of disease onset and symptom burden that diminishes quality of life, the need to characterize associations between CSU and SjD is of high importance. Firstly, it may elucidate unique aspects driving underlying pathogenesis; and secondly, it informs disease patterns and clinical course, thereby empowering patients and clinicians with this knowledge. Unfortunately, to date, there is a paucity of literature surrounding the natural history of CSU in primary SjD (SjD/CSU). Herein, we described the clinical course of patients with SjD/CSU at a single tertiary centre in Western Sydney, Australia, over a six-year period between June 2018 and June 2024. CSU was defined as the persistence of spontaneous urticaria (> 6 weeks) with unclear precipitating cause(s) [1].

In this six-year period, 153 patients were diagnosed with primary SjD by the American College of Rheumatology-European Alliance of Associations for Rheumatology 2016 criteria [3]. Six patients had SjD/CSU, giving a prevalence of 3.9%. All patients were female and had a mean ± standard deviation (SD) age of 42 ± 7 years by census date. The mean age of CSU onset was 37 ± 8 years and SjD, 35 ± 7 years (Table 1). Their clinical courses are summarized in Appendix 1.

We identified 18 random non-SjD/CSU patients that were gender-, age- and race-matched to our 6 SjD/CSU patients. A 3:1 matching ratio was used to ensure sufficient statistical power in our study. The non-SjD/CSU cohort had a mean age of 41 ± 11 years (Table 2). The SjD/CSU cohort had a higher rate of autoimmune comorbidities ($p = 0.035$) (Table 2).

There were no significant differences in CSU clinical course or atopic status in both groups (Table 2). This differed from a single-centre study which described a median CSU duration of 4 years, and a shorter disease duration (just over 3 years) amongst patients with autoimmune/thyroid disease [4].

Current CSU management guidelines recommend second generation antihistamines (SGA) with dose-intensification up to four times daily [1]. Additional agents such as leukotriene antagonists or H2-antagonists (e.g., famotidine, nizatidine) are no longer recommended given limited efficacy, although patients may have received this in line with evidence at the time [1]. The stepwise escalation of therapy was adopted by both patient cohorts without discernible differences (Table 2). Despite the advent of

TABLE 1 | Baseline characteristics of patients with Sjögren's disease and chronic spontaneous urticaria (CSU).

	Patient A	Patient B	Patient C	Patient D	Patient E	Patient F
Demographics						
Gender	Female	Female	Female	Female	Female	Female
Heritage	Asian	Asian	Asian	Asian	Caucasian	Asian
Age (years) at census date	38	52	36	45	34	44
Clinical course						
Age (years) of CSU onset	35	46	34	43	24	41
Age (years) of CSU in remission	36	53	35	46	N/A	N/A
Age (year) of SjD onset	32	41	29	45	29	37
Keratoconjunctivitis sicca	Y	Y	Y	Y	Y	Y
Xerostomia	Y	N	Y	N	N	Y
Extra-glandular manifestations	Arthralgia Lymphopenia	Arthralgia	Arthralgia Fatigue Cryoglobulinemia	Cytopenias	Arthralgia Fatigue	Cutaneous
Immunomodulatory medications (baseline)	Nil	Nil	Nil	Nil	Hydroxychloroquine	Nil
CSU meds						
FGA	N	N	N	N	N	N
SGA	Y	Y	Y	Y	Y	Y
H2A	N	N	N	N	N	N
LTA	N	N	N	N	N	N
OMZ	N	N	N	N	Y	N
Autoantibodies	Anti-Ro60 Anti-Ro52 Anti-La RhF	Anti-Ro60	Anti-Ro60 Anti-Ro52 Anti-La RhF	Anti-Ro60	Anti-Ro52	Anti-Ro52 Anti-Ro60
B cells (% of lymphocytes) (normal 5%–20%)	2	19	25	15	9	Not measured
Comorbidities	Hypothyroidism	Hypothyroidism	Coeliac disease	Nil	Allergic rhinitis	Latent tuberculosis
ESSDAI	3	0	1	0	2	0

Abbreviations: ESSDAI, EULAR Sjögren's syndrome disease activity index; FGA, first-generation antihistamine; H2A, histamine type-2 receptor antagonists; LTA, leukotriene antagonist; N, no; N/A, not applicable; OMZ, omalizumab; RhF, rheumatoid factor; SGA, second-generation antihistamine; Y, yes.

TABLE 2 | Clinical and demographic characteristics of both patient cohorts. Data is presented as absolute numbers with percentages for categorical variables or mean ± SD for continuous normally distributed variables. The denominator is represented at the top of the column or, where missing data is present, listed in each table's cell.

	CSU and SjD patients $N = 6$ (%)	CSU without SjD patients $N = 18$ (%)	p for differences
Race			
White/Caucasian	1 (17)	6 (33)	0.437
Asian/middle-Eastern	5 (83)	12 (67)	
Mean age at census date (years) ± SD	42.2 ± 6.8	40.7 ± 11.3	0.764
Mean age of CSU onset (years) ± SD	37.3 ± 7.9	32.0 ± 11.1	0.294
Mean CSU duration (years) ± SD	4.8 ± 3.5	6.5 ± 4.6	0.419
CSU status			
CR	2 (33)	9 (50)	0.762
PR	2 (33)	5 (28)	
Persistent	2 (33)	4 (22)	
ANA median titre	1:640	1:80	**< 0.001**
Anti-thyroid antibodies (IgG)	2 (33)	4/13 (31)	> 0.999
Basophils ($\times 10^9$/L) ± SD [absolute]	0.02 ± 0.04	0.03 ± 0.05	0.605
% of leukocytes ± SD	0.3 ± 0.7	0.3 ± 0.6	> 0.999
Eosinophils ($\times 10^9$/L) ± SD	0.17 ± 0.16	0.23 ± 0.46	0.760
% of leukocytes ± SD	2.9 ± 2.1	2.7 ± 4.3	0.915
CSU meds			
FGA	0 (0)	1 (6)	> 0.999
SGA	6 (100)	18 (100)	> 0.999
H2 antagonists	0 (0)	2 (11)	> 0.999
LTA	0 (0)	1 (6)	> 0.999
OMZ	1 (17)	2 (11)	> 0.999
Co-morbidities			
Allergic	0 (0)	8 (44)	0.066
Autoimmune	3 (50)	1 (6)	**0.035**

Note: Bolded p values represent significant values < 0.05.
Abbreviations: CR, complete remission; CSU, chronic spontaneous urticaria; FGA, first-generation antihistamine; H2A, histamine type-2 receptor antagonists; LTA, leukotriene antagonist; N/A, not applicable; OMZ, omalizumab; PR, partial remission; RhF, rheumatoid factor; SD, standard deviation; SGA, second-generation antihistamine; SjD, Sjögren's disease.

omalizumab, a subset of CSU patients remains treatment refractory. Predictors of omalizumab efficacy include elevated baseline total IgE level, whereas positive ANA portended poor response [5]. This was not the case for our patient cohort, with only 1 SjD/CSU patient requiring omalizumab, and remains in clinical remission. One possible explanation for effective management with SGA and omalizumab alone in our SjD/CSU cohort could be ascribed to hydroxychloroquine, prescribed for some of our SjD patients. In fact, the immunomodulatory role of hydroxychloroquine at 200–400 mg daily had been demonstrably well-tolerated and effective in achieving partial and sustained response in CSU patients failing omalizumab and could be a worthy alternative given favorable safety profile [6].

Other emerging therapies, targeting downstream effectors of mast cell activation are in the pipeline. Bruton tyrosine kinase (BTK) is expressed on B cells and myeloid cells such as mast cells. The inhibition of BTK and its downstream proinflammatory effects has proven effective in CSU, and also has relevance in SjD by targeting B cells [7]. Perhaps B cell dysregulation is a common denominator that drives CSU and SjD, either due to B cell hyper-activity, secretion of autoantibodies that bind to FcεRI triggering mast cell or basophil degranulation, or other pathways mediating Fc receptor interactions [7]. Indeed, a few of our SjD/CSU patients did display increased levels of circulating B cells, suggesting a degree of B cell hyper-activity (Table 1).

Consistent with current literature, patients with SjD/CSU in our study had more comorbid autoimmune disease (50%, $n = 3$), including coeliac disease, compared to non-SjD/CSU patients (Table 2). Moreover, 33% ($n = 2$) of our SjD/CSU patients had positive anti-TPO antibodies, in line with current understanding of the role of anti-TPO antibody in CSU pathogenesis (Table 2) [8]. Given the high risk of progression to overt thyroid disease, close surveillance in this CSU cohort is important to initiate investigations and treatment expediently [9]. Potential biomarkers of interest may include high anti-TPO titres, low total IgE, basopaenia and eosinopaenia [10]. Notably, there were no significant differences in eosinophil and basophil counts in our cohort (Table 2).

There are some limitations to this study including the small sample size from a single centre, which limits the generalisability and the power to determine differences between groups. In addition, as a retrospective observational study, some parameters of interest (e.g., total IgE) were not recorded at initial diagnosis. Longitudinal studies with a greater sample size would be ideal to further confirm whether SjD alters the natural history of CSU.

Nevertheless, our study's strength lies in being the first case series to describe the clinical course of CSU in patients with SjD. By defining the CSU/SjD subset as a rare cluster of SjD with prominent autoimmunity features, we offer new insights and perspectives. Specifically, we describe the clinical course, treatments and pathology in detail. Our investigation also highlights the importance of clinicians evaluating CSU patients for concurrent autoimmune disorders, including SjD. Furthermore, our findings spark interest in exploring immunomodulatory therapies that could potentially benefit both CSU and SjD; indeed, future studies evaluating the impact of disease-modifying antirheumatic drugs in CSU/SjD would be helpful.

Author Contributions

The authors take full responsibility for this article.

Acknowledgments

The authors have nothing to report.

Conflicts of Interest

Adrian Lee has received a speaker honorarium from Novartis.

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.

Michelle Lin
Adrian Y. S. Lee

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Appendix 1

Clinical Summaries of the Six Sjögren's Disease (SjD) Patients With Concomitant Chronic Spontaneous Urticaria (CSU)

Patient A

Patient A initially presented to Hematology in her early 30s for work-up of chronic lymphopaenia. On further history, she complained of fatigue, keratoconjunctivitis sicca and xerostomia. She tested positive for SjD-associated autoantibodies and was referred to the Immunology clinic and subsequently confirmed the diagnosis of SjD.

At age 35, she developed widespread urticaria almost immediately post-partum, some without clear precipitants and others exacerbated by physical pressure. There was associated angioedema of her face and lips. The patient attempted dietary restriction but this made no difference to the severity of recurrent urticaria. She responded well to daily antihistamines and was able to wean off medications in a few months. Her CSU remains in remission.

Patient B

Patient B presented to her GP at age 40 with fatigue and positive autoimmune serology. Over the next few years, she developed small joint arthralgias and xerostomia. A minor salivary gland biopsy confirmed the diagnosis of SjD.

She also reports recurrent urticaria, often in context of life stressors in the years preceding SjD diagnosis. The lesions tend to arise in pressure areas (e.g., near bra line) and on the legs and is managed, due to patient

choice, with topical steroids. She declined oral antihistamine therapy for personal reasons.

Patient C

Patient C presented in their late 20s with active synovitis of the small joints in the hand and wrist post-partum. She was initially diagnosed with "rheumatism" treated empirically with hydroxychloroquine without improvement, which she self-ceased thereafter. Xerostomia and keratoconjunctivitis sicca emerged several years later and was managed conservatively with topical lubricants. In her early 30s, she developed recurring widespread urticaria with no identifiable physical triggers. The skin lesions were exacerbated by heat and pressure from clothing, managed with antihistamines.

Patient D

Patient D presented in her 40s with several months of recurring urticarial lesions that appear spontaneously and exacerbated by pressure and heat. Autoimmune serology at that time revealed a positive anti-Ro60 with concurrent neutropenia and lymphopenia without clinical sequelae and resolved on subsequent testing. Several years later, she complained of new keratoconjunctivitis sicca with positive Schirmer's test. There were no other features of SjD. Her CSU responded well to regular antihistamines, and she is now on as required dosing, only experiencing mild flares localized to the leg after hot showers. She has a history of pituitary microadenoma managed conservatively.

Patient E

Patient E presented in her mid-late 20s with concomitant fatigue, alopecia, widespread arthralgias and later, keratoconjunctivitis sicca and xerostomia with reduced unstimulated whole salivary flow rate. Autoimmune serology revealed monopositive anti-Ro52. Commencement of hydroxychloroquine improved her arthralgias and some of her CSU.

She was diagnosed with CSU in her late 20s with recurrent pruritic wheals and angioedema that was refractory to first-line therapy of second-generation antihistamines (SGAs). She was commenced on omalizumab in her 30s to good effect, and now maintains 6-weekly dosing with SGAs as required. Whilst she has had intermittent flares at the 5-week mark post-injection, the dosing schedule remains at 6-weekly as per patient preference.

Patient F

Patient F presented in her 40s with 12 months of widespread urticaria responsive to antihistamines. On further questioning, she reported several years of sicca symptoms of her eyes and mouth, and intermittent malar rash. There were no other extra-glandular symptoms. Systemic lupus erythematosus was excluded. On the basis of positive anti-Ro52/Ro60 autoantibodies and a positive Schirmer's test, she was diagnosed with SjD. She was commenced on a regular and maximal dose of second-generation antihistamines to substantial improvement in her urticaria. Patient F was subsequently diagnosed with latent tuberculosis; at the time of writing, she had not yet commenced any antituberculosis therapy.

International Journal of Rheumatic Diseases

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International Journal of Rheumatic Diseases

ORIGINAL ARTICLE

Comprehensive Economic Analysis of Healthcare Costs in Ankylosing Spondylitis: Treatment Strategies and Socioeconomic Implications

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Received: 1 February 2025 | **Revised:** 5 September 2025 | **Accepted:** 8 October 2025

Funding: This study was supported by ① The National Natural Science Foundation of China (Grant number: NSFC82360422); ② Joint Project on Regional High-Incidence Diseases Research of Guangxi Natural Science Foundation (Grant number: 2024GXNSFAA010073); ③ Guangxi Young and Middle-aged Teacher's Basic Ability Promoting Project (Grant number: 2023KY0115); ④ The "Medical Excellence Award" Funded by the Creative Research Development Grant from the First Affiliated Hospital of Guangxi Medical University; ⑤ Clinical Research Climbing Plan Project of the First Affiliated Hospital of Guangxi Medical University in 2023 (Grant number: YYZS2023008); ⑥ Innovation Project of Guangxi Graduate Education (Grant number: JGY2024094); ⑦ Guangxi Zhuang Autonomous Region "Four New" Research and Practice Project (Grant number: SX202319); ⑧ Guangxi Medical and Health Appropriate Technology Development and Promotion Project (Grant number: S2024017). ⑨ First-class discipline innovation-driven talent program of Guangxi Medical University. Funding bodies had not participated in the design of the study, collection, interpretation, and analysis of the data, or in writing the manuscript.

Keywords: ankylosing spondylitis | catastrophic health expenditure | cost analysis | medical costs

ABSTRACT

Background: Ankylosing spondylitis (AS) is a chronic inflammatory disorder that imposes a significant economic burden through high healthcare costs. Prior studies have explored AS-related expenditures, but a comprehensive analysis of cost-related factors is lacking. This study aims to fill this gap.

Methods: We analyzed data from 6149 AS patients (2018–2024) at two tertiary hospitals in Guangxi, China, and classified them as surgical or non-surgical; inpatients were categorized by catastrophic health expenditures (CHE; > 50% of household income). Descriptive statistics and the Kruskal–Wallis test were used to assess patient characteristics and cost differences, whereas propensity score matching and multivariable logistic regression were used to identify independent CHE predictors.

Results: A total of 6149 AS patients were included. Surgical patients were older and incurred significantly higher inpatient costs (USD 9457.21 vs. USD 1177.10 for non-surgical patients). General medical service costs, imaging examination costs, Western medicine costs, and medical supply costs are risk factors affecting CHE in hospitalized patients.

Conclusion: AS imposes a substantial economic burden, particularly on surgical patients. Key cost drivers, including general medical services, imaging, pharmaceuticals, and medical supplies, markedly increase the risk of catastrophic expenditures. Implementing policy reforms to enhance insurance coverage, alongside clinical cost-control strategies such as rational imaging

Abbreviations: ANOVA, analysis of variance; AS, ankylosing spondylitis; ASAS, Assessment of SpondyloArthritis International Society; CHE, catastrophic health expenditure; CI, confidence interval; OR, odds ratio; PSM, propensity score matching; SMD, standardized mean difference; USD, United States Dollar; VIF, variance inflation factor.

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use, adoption of generic medicines, and optimized management of medical supplies, is essential to alleviate financial strain and improve the sustainability of AS care.

1 | Introduction

Chronic illnesses, including ankylosing spondylitis (AS), have far-reaching consequences, including physical pain, impaired function, reduced quality of life, and detrimental effects on employment prospects and out-of-pocket expenses [1, 2]. Moreover, high-prevalence diseases impose a substantial burden on society, attributable to increased overall medical costs, non-medical costs, and disability benefits resulting from workforce withdrawal [3, 4]. AS is a chronic and progressive rheumatic disorder characterized by painful inflammation affecting the sacroiliac joints, axial skeleton, and peripheral joints [5, 6]. In advanced stages, the fusion of soft tissues or bones around the spine or hip joints can result in severe deformities and disabilities, significantly impairing patients' daily functioning and work capacity. Currently, there is no cure for AS, and lifelong medication is often necessary [7]. Typically, AS onset occurs between the ages of 20 and 30 [8], resulting in a significant male predominance, with a male–female ratio of about 2–3:1 [1]. Furthermore, incidence rates vary across countries, regions, and ethnic groups worldwide [8, 9]. Owing to its relatively young onset, individuals with AS must adapt to the disease for most of their lives [10]. Consistent with other chronic conditions, AS affects quality of life, morbidity, mortality, work participation rates (both paid and unpaid), and healthcare costs [11, 12].

In recent years, advancements in diagnostic technology and treatment methods have substantially improved the management of AS patients. Nevertheless, long-term AS management necessitates considerable medical resources, resulting in a significant economic burden on patients and society [13, 14]. Previous studies have focused primarily on direct medical costs and lack a comprehensive analysis of diverse treatment modalities and influencing factors [15]. This study used comprehensive statistical analysis methods to conduct a multidimensional analysis of the outpatient, inpatient, and surgical treatment costs incurred by patients with ankylosing spondylitis across multiple treatment centers. This study leveraged a large cohort of AS patients and employed rigorous statistical analyses to examine cost disparities and influencing factors across outpatient, inpatient, and surgical treatments. It further identified key determinants of catastrophic expenditures among inpatients. By including multilevel and diverse patient groups, this research ensured comprehensive and representative data coverage, providing a solid scientific basis for understanding the economic burden of AS. This research aims to inform medical resource allocation and policy formulation. Ultimately, this study offers a scientific basis for optimizing medical management and policy development by systematically analyzing AS patients' medical expenses and influencing factors. The findings from this study offer significant insights that can inform comprehensive management strategies for AS patients and support the development and implementation of relevant policies.

2 | Methods and Materials

2.1 | Study Population

Patients who were diagnosed with AS at the First Affiliated Hospital of Guangxi Medical University and the Fourth People's Hospital of Nanning from January 2018 to April 2024 were enrolled in this study. Diagnoses were established based on the 1984 modified New York criteria and the 2009 Assessment of SpondyloArthritis International Society (ASAS) classification criteria [9]. To ensure the accuracy of the diagnosis, all patients were strictly evaluated and diagnosed by experts in the field of AS according to the relevant classification criteria to ensure that the diagnostic process complied with internationally recognized professional standards.

2.2 | Data Sources and Ethics

The outpatient data for this study included consultation times, demographic characteristics, insurance types, occupational information, and various expenditure categories. Inpatient data included admission times, lengths of stay, total costs, and detailed expense items (including medical services, treatment operations, nursing care, diagnostic procedures, laboratory tests, imaging examinations, and pharmaceuticals). All analyzed costs reflected original expenses incurred prior to medical insurance reimbursement. The dataset excluded personally identifiable information, such as, patient names, hospitalization registration numbers, telephone numbers, addresses, and other sensitive details. In compliance with the regulations established by the Ethics Committee, anonymization of the data was performed prior to analysis, rendering written informed consent from individual patients unnecessary, as the study did not involve sensitive or private patient information. We conducted this study in strict accordance with the ethical principles of the Declaration of Helsinki and obtained formal approval from the Ethics Committees of the First Affiliated Hospital of Guangxi Medical University and the Fourth People's Hospital of Nanning (Approval number: 2024-E762-01, 1.0/2024.04.24).

2.3 | Methods

We established the following criteria to determine data inclusion and exclusion criteria for this study: (1) ankylosing spondylitis was designated as the primary diagnosis (ICD-10 code M45.x00 at inpatient discharge and outpatient visits); (2) hospital visits occurred between August 14, 2018, and March 19, 2024; (3) data with substantial missing information were excluded; and (4) outpatient data were stratified by visit frequency for patients with repeated visits. A total of 6149 patients fulfilled the inclusion criteria for this study. We evaluated the severity of ankylosing spondylitis in these

Summary

- What is already known about this topic
  - Prior research on AS has focused primarily on isolated aspects of healthcare costs and the economic burden of this chronic disease. Although some studies have explored the financial implications of various treatment modalities, there is a notable gap in comprehensive analyses that integrate multiple factors influencing medical expenditures.
- What this study adds
  - This study provides a comprehensive economic analysis of healthcare costs in patients with ankylosing spondylitis (AS), integrating multiple cost-related factors and treatment modalities. It quantifies the significant cost disparity between surgical (USD 9457.21) and non-surgical (USD 1177.10) patients, highlighting the heightened financial burden on surgical patients. By identifying general medical service costs, imaging examination costs, Western medicine costs, and medical supply costs as key risk factors for catastrophic inpatient expenditures, this study offers actionable insights for targeted interventions. Propensity score matching (PSM) was employed to effectively control for confounding variables, ensuring robust adjustment for baseline differences. By integrating univariate and multivariate logistic regression analyses, this study systematically identified key risk factors with high precision. This dual analytical approach enhances the reliability and robustness of the findings, addressing critical gaps in prior research that lacked such comprehensive and methodologically rigorous methodologies.
- How this study might affect research, practice or policy
  - These findings have important implications for future research, clinical practice, and healthcare policy. By identifying key determinants of medical expenditures in AS, this study provides a foundation for exploring cost-effective treatment strategies. Clinically, insights can guide healthcare providers in making informed decisions about treatment options. At the policy level, the study advocates for tailored healthcare policies that address the financial burden on AS patients, emphasizing improved insurance coverage and resource allocation to enhance treatment outcomes and reduce economic disparities.

patients and developed treatment plans that strictly adhered to the Spine-Related Disease Classification System outlined by the Global Spine Care Initiative [16]. Patients with Grade I or II AS, characterized by mild symptoms, received pharmacological treatment in the outpatient department following evaluation by experienced specialists. Conversely, patients with Grade III or higher AS, exhibiting pronounced symptoms and inadequate response to outpatient treatment, underwent further evaluation by clinical specialists for potential hospitalization and conservative or surgical treatment tailored to their condition.

2.4 | Definitions of Catastrophic Spending

In this study, catastrophic health expenditures were defined as medical expenses exceeding 50% of total household income. Household income was calculated as the mean annual per capita disposable income in the Guangxi Zhuang Autonomous Region from 2018 to 2024, sourced from the National Bureau of Statistics of China, weighted by the average household size to estimate household-level income. The results of annual household income per capita from 2018 to 2024 are detailed in Table S16. Catastrophic expenditures refer to the substantial financial burden imposed by excessive medical expenses, potentially compromising basic living expenses or leading to poverty [17]. Medical expenses (encompassing hospitalization and outpatient costs) were calculated for each patient. The likelihood of catastrophic healthcare expenditures among outpatients with AS is minimal, with a probability of $<1\%$. In contrast, inpatients face a substantially greater risk, with about 50% experiencing catastrophic expenditures. Consequently, this study focused on analyzing the medical expenditures of inpatients incurring catastrophic costs to elucidate the underlying factors contributing to this economic burden.

2.5 | Statistical Analysis

This study utilized a comprehensive set of statistical methods to evaluate medical expenditures and associated factors in patients with AS. Descriptive statistics were employed to summarize patient characteristics (e.g., age, gender, insurance type) and cost distributions across outpatient and inpatient groups. To control for confounding variables, propensity score matching (PSM) was applied to balance baseline characteristics (e.g., age, gender, disease severity, and insurance type) between surgical and non-surgical patients [18]. Matching balance was assessed using standardized mean differences (SMD), standardized median differences, and pseudo-R^2 values, with SMD <0.1 indicating adequate balance [19]. Cost differences between groups were compared using one-way analysis of variance (ANOVA) for normally distributed data or the Kruskal–Wallis test for non-normally distributed data, with post hoc tests for significant results [20]. A significance level of 0.05 was used for all hypothesis tests. To identify risk factors for catastrophic health expenditures among inpatients, univariate analyses were used to screen potential predictors (e.g., general medical service costs, imaging examination costs, Western medicine costs, medical supplies costs), followed by multivariate binary logistic regression to estimate adjusted odds ratios (ORs) and 95% confidence intervals (CIs). Long-term economic burden was assessed by analyzing cumulative costs from multiple outpatient visits, hospitalizations, and surgeries, stratified by disease severity and insurance type. Variance analysis compared cost differences across strata. Sensitivity analyses, including alternative PSM models and varying catastrophic expenditure thresholds (e.g., 40% or 60% of household income), were conducted to evaluate the robustness of the findings. All the statistical analyses were performed using R (version 4.3.1) or SPSS (version 27.0).

3 | Results

3.1 | Baseline Demographics and Clinical Profiles of the Patients Enrolled in the Study

A total of 6149 patients diagnosed with AS were enrolled in this study. The baseline demographic characteristics assessed included sex, age, occupation, and type of health insurance. We conducted a comparative analysis of surgical and non-surgical patients both before and after applying PSM. The results of the matching process revealed significant discrepancies in key characteristics, such as sex and age, between surgical and non-surgical patients prior to matching. After matching, statistical analysis revealed no significant differences in any covariates between the groups, confirming that the matched cohorts were well balanced with respect to baseline characteristics. The demographic information, outpatient expenses, and hospitalization costs of the patients are detailed in Table S1.

3.2 | Summary of Cost Disparities Between Surgical and Non-Surgical AS Patients

The economic analysis of healthcare costs for AS reveals significant disparities between surgical and non-surgical inpatients, with surgical patients incurring substantially higher median costs across multiple expenditure categories ($p < 0.05$). As shown in Table S1. The total inpatient costs for surgical patients (USD 9457.21) are about eight times higher than those for non-surgical patients (USD 1177.10), driven by the complexity of surgical interventions. The key cost drivers include surgical treatment costs (USD 1022.00 vs. USD 0.00), medical supplies (USD 2300.00 vs. USD 19.10), and imaging examinations (USD 327.00 vs. USD 179.33), reflecting the need for specialized procedures (e.g., spinal fusion), costly implants, and advanced diagnostics (e.g., MRI, CT scans). Surgical patients also face higher general medical service costs (USD 67.97 vs. USD 44.38), general treatment and procedure costs (USD 95.20 vs. USD 18.10), and nursing costs (USD 38.78 vs. USD 23.38) due to extensive pre- and post-operative care, multidisciplinary team involvement, and intensive monitoring. Additionally, laboratory test costs (USD 265.10 vs. USD 204.60), Western medicine costs (USD 385.64 vs. USD 274.31), and non-surgical treatment costs (USD 120.51 vs. USD 34.41) are elevated in surgical patients, who require comprehensive testing, additional medications (e.g., analgesics, prophylactics), and adjunctive therapies. Minor antibiotic costs (USD 0.70 vs. USD 0.00) arise from prophylactic use in surgery. No significant differences were observed in pathology diagnostic costs (USD 0.00 for both, $p = 0.061$) or traditional Chinese medicine costs (USD 0.00 for both), indicating their limited role in AS inpatient care. These findings demonstrate the substantial costs associated with the surgical management of AS and indicate the need for cost-effective interventions to reduce the economic burden on patients.

3.3 | Stratified Analysis of Outpatient Expenses

The average total outpatient cost for patients was USD 393.43; however, there were significant differences in outpatient costs across different sexes, ages, health insurance types, and occupations [21]. The Kolmogorov–Smirnov test indicated that total outpatient costs significantly deviated from a normal distribution ($p < 0.01$; see Table S2). Therefore, we employed the non-parametric Kruskal-Wallis test to compare median costs [22]. Specifically, the outpatient costs for male patients (USD 149.85) were significantly higher than those for female patients (USD 121.42). Significant differences in outpatient costs were also observed among patients with different types of health insurance. Patients with employee insurance had the highest costs (USD 149.85), followed by self-paying patients (USD 131.80), whereas patients with resident insurance had the lowest costs (USD 141.88) ($p < 0.01$) [23]. Among the different occupations, workers, civil servants, and students had significantly higher outpatient costs than other occupational groups ($p < 0.01$) [19]. An in-depth presentation of the results can be found in Table S3.

3.4 | Stratified Analysis of Hospitalization Costs and Severity

There were significant differences in total hospitalization costs and individual expense categories between surgical and non-surgical patients. The Kolmogorov–Smirnov test revealed that hospitalization costs deviated from a normal distribution ($p < 0.01$) (see Table S4). As a result, a non-parametric test was applied, and median costs were compared [22]. The results revealed that the total costs for surgical patients (USD 9457.21) were significantly greater than those for non-surgical patients (USD 1177.10). Compared with non-surgical patients, surgical patients incurred significantly higher costs in general medical services, treatment procedures, nursing care, laboratory tests, imaging examinations, non-surgical treatments, surgical treatments, Western medicine, antibiotics, and traditional Chinese medicine ($p < 0.01$). In terms of surgical fees and medical supplies, the expenditure for surgical patients was notably greater than that for non-surgical patients. Pathological diagnosis costs were not significantly different between surgical and non-surgical patients ($p > 0.05$). The detailed results are provided in Table 1. We further examined the differences in total hospitalization costs between surgical and non-surgical patients. A normality test for total costs yielded a p-value of < 0.01, indicating a non-normal distribution. Consequently, we applied the Wilcoxon rank-sum test, which revealed that the median total cost for surgical patients (USD 12 105.81) was significantly greater than that for non-surgical patients (USD 152.83) ($z = 19.916$, $p < 0.01$). The detailed results are provided in Table S5. The PSM results showed that, after matching, balance tests confirmed no significant differences in the mean covariate values between hospitalized surgical and non-surgical patients [19]. The results are shown in Table S6. A significant difference in total costs was found between the treatment group (surgical) and the control group (non-surgical) before matching ($p < 0.05$), with the treatment group incurring USD 12 182.63 more in total costs than the control group. Following covariate adjustment, matching using the K-nearest neighbor method revealed that total costs were USD 12 192.768 higher in the treatment group. The radius and kernel matching methods yielded similar results, with total costs being USD 12 177.223 and USD 12 176.812 higher in the treatment group, respectively. These findings are detailed in

TABLE 1 | Comparison of total hospitalization costs and subitem costs between surgical and non-surgical patients.

Variable	Group	Q1	*M*	Q3	*z*	*p*
Total inpatient costs	Yes	USD 4580.65	USD 9457.21	USD 13 145.03	20.886	0.000
	No	USD 811.17	USD 1177.10	USD 2010.59		
General medical service costs	Yes	USD 46.14	USD 67.97	USD 104.50	9.025	0.000
	No	USD 22.96	USD 44.38	USD 70.56		
General treatment and procedure costs	Yes	USD 65.01	USD 95.20	USD 145.33	15.911	0.000
	No	USD 5.32	USD 18.16	USD 53.16		
Nursing costs	Yes	USD 28.49	USD 38.78	USD 56.56	10.733	0.000
	No	USD 11.83	USD 23.38	USD 36.82		
Pathology diagnostic costs	Yes	USD 0.00	USD 0.00	USD 26.60	1.871	0.061
	No	USD 0.00	USD 0.00	USD 23.80		
Laboratory test costs	Yes	USD 213.63	USD 265.10	USD 371.29	6.862	0.000
	No	USD 122.71	USD 204.60	USD 324.88		
Imaging examination costs	Yes	USD 228.52	USD 327.03	USD 486.68	10.445	0.000
	No	USD 64.68	USD 179.33	USD 309.34		
Non-surgical treatment costs	Yes	USD 47.35	USD 120.51	USD 281.55	6.468	0.000
	No	USD 4.20	USD 34.41	USD 170.97		
Surgical treatment costs	Yes	USD 849.30	USD 1022.00	USD 1294.00	24.125	0.000
	No	USD 0.00	USD 0.00	USD 88.20		
Western medicine costs	Yes	USD 257.61	USD 385.64	USD 653.07	5.828	0.000
	No	USD 88.97	USD 274.31	USD 619.26		
Antibiotic costs	Yes	USD 0.00	USD 0.76	USD 18.91	10.125	0.000
	No	USD 0.00	USD 0.00	USD 0.00		
Traditional Chinese medicine costs	Yes	USD 0.00	USD 0.00	USD 5.80	2.922	0.003
	No	USD 0.00	USD 0.00	USD 2.60		
Medical supplies costs	Yes	USD 1271.00	USD 2300.00	USD 6794.00	20.511	0.000
	No	USD 5.64	USD 19.10	USD 109.70		

Note: Yes = Surgical patients; No = Non-surgical patients.
Abbreviation: USD, United States Dollar.

Table S7. The multivariate logistic regression analysis presented in Table S8 identified key factors influencing the probability of hospitalization for surgical intervention. Focusing on health insurance types—categorized as 1 for Self-Payment, 2 for Resident Health Insurance, and 3 for Employee Health Insurance—the analysis reveals a significant association. The coefficient (B) for insurance type is 0.393 ($p < 0.01$), with an odds ratio (Exp(B)) of 1.482 and a 95% confidence interval of 1.366–1.608, indicating that individuals with higher insurance categories (e.g., Employee Health Insurance) are 48.2% more likely to undergo surgical intervention than those with lower categories (e.g., Self-Payment). Additionally, gender and age emerged as significant predictors, with males exhibiting a greater propensity for surgery than females do, which is consistent with the epidemiological profile of ankylosing spondylitis, where males are more predisposed to this condition. The increased likelihood of surgical intervention with advancing age also aligns with the progressive nature of ankylosing spondylitis, where late-stage disease progression may necessitate surgical treatment [24].

3.5 | Analysis of the Number of Visits and the Long-Term Economic Burden

A stratified analysis based on the number of outpatient visits was performed to examine the distribution and differences in costs across various visit frequency groups. Patients were divided into four groups based on the number of outpatient visits. The statistical findings are as follows: the group with 1–20 visits ($N = 5884$) had an average outpatient cost of USD 313.40; the group with 20–39 visits ($N = 225$) had an average cost of

TABLE 2 | Descriptive statistical analysis results of total expenses by outpatient visits.

Outpatient visit counts (Range)	Sample size (*N*)	Mean expense (USD)	Standard deviation (USD)	95% C.I. for mean (USD)	
				Lower bound	Upper bound
[1,20]	5884	USD 313.4011	USD 521.60195	USD 300.0707	USD 326.7314
[20,39]	225	USD 1996.3467	USD 1162.92758	USD 1843.5681	USD 2149.1252
[39,58]	31	USD 2876.4384	USD 976.40290	USD 2518.2909	USD 3234.5859
[58,77]	9	USD 4091.4789	USD 1620.58122	USD 2845.7899	USD 5337.1679
Total	6149	USD 393.4335	USD 684.80113	USD 376.3138	USD 410.5532

TABLE 3 | Descriptive statistical analysis results of total costs by medical insurance type.

Payment types for medical expenses	Sample size (N)	Mean expense (USD)	Standard deviation (USD)	95% C.I. for mean	
				Lower bound	Upper bound
Employee health insurance	594	USD 476.8105	USD 772.17918	USD 414.5862	USD 539.0349
Resident health insurance	998	USD 414.9406	USD 715.60791	USD 370.4892	USD 459.3920
Self-payment	4557	USD 377.8553	USD 664.75333	USD 358.5496	USD 397.1609
Total	6149	USD 393.4335	USD 684.80113	USD 376.3138	USD 410.5532

USD 1996.35; the group with 39–58 visits ($N=31$) incurred USD 2876.44 on average; and the group with 58–77 visits ($N=9$) had a mean cost of USD 4091.48. The overall mean outpatient cost was USD 393.43. The detailed results are presented in Table 2. Levene's test revealed significant variance heterogeneity (Levene = 145.309, $p<0.01$), so Tamhane's method was used for post hoc comparisons [25]. The detailed results are shown in Table S9. Analysis of variance (ANOVA) revealed significant differences in outpatient costs across the visit frequency groups ($F=975.324$, $p<0.01$), with outpatient costs increasing significantly with an increasing number of visits. The detailed results are provided in Table S10. Furthermore, pairwise comparisons of total outpatient costs across the visit frequency groups revealed significant differences between groups. The detailed results are presented in Table S11. The cumulative costs incurred throughout the disease management process, encompassing multiple outpatient visits, hospitalizations, and surgical expenses, indicate that longer and more complex disease courses are associated with higher mean outpatient costs. This suggests a positive correlation between treatment duration and financial burden on patients [26].

3.6 | Medical Insurance Type Stratification

We conducted a stratified analysis to assess the impact of insurance coverage and reimbursement rates on the financial burden of patients with different insurance types. Patients were divided into three groups based on their type of insurance. The statistical analysis yielded the following results: the average total outpatient cost was USD 476.8105 for patients with employee insurance ($N=594$), USD 414.9406 for those with resident insurance ($N=998$), and USD 393.4335 for self-paying patients ($N=4557$). The detailed results are shown in Table 3. Levene's test for homogeneity of variance revealed unequal variances (Levene = 13.397, $p<0.01$); therefore, Tamhane's method was applied for post hoc comparisons [25]. The results are presented in detail in Table S12. Analysis of variance (ANOVA) revealed significant differences in outpatient costs across the different insurance types ($F=6.084$, $p<0.01$), with patients covered by employee insurance incurring significantly higher outpatient costs than self-paying patients [27]. The detailed results are shown in Table S13. Additionally, a comparison of total outpatient costs across various insurance types revealed significant differences, as outlined in Table S14.

3.7 | Analysis of the Proportion of Catastrophic Expenditures and Their Influencing Factors

This study included 6149 patients, of whom 464 had medical expenses exceeding the catastrophic expenditure threshold, with a catastrophic expenditure incidence rate of 7.5%. This indicates that most patients still face financial difficulties because their medical expenses exceed a certain proportion of their family income. Among them, almost all patients with catastrophic expenditures were hospitalized patients, so we investigated the medical expenditures of 972 hospitalized patients. The baseline characteristics of the hospitalized patients and the distribution of medical expenditure types are detailed in Table 4. The univariate logistic regression model tested the key factors affecting catastrophic expenditures, including general medical service costs, general treatment and surgical costs, pathological diagnosis costs, laboratory examination costs, imaging examination costs, non-surgical treatment costs, surgical treatment costs, Western medicine costs, antibiotic costs, traditional Chinese medicine costs, medical supply costs, and the number of hospitalized patients [28]. The specific results are shown in Table 5. The multivariate logistic regression model further revealed that general medical service costs, imaging examination costs, Western medicine costs, and medical consumable costs were important factors affecting the occurrence of catastrophic expenditures.

TABLE 4 | Baseline characteristics and medical expenditure profiles of the overall inpatient cohort and by catastrophic spending groups.

Characteristics	Overall ($n = 972$)	Non-catastrophic spending group ($n = 509$)	Catastrophic spending group ($n = 463$)	p
Sex (%)				
Male	820 (84.4)	418 (82.1)	402 (86.8)	0.044
Female	152 (15.6)	91 (17.9)	61 (13.2)	
Surgical status				
Yes	237 (24.4)	505 (99.2)	233 (50.3)	< 0.001
No	735 (75.6)	4 (0.8)	230 (49.7)	
Age (median [IQR])	39 (30, 54)	37 (27, 52)	41 (33, 55)	< 0.001
Occupation (%)				
Employees of enterprises and public institutions	128 (13.2)	79 (15.5)	49 (10.6)	< 0.001
Farmer	68 (7.0)	58 (11.4)	10 (2.2)	
Self-employed group	54 (5.6)	28 (5.5)	26 (5.6)	
Retiree	572 (58.8)	259 (50.9)	313 (67.6)	
Unemployed	35 (3.6)	24 (4.7)	11 (2.4)	
Government official	42 (4.3)	22 (4.3)	20 (4.3)	
Student	17 (1.7)	9 (1.8)	8 (1.7)	
Industrial worker	56 (5.8)	30 (5.9)	26 (5.6)	
Health insurance types (%)				
Employee health insurance	199 (20.5)	116 (22.8)	83 (17.9)	< 0.001
Resident health insurance	706 (72.6)	345 (67.8)	361 (78.0)	
Self-payment	67 (6.9)	48 (9.4)	19 (4.1)	
Medical expenditure indices				
General medical service costs (median [IQR])	50.44 (27.85, 77.35)	33.32 (13.86, 54.81)	68.94 (46.61, 102.17)	< 0.001
General treatment and procedure costs (median [IQR])	34.95 (7.89, 81.18)	8.96 (3.36, 24.95)	78.06 (49.37, 125.39)	< 0.001
Pathology diagnostic costs (median [IQR])	0.00 (0.00, 25.20)	0.00 (0.00, 18.90)	0.00 (0.00, 28.73)	< 0.001
Laboratory test costs (median [IQR])	228.44 (140.80, 343.95)	164.84 (89.25, 261.28)	277.16 (214.38, 419.41)	< 0.001
Imaging examination costs (median [IQR])	218.23 (81.02, 357.97)	117.87 (18.40, 226.69)	318.33 (219.02, 481.73)	< 0.001
Non surgical treatment costs (median [IQR])	57.01 (4.90, 196.51)	17.47 (0.00, 96.22)	120.51 (35.03, 290.41)	< 0.001
Surgical treatment costs (median [IQR])	2.69 (0.00, 734.78)	0.00 (0.00, 2.37)	754.52 (10.46, 1028.15)	< 0.001
Western medicine costs (median [IQR])	321.59 (129.52, 625.53)	168.42 (57.89, 442.51)	438.67 (267.72, 825.34)	< 0.001
Antibiotic costs (median [IQR])	0.00 (0.00, 1.01)	0.00 (0.00, 0.00)	0.00 (0.00, 22.36)	< 0.001

(Continues)

TABLE 4 | (Continued)

Characteristics	Overall ($n = 972$)	Non-catastrophic spending group ($n = 509$)	Catastrophic spending group ($n = 463$)	p
Traditional Chinese medicine costs (median [IQR])	0.00 (0.00, 4.16)	0.00 (0.00, 0.00)	0.00 (0.00, 6.79)	< 0.001
Medical supplies costs (median [IQR])	48.47 (8.14, 1637.59)	9.25 (3.91, 33.61)	1820.62 (158.74, 7895.91)	< 0.001
Number of hospital admissions (median [IQR])	1.00 (1.00, 3.00)	2.00 (1.00, 4.00)	1.00 (1.00, 2.00)	< 0.001

Note: Data presented as median (IQR) for continuous variables and number (%) for categorical variables.
Abbreviation: IQR, interquartile range.

The VIF analysis is presented in "Supplementary Table S15". VIF analysis of medical expenditure indices: All medical expenditure indices present VIF values below the commonly accepted threshold of 5. This suggests that multicollinearity is not a significant concern in the dataset. Consequently, the results can be considered robust, supporting the reliability of the regression model.

4 | Discussion

Using a cohort of 6149 ankylosing spondylitis (AS) patients from the First Affiliated Hospital of Guangxi Medical University and the Fourth People's Hospital of Nanning, this study systematically examined the medical costs associated with AS, offering comprehensive insights into the economic burden on both patients and the healthcare system. This research compared cost disparities between surgical and non-surgical treatments, identified key risk factors for catastrophic medical expenditures, and explored the economic implications of long-term AS management. The following discussion provides a rigorous scientific analysis of the findings.

The study revealed that the median medical cost for surgical patients was USD 9457.21, about eight times higher than that of non-surgical patients at USD 1177.10. This substantial cost difference is attributed primarily to the resource-intensive nature of surgical interventions, including surgical fees, medical supplies (e.g., implants), and imaging examinations (e.g., MRI and CT scans). Surgical patients are often in advanced disease stages and present with severe deformities such as spinal fusion, necessitating complex and costly procedures. This aligns with the literature [6, 29, 30]. In contrast, non-surgical patients incurred lower costs, with outpatient expenses averaging USD 393.43, influenced by factors such as gender, age, and insurance type. Notably, there is a significant association between health insurance type and the likelihood of hospitalization for surgical intervention in patients with AS. The results revealed that individuals in higher insurance categories (e.g., employee health insurance) were 48.2% more likely to receive surgical intervention than those in lower insurance categories (e.g., self-pay). This finding highlights the role of socioeconomic factors, particularly access to comprehensive health insurance, in influencing treatment pathways for AS, a chronic inflammatory disease that often requires surgical intervention in its advanced stages. The association between insurance type and surgical intervention may reflect differences in access to healthcare resources. Compared with resident health insurance or self-pay plans, employee health insurance, which is often associated with formal employment and higher socioeconomic status, tends to provide broader coverage and higher reimbursement rates. This expanded coverage may facilitate access to specialist care, including consultations with rheumatologists and orthopedists, diagnostic imaging, and elective surgical procedures such as spinal correction or joint replacement, which are common in advanced AS [31]. In contrast, patients who rely on self-pay may face financial barriers that prevent them from undergoing costly surgical procedures, opting instead for conservative management strategies such as medication or physical therapy. The significant OR of 1.482 indicated that insurance type was not just a passive socioeconomic marker but also a determinant of clinical decision-making and access to treatment for AS.

Through univariate combined with multivariate logistic regression analysis, the study identified general medical service fees, imaging examination fees, Western medicine fees, and medical supply fees as primary risk factors for catastrophic health expenditure (CHE) among hospitalized patients [32, 33]. The model's robustness was confirmed by low variance inflation factor (VIF) values. About 50% of hospitalized patients experienced medical expenses exceeding 50% of their household income, classified as catastrophic expenditures, with surgical patients being particularly affected [34–36]. This high prevalence highlights the severe financial strain that AS management imposes on patients, especially those requiring complex treatments. From a scientific perspective, this finding exposes inadequacies in the current insurance system and calls for detailed quantification of these cost drivers to inform targeted financial support policies aimed at alleviating patients' economic burdens. Clinically, healthcare providers should prioritize cost-effective practices, such as following evidence-based imaging guidelines to minimize unnecessary testing or choosing generic drugs to reduce the cost of Western medicines [37]. Hospitals can also improve supply chain efficiencies, such as the bulk purchasing of supplies, to reduce costs without compromising quality of care. Providing financial counseling to hospitalized patients, especially those with greater imaging or medication needs, can help identify CHE risk early and connect patients to insurance or social support resources. From a policy perspective, the results highlight the need to strengthen health insurance coverage for high-cost

TABLE 5 | Univariate and multivariate analysis of influencing factors.

	Univariate analysis		Multivariate analysis	
Characteristics	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
General medical service costs	4.77 (3.80–6.08)	< 0.001	2.30 (1.29–4.15)	0.005
General treatment and procedure costs	4.93 (4.10–6.02)	< 0.001	0.83 (0.57–1.20)	0.329
Pathology diagnostic costs	1.14 (1.07–1.23)	< 0.001	1.02 (0.87–1.19)	0.808
Laboratory test costs	4.81 (3.77–6.24)	< 0.001	1.18 (0.71–2.06)	0.543
Imaging examination costs	3.06 (2.56–3.70)	< 0.001	1.95 (1.45–2.69)	< 0.001
Non surgical treatment costs	1.41 (1.32–1.51)	< 0.001	1.14 (0.99–1.32)	0.074
Surgical treatment costs	1.64 (1.55–1.74)	< 0.001	1.14 (0.96–1.37)	0.141
Western medicine costs	2.50 (2.16–2.92)	< 0.001	4.29 (3.00–6.31)	< 0.001
Antibiotic costs	1.67 (1.51–1.87)	< 0.001	1.16 (0.98–1.38)	0.091
Traditional Chinese medicine costs	1.19 (1.08–1.30)	< 0.001	1.18 (0.99–1.41)	0.069
Medical supplies costs	2.52 (2.27–2.82)	< 0.001	2.78 (2.10–3.76)	< 0.001
Number of hospital admissions	0.47 (0.37–0.59)	< 0.001	1.09 (0.70–1.70)	0.694

Abbreviations: CI, confidence interval; OR, odds ratio.

inpatient services. Based on the baseline characteristics and medical expenditure profiles of inpatients overall and in catastrophic spending groups, patients with limited insurance coverage (e.g., self-pay or resident health insurance patients) may be particularly vulnerable to CHE. Increasing reimbursement for imaging, drugs, and consumables or setting a cap on out-of-pocket expenses could protect patients from financial hardship [38]. In addition, public health strategies aimed at early diagnosis and outpatient management of conditions that require hospitalization could reduce the need for costly hospitalizations and, therefore, reduce the incidence of CHE.

With respect to the long-term economic burden, the analysis of outpatient visit frequency demonstrated a positive correlation between treatment duration and costs. Patients with 58–77 visits incurred an average cost of USD 4091.48, whereas those with 1–20 visits incurred an average cost of USD 313.40 (ANOVA, $F = 975.324$, $p < 0.01$). This indicates that patients with poorly controlled or more severe disease face escalating costs over time, underscoring the challenges of long-term management. Specifically, this emphasizes the need for optimized early disease management. Future research should explore whether early adoption of biologics or multidisciplinary approaches can effectively reduce visit frequency and associated costs, thereby mitigating the long-term economic impact [39–41].

Stratified analysis by insurance type revealed that outpatient costs for patients with employee insurance were USD 476.81, higher than USD 414.94 for those with resident insurance and USD 393.43 for self-pay patients. This discrepancy may stem from better access to advanced treatments or higher reimbursement rates for employee-insured individuals. However, significant differences were observed in the risk of catastrophic expenditures among hospitalized patients across insurance types, suggesting that current insurance schemes offer limited protection against high-cost hospital expenditures, particularly for surgical patients [35, 42–44]. Specifically, this points to inequities in medical resource allocation and necessitates an evaluation of the actual coverage provided by different insurance plans to reduce the financial burden on self-pay patients and enhance resource distribution.

Methodologically, the study employed propensity score matching (PSM) to control for confounding variables such as, age, gender, and disease severity, achieving post-matching standardized mean differences (SMD) < 0.1. This ensured that cost differences were attributable to treatment modalities rather than baseline characteristics. The integration of univariate and multivariate analyses, along with sensitivity analyses at varying expenditure thresholds, further supported the reliability of the findings. Nonetheless, the study has several limitations: data were obtained from two tertiary medical centers, potentially limiting generalizability; indirect costs (e.g., productivity losses) were excluded, possibly underestimating the total economic burden. While the methodological rigor lends high credibility to the results, future research should encompass multicenter studies and incorporate indirect costs to provide a more comprehensive understanding of the economic impact of AS.

5 | Conclusion

This study underscores the substantial economic burden of AS, particularly for surgical patients, with general medical services, imaging examinations, pharmaceuticals, and medical supplies markedly increasing the risk of catastrophic expenditures. The implementation of healthcare policy reforms to increase insurance coverage, alongside clinical cost-control strategies such as rational imaging use, the adoption of generic medicines, and optimized medical supply management, is essential for alleviating financial strain and enhancing the sustainability of AS care.

Author Contributions

Xiaopeng Qin, Zhuo Chen, and Jie Ma participated in the conceptualization and methodology design of the study. Yuhang Luo, Rongqing He, Boli Qin, Quan Pan, and Chenxing Zhou were in charge of data curation and investigation. Tianyou Chen, Songze Wu, Jiarui Chen, Jiang Xue, and Kechang He analyzed and visualized the data. Xinli Zhan and Chong Liu: Writing – Reviewing and Editing. All authors contributed to the article and approved the submitted version.

Acknowledgments

We are very grateful to Prof. Chong Liu and Prof. Xinli Zhan (Spine and Osteopathy Ward, The First Affiliated Hospital of Guangxi Medical University), Prof. Jie Ma (Surgical Ward, The Fourth People's Hospital of Nanning, Nanning, Guangxi, China) for support in all stages of this study.

Consent

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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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Basic information and medical costs of ankylosing spondylitis patients from 2018 to 2024. **Table S2:** Normality test results for total outpatient costs. **Table S3:** Comparison of medical costs by sex, insurance type, and occupation. **Table S4:** Normality test results for total hospitalization expenses. **Table S5:** Comparison of the average total costs between surgical and non-surgical inpatients. **Table S6:** Balance check results of covariates before and after matching. **Table S7:** Comparison of total costs for surgical and non-surgical patients under different matching methods. **Table** S**8**. Results of logistic regression analysis of factors affecting the probability of hospitalization for surgery. **Table S9:** Results of the variance homogeneity test based on total outpatient expenses. **Table S10:** Results of variance analysis among groups according to total outpatient expenses. **Table S11:** Results of the analysis of the average difference in total costs by number of outpatient visits. **Table S12:** Results of the variance homogeneity test for total costs stratified by medical insurance type. **Table S13:**. Results of variance analysis among groups based on total medical cost. **Table S14:** Results of the analysis of the average difference in total costs by medical insurance type. **Table S15:** Variance Inflation Factor (VIF) analysis of medical expenditure indices. **Table S16:** Results of annual per capita household income from 2018 to 2024.

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EDITORIAL

The AYR APLAR 2025 Social Media Coverage: From Halls to Highlights

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Received: 29 September 2025 | **Revised:** 29 September 2025 | **Accepted:** 24 October 2025

Keywords: medical education | online networking | rheumatology events | social media

The APLAR–AYR Social Media Committee marked a significant milestone during the recent APLAR 2025 Congress in Fukuoka, Japan, by launching its inaugural official media coverage on Instagram and LinkedIn (Figure 1) This initiative reflects a commitment to ensuring that rheumatology in the Asia–Pacific region adapts to the digital landscape where younger physicians, trainees, and patients increasingly engage. Social media has emerged as a powerful platform for public health communication, advocacy, and dissemination of the latest developments in rheumatology. By curating content that resonated both with peers and the public, the Committee amplified APLAR's voice and presence in real time. We are grateful for the Society's support and encouragement and hope to inspire more AYR members to join our efforts.

In the weeks leading up to the Congress, the Committee shared practical information to build anticipation—guides for first-time attendees, networking opportunities, and highlights of workshops and AYR-organized sessions.

During the event itself, members conducted short interviews with key faculty, capturing both scientific insights and motivational messages. Notable interviews already released as of this writing include Professor Lai-Shan Tam on comorbidities in spondylarthritis, Professor Eric Morand on outcome measures in systemic lupus erythematosus (SLE), Professors Marta Mosca and Laurent Arnaud on advances in SLE treatment, Professors Jemima Albayda and Peter Siu on musculoskeletal ultrasound, Professor Bhaskar Dasgupta on vascular ultrasound, and Professor Tsutomu Takeuchi on DMARD updates. Additional interviews and multimedia content remain in the pipeline, underscoring the Committee's intent to maintain postconference engagement.

Reflecting on the experience, Committee members identified both challenges and rewards. Technical logistics—navigating equipment, recording quality, and editing—proved demanding, while the immediacy of on-camera presence tested confidence and adaptability. Yet these were balanced by unique opportunities: engaging directly with internationally renowned speakers, receiving positive feedback from colleagues, and witnessing heightened interest in AYR's social media outputs. The impact and reach can be seen in the online metrics of the platform (Figure 1).

The arrival and development of the AYR's social media accounts will hopefully address the demands of keeping up to date with the fast-paced world of rheumatology. May it serve as a bridge to further promote APLAR's mission and vision to make a space for inclusion, develop leaders for future generations, and to provide meaningful regional engagement to advance rheumatology across the globe.

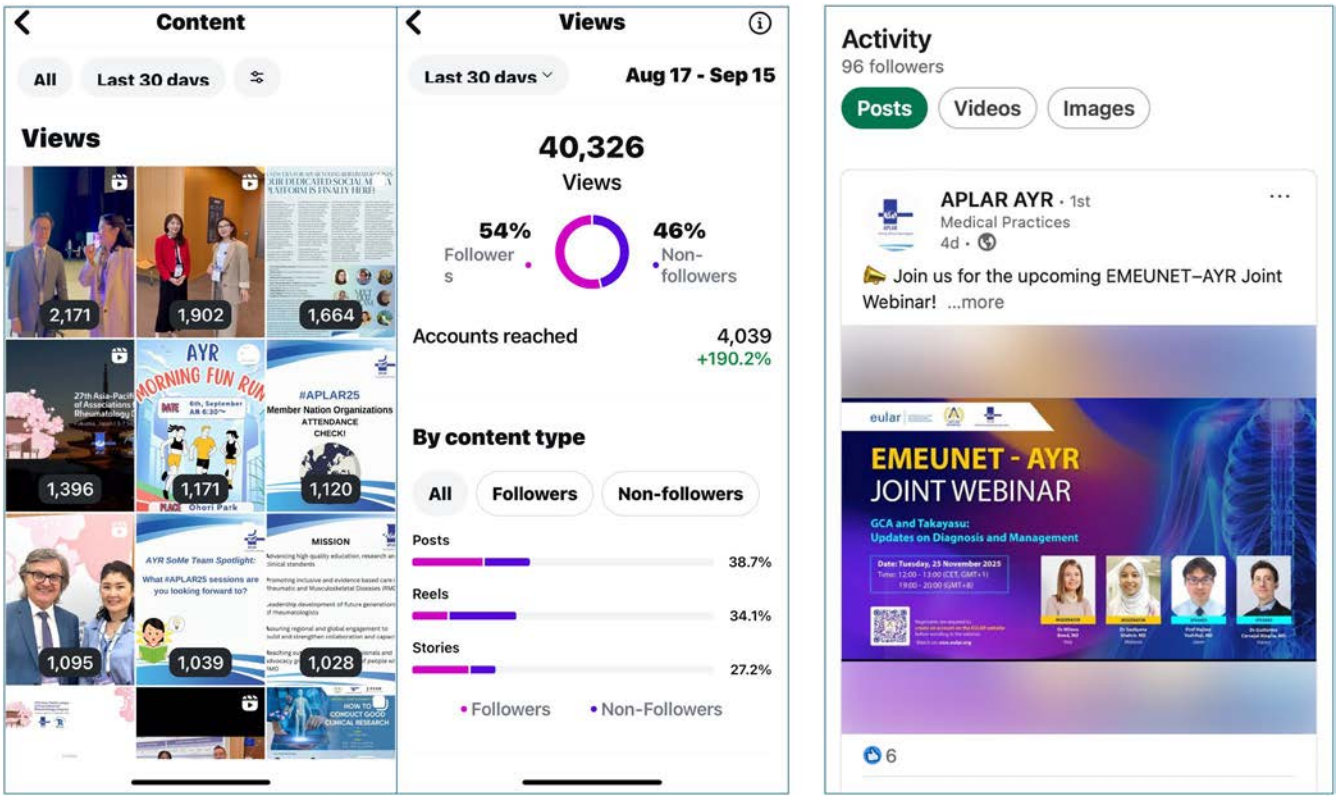

FIGURE 1 | Screencapture of The AYR Instagram Page (https://www.instagram.com/aplar_ayr/) and The AYR LinkedIn Page (https://www.linkedin.com/in/aplar-ayr-831135366/).

Author Contributions

L.S.T. for initial draft and final format. M.H.M.Z.S., S.A. conceptualized and provided additional information. G.T., G.H. for editing and guidance.

Acknowledgments

The authors would like to thank the APLAR and AYR board for their support, as well as the speakers interviewed during the event. The views expressed and any errors are solely those of the author.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

International Journal of Rheumatic Diseases

WILEY

International Journal of Rheumatic Diseases

EDITORIAL

Live-Attenuated Influenza Vaccine in Pediatric: Safety Profile and Broader Implications for Immune-Mediated Diseases

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Received: 27 August 2025 | **Revised:** 27 August 2025 | **Accepted:** 14 October 2025

Funding: The authors received no specific funding for this work.

Keywords: asthma | influenza | live-attenuated vaccine | pediatric immunology

1 | Introduction

Influenza remains a leading cause of respiratory morbidity worldwide. Children with chronic conditions, such as asthma, suffer disproportionately higher rates of exacerbation, hospitalization, and even mortality. Vaccination is therefore indispensable. For decades, inactivated influenza vaccines have been the standard, offering proven safety in high-risk groups. Live-attenuated influenza vaccine, administered intranasally, introduces advantages of needle-free delivery and induction of mucosal immunity, yet has been historically limited by concerns of airway reactivity. The evolving evidence in asthma provides an important model that may inform vaccine policy for patients with immune-mediated diseases.

2 | Asthma as a Paradigm Shift

Asthma was once considered a contraindication for LAIV. Early surveillance data linked the vaccine to wheezing and hospitalization in infants younger than two, leading to strict contraindications that extended to young children with asthma or recurrent wheeze. This conservative stance persisted for years. However, newer studies have challenged these assumptions. A pivotal randomized trial in children aged 5–17 showed no increase in exacerbations or lung function decline with LAIV compared to inactivated vaccine, and adverse events were even less frequent in some cases [1]. Large observational studies, including Sniffle-2 with over 4700 asthmatic children, confirmed no rise in lower respiratory events [2]. Importantly, efficacy has also been demonstrated. A European phase III trial showed a 35% greater reduction in laboratory-confirmed influenza with LAIV than with inactivated vaccine, while asthma control remained stable [3]. These data shifted professional guidelines: both the American Academy of Pediatrics and the CDC now permit the use of LAIV in children aged two and older with well-controlled asthma [4].

3 | Limitations of Live Vaccines in Immune-Mediated Diseases

While asthma illustrates how contraindications can evolve, rheumatology offers an unresolved challenge. Live vaccines have long been withheld from patients with systemic lupus erythematosus, rheumatoid arthritis, juvenile idiopathic arthritis, and other autoimmune conditions, particularly when patients are on immunosuppressive therapy. The rationale has been to avoid uncontrolled infection or triggering of disease activity. This caution, however, creates a paradox: those most at risk of

Abbreviations: IIV, inactivated influenza vaccine; LAIV, live-attenuated influenza vaccine; RCT, randomized controlled trial.

severe influenza complications are systematically excluded from receiving vaccines that may provide effective protection. In clinical practice, this results in a persistent vulnerability among patients who are immunologically compromised. The asthma-LAIV experience highlights that exclusions based solely on theoretical risks may ultimately deprive high-risk populations of potential benefits.

4 | New Delivery Routes and Immunologic Rationale

The safety of LAIV in asthma is rooted in its unique immunologic mechanism. Replication confined to the nasopharyngeal mucosa stimulates secretory IgA and tissue-resident T-cell responses, mimicking natural infection while avoiding systemic spread [1, 3]. This not only explains its tolerability but also its ability to confer broader cross-protection against drifted strains. For patients with immune-mediated diseases, mucosal vaccination strategies may offer a safer alternative to traditional systemic live vaccines. The intranasal route is the best studied, but oral and inhaled vaccines are under development. These approaches have the potential to harness localized immunity, reduce systemic exposure, and improve safety for patients who remain excluded from current recommendations. The critical question for the future is whether nasal delivery represents the optimal route, or whether other mucosal platforms may provide additional advantages.

5 | Real-World Data and the Need for Reassessment

Moving beyond historical prohibitions requires robust evidence. Randomized trials often exclude patients with autoimmune diseases or those receiving biologics, leaving major evidence gaps. Real-world data are therefore essential. Platforms such as TriNetX and the NHIRD provide large-scale datasets that can evaluate vaccine safety and effectiveness in immune-mediated conditions. Recent *IJRD* publications have underscored both the opportunities and the limitations of such data, noting their power to capture outcomes at scale while cautioning about confounding and data heterogeneity [5]. The reversal of LAIV contraindications in asthma was only possible after the convergence of randomized trials and observational studies. A similar integration of evidence is needed for patients with rheumatic diseases to reassess whether current contraindications remain justified.

6 | Opinion and Future Perspectives

The trajectory of LAIV from contraindication to cautious endorsement in asthma offers valuable lessons for rheumatology. Contraindications should not remain static; they must evolve as new data emerge. The absolute exclusion of patients with autoimmune diseases from live vaccination may be overly restrictive. Instead, risk stratification, careful monitoring, and exploration of mucosal delivery routes may allow safe immunization in selected populations. Advances in nasal, oral, and inhaled vaccines, combined with real-world analyses from TriNetX and national databases, provide unprecedented opportunities to revisit long-held assumptions. The rheumatology community should remain open to reevaluating historical restrictions, just as pediatrics did with asthma.

7 | Conclusion

Evidence now supports LAIV as safe and effective in children with asthma, overturning decades of concern [1–3]. For patients with immune-mediated diseases, the lesson is clear: evidence rather than tradition should guide vaccination policy. Mucosal vaccination strategies, exemplified by LAIV, may hold promise for extending protection to autoimmune and immunosuppressed populations who remain at high risk for infection. The time has come to reassess blanket prohibitions and to explore whether mucosal vaccines can offer a safe and effective path forward [5].

Author Contributions

Yun-Cheng Tsai: writing – original draft. **Hao-Yun Chen:** writing – original draft. **Yi-Hsuan Tu:** writing – original draft. **Po-Cheng Shih:** writing – review and editing.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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