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REVIEW

2024 Update of the Asia-Pacific League of Associations for Rheumatology (APLAR) Recommendations for Rheumatoid Arthritis Management

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ABSTRACT

Aim: To update the Asia-Pacific League of Associations for Rheumatology (APLAR) treatment recommendations for rheumatoid arthritis (RA) by incorporating new evidence and reassessing the validity of previous guidance:

Methods: A literature search for relevant publications from January 2018 to August 2023 was conducted, supplemented by earlier studies where relevant. Recommendations were formulated based on this evidence and refined through a modified-Delphi process during a series of online meetings. The quality of evidence and strength of recommendations were assessed using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach.

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Results: This update comprises 14 statements that achieved consensus during the meetings. Topics covered include measurement of disease activity and treatment response, the use of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), the use of targeted therapies, vaccination and screening for infections and the use of DMARDs during pregnancy. The recommendations address the selection of disease activity scores, initiation and intensification of therapy using csDMARDs and targeted therapies, and management of RA in patients at risk of reactivation of infectious diseases. These recommendations are discussed in the context of the clinical landscape encountered in the Asia-Pacific region.
Conclusion: These updated recommendations complement previous APLAR guidelines and aim to support best practice management of RA across the Asia-Pacific region. They provide a practical framework for national rheumatology associations to develop local guidelines adapted to their specific needs and clinical practice.

1 | Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease that is characterized by inflammation, pain, stiffness, and progressive joint degradation, which cause substantial morbidity and mortality if inadequately treated [1]. RA is also associated with lost productivity and consequent socioeconomic burdens as well as diminished quality of life [2]. Although the prevalence of RA in Asia (~0.3%) is lower than that reported in North America or Europe (0.5%–1%) [1, 3], the absolute prevalence of RA is high, and the incidence of RA and the associated burden are increasing [2].

Disease-modifying antirheumatic drugs (DMARDs) are the mainstay of RA treatment [1]. Timely treatment with DMARDs effectively alters the clinical course, with slowing or cessation of joint damage [1, 4]. Frequently used conventional synthetic DMARDs (csDMARDs) include methotrexate (MTX), leflunomide, sulfasalazine (SSZ), and hydroxychloroquine (HCQ) [1], and other csDMARDs may be available in different countries/regions. Biologic DMARDs (bDMARDs) with diverse mechanisms of action are available, including tumor necrosis factor (TNF) inhibitors, interleukin-6 (IL-6) inhibitors, modulators of T-cell costimulation, and anti-CD20 (β cell depletion) [1]. Additionally, the Janus kinase (JAK) – signal transducers and activators of transcription (STAT) signaling pathway can be targeted with JAK inhibitors, members of an evolving class of agents referred to as targeted synthetic DMARDs (tsDMARDs) [1]. In this 2024 update of the Asia-Pacific League of Associations for Rheumatology (APLAR) recommendations for treatment of RA, the term "targeted therapy" covers both bDMARDs and tsDMARDs and is denoted "b/tsDMARDs".

Our original 2015 APLAR guideline summarized international clinical practice recommendations for RA published from January 2000 to December 2013 [5]. An updated APLAR guideline was published in 2018 to include newer literature, with a focus on the growing evidence for targeted therapies [6]. Due to the expanding range of approved targeted therapies and their growing use in the Asia-Pacific (AP) region, a review and revision of this guidance is warranted.

The 2024 APLAR guideline update summarized herein was developed in accordance with the overarching principles summarized in Box 1. Pertinently, these augmented recommendations were developed with AP patient populations in mind and considered the optimization of medical outcomes and provision of effective solutions for resource-limited settings in some countries within the AP region. In circumstances where these aims are incompatible, we have offered guidance for both situations.

BOX 1 | Overarching Principles Guiding APLAR 2024 Update.

- RA treatment should be initiated without delay upon diagnosis and adjusted based on a shared decision by both the patient and the clinician to maintain physical functioning and good quality of life through achieving sustained remission, or low disease activity when remission may not be an achievable target.
- Healthcare providers should strive to ensure access to the best possible treatment(s) for patients with RA.
- The choice of treatment is based on disease activity and risk assessment that includes prognostic factors and comorbidities.
- Routine assessment of disease activity is essential to achieving treatment goals. If the desired target is not achieved, treatment should be modified. Once the target is attained, it should be maintained. Tapering should be considered in patients who achieve stable remission.
- Rheumatologists should ideally be the principal healthcare providers for patients with RA.

Importantly, we believe that clinicians should discuss overall therapeutic goals and appropriate treatment options with patients in a shared decision-making process, considering all pertinent risk factors when prescribing therapy.

2 | Materials and Methods

In this 2024 update to the APLAR treatment guidelines for RA, Steering Committee members involved in developing the 2015 and 2018 guidelines were invited to form the Working Group for the update. During the first of three meetings, the Working Group re-evaluated clinical questions that guided the literature search for the 2015 and 2018 APLAR recommendations. The Working Group reached agreement on topics for discussion that formed the basis for the literature search strategy for the 2024 update.

Following the first meeting, we searched MEDLINE via PubMed, EMBASE, and the Cochrane Library for relevant randomized controlled trials (RCTs), observational studies, guideline publications, and meta-analyses. Although literature published from January 2018 to August 2023 (following the 2018 APLAR update) was prioritized, older literature was

revisited where relevant to the topic. Articles were assigned for review by Working Group members, who evaluated the evidence reported according to the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach, which classifies quality of evidence considering factors such as study limitations, inconsistency of results, imprecision, and reporting bias, and classifies recommendations as "strong" or "weak" depending on evidence quality and uncertainty of the balance of benefit versus risk, variability in values, and other factors [7].

In the second and third meetings, the Working Group presented and discussed published evidence to ascertain its relevance to the 2024 guideline update. Using the GRADE approach, the strength of a recommendation and quality of evidence ("very low," "low," "moderate," and "high") were assigned grades to yield a single overall grade (Table 1) [8]. The Working Group drafted recommendation statements that were then refined during the meeting and in subsequent correspondence as the discussion of evidence continued. Using a modified Delphi technique, the voting group rated their agreement with each recommendation on a five-point Likert scale (5, strongly agree; 4, agree; 3, neither agree nor disagree; 2, disagree; 1 strongly disagree); agreement (i.e., "strongly agree" or "agree") by 75% of all voting members was defined as the threshold for accepting a statement.

Following the third meeting, a voting group, comprising country representatives nominated by the national rheumatology associations within APLAR, was convened. After the meeting, online discussions were used to finalize the wording of each statement, and a further confirmatory vote was taken using the same Likert scale and agreement threshold as used in earlier rounds of evaluation.

TABLE 1 | Meaning of GRADE levels for quality of evidence.

GRADE	Quality	Meaning
A	High	We are very confident that the true effect lies close to that of the estimate of the effect
B	Moderate	We are moderately confident in the effect estimate The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
C	Low	Our confidence in the effect estimate is limited The true effect may be substantially different from the estimate of the effect.
D	Very low	We have very little confidence in the effect estimate The true effect is likely to be substantially different from the estimate of the effect

Note: Reproduced from Balshem et al. [8].

3 | Results

Fourteen statements achieved the threshold for consensus. Table 2 presents each statement with its level of agreement (percentage of experts responded "strongly agree" or "agree" during evaluation), overall GRADE, strength of recommendation (1, strong; 2, weak), and a discussion of the supporting evidence follows below.

3.1 | Monitoring

Statement 1. *Assessing disease activity and safety before initiating therapy and monitoring during therapy, preferably every 1–3 months, is recommended.*

Agreement: 100%; GRADE: A (High); Strength: 1 (Strong)

In alignment with other expert groups [5, 9, 10] we recommend that disease activity be monitored at 1 to 3-monthly intervals. This is a slightly modified version of Statement 5 in the 2015 APLAR guidance that recommended 1–3 monthly monitoring for all patients with recently diagnosed RA or active disease [5]. For patients with higher disease activity, shorter monitoring intervals (e.g., monthly monitoring) are preferable.

Evidence supporting this recommendation is found in several key studies. A pooled analysis of SDAI and CDAI scores from clinical trials concluded that patients treated with bDMARDs and/or MTX who did not achieve a minor response (SDAI 50%) at 3 months were highly unlikely to achieve treatment targets by 6 months [11], showing the importance of early and frequent monitoring.

Additional evidence is found in a randomized study comparing two strategies: a conventional MTX treatment approach (clinic visits, assessments and dose adjustments every 3 months) and an intensive approach with monthly intervals [12]. More patients in the intensive group achieved a period of remission compared with the conventional group during the 2-year study period (76 [50%] vs. 55 [37%], respectively; $p = 0.03$) [12].

Further evidence of the benefits of early and frequent monitoring is found in the BeSt Study. In this study, patients were randomized to four groups: sequential DMARD monotherapy, step-up combination therapy, initial combination therapy with tapered high-dose prednisone, or initial use of the TNF inhibitor infliximab, with all groups having treatment adjustments at 3-monthly intervals [13]. Although patients in the initial combination and infliximab groups experienced earlier functional improvement than the other groups ($p < 0.001$), there was marked improvement in disease activity across all four groups [13]. Overall, 32% of patients achieved remission (DAS44 of < 1.6) at the end of the first year, which the investigators attributed to frequent monitoring and treatment adjustments [13].

TABLE 2 | Summary of recommendations.

Statement	Agreement	GRADE	Strength
1. Assessing disease activity and safety before initiating therapy and monitoring during therapy, preferably every 1–3 months, is recommended	100%	A (High)	1 (Strong)
2. A validated and practical standardized measure of disease activity should be routinely performed to measure disease activity and to assess patients' response to treatment	100%	B (Moderate)	1 (Strong)
3. Methotrexate should be initiated at a dose of 7.5–15.0 mg/week and rapidly escalated to the maximum tolerated and effective dose as needed. In the case of methotrexate intolerance, other csDMARDs may be considered	95%	B (Moderate)	2 (Conditional)
4. Oral glucocorticoids may be considered for the control of active rheumatoid arthritis as a bridging therapy together with csDMARDs at a dose of less than 7.5 mg/day for prednisolone or equivalent and should be tapered and discontinued as soon as possible	95%	B (Moderate)	1 (Strong)
5. In patients who have an inadequate response to methotrexate monotherapy without poor prognostic factors, the addition of other csDMARDs such as sulfasalazine and/or hydroxychloroquine may be considered	100%	B (Moderate)	2 (Conditional)
6. A b/tsDMARD should be promptly considered without delay in patients with poor prognostic factors and inadequate response to csDMARDs, as well as in those with csDMARD intolerance	100%	A (High)	1 (Strong)
7. Patients who do not achieve remission or low disease activity with b/tsDMARD therapy are recommended to switch to another b/tsDMARD, preferably with a different mechanism of action	100%	B (Moderate)	1 (Strong)
8. b/tsDMARDs are most effective when combined with a csDMARD, particularly methotrexate. For patients intolerant to csDMARDs, an IL-6 pathway inhibitor or a tsDMARD may be preferred for monotherapy. Additionally, some TNF inhibitors are approved for monotherapy and may be considered	100%	B (Moderate)	1 (Strong)
9. After achieving sustained remission for at least 6–12 months, tapering of cs/b/tsDMARDs may be considered following glucocorticoid withdrawal	100%	A (High)	1 (Strong)
10. cs/b/tsDMARDs may be tapered to the lowest effective dose	100	B (Moderate)	1 (Strong)
11. If vaccination is required during treatment, temporary discontinuation of methotrexate and delayed administration of rituximab for 1–2 weeks after vaccination may be considered if disease activity allows	95%	B (Moderate)	2 (Conditional)
12. Screening and management of tuberculosis, hepatitis B and hepatitis C infections are recommended before initiating any DMARD treatment, following national guidelines. Patients with active or chronic infections should be referred to the appropriate specialists	100%	A (High)	1 (Strong)
13. Surveillance is necessary for detecting malignancy and assessing the risk of cardiovascular disease	90%	B (Moderate)	2 (Conditional)
14. Patients with rheumatoid arthritis who are pregnant or planning pregnancy and require medical therapy should continue or switch to pregnancy compatible DMARDs to control disease activity	100%	B (Moderate)	2 (Conditional)

Note: Agreement is the percentage of respondents who replied "strongly agree" or "agree" during evaluation.
Abbreviations: b, biologic; cs, conventional synthetic; DMARD, disease-modifying antirheumatic drug; IL-6, interleukin 6; LoE, level of evidence; TNF, tumor necrosis factor; ts, targeted synthetic.

Frequent monitoring may also help reduce the burden of RA on the healthcare system in the long-term. In an extension study of a randomized trial comparing RA patients with "direct access" (reviews initiated at patient request with access to a rheumatologist within 10 working days and immediate access to advice from nurses) to usual practice (3- or 6-monthly reviews), the direct access group had 38% fewer hospital appointments over 6 years [14].

In some areas of the AP region, geographical access to rheumatology centers may pose a challenge to frequent monitoring. However, the COVID-19 pandemic has accelerated the adoption

of telemedicine in rheumatology, and APLAR recommendations regarding its use have been published [15].

Statement 2. *A validated and practical standardized measure of disease activity should be routinely performed to measure disease activity and to assess patients' response to treatment.*

Agreement: 100%; GRADE: B (Moderate); Strength: 1 (Strong)

This is a reiteration of the recommendation in APLAR's 2015 guidelines (Statement 6), with a minor wording update to emphasize that validated disease measures should be used [5].

A diverse and growing evidence base supports the routine use of disease activity scores in clinical practice, and the selection of a particular score can be made based on the local resources (e.g., for biomarker testing), and healthcare professionals' (HCP) and patients' preferences. Developments in digital health tools allow increased disease monitoring to be achieved without increasing clinic visits. A study comparing standard monitoring during clinic visits and "connected monitoring," using a smartphone and self-assessed disease scores, found the latter could reduce the number of HCP visits versus conventional monitoring in patients initiating a new DMARD [16]. Patients in the conventional and connected monitoring groups had similar rates of low disease activity (Disease Activity Score using 28 joint counts; DAS28 ≤ 3.2, 62.8% vs. 59.1%, respectively) or remission (DAS28 < 2.6, 46.5% vs. 36.4%) at 6 months [16].

Evidence from randomized controlled trials (RCTs) also demonstrates the benefits of planned monitoring. In a randomized 24-week study, scheduled measurement of DAS28 was associated with more DMARD adjustments and a higher proportion of patients achieving a DAS28 score of ≤ 3.2 versus standard care (31% vs. 16%, respectively; $p = 0.028$) [17]. Similarly, the randomized Tight Control of Rheumatoid Arthritis (TICORA) study showed that intensive management, which included monthly assessments of a validated disease activity score, led to greater improvements in disease activity, radiographic progression, physical function and quality of life compared with patients receiving routine care [18].

A limitation of some widely-used disease scores (e.g., DAS28, simplified disease activity index [SDAI] and clinical disease activity index [CDAI]) is their non-specificity or inclusion of subjective measures of disease activity [19]. The multi-biomarker disease activity (MBDA) is an objective measure of disease activity for RA patients designed to complement these conventional measures [19], and a systematic review and meta-analysis showed the MBDA correlates with many conventional scores and is a reliable prognostic marker of radiographic progression [19]. Additionally, patients' perceptions of their disease severity are important. A study examining multiple disease activity measures in relation to patients' perceptions of their own symptomatic status (patient acceptable symptom state; PASS) found that the CDAI demonstrated the best performance regarding PASS [20].

Overall, these data emphasize the fundamental role of regular disease activity measurement during RA therapy. The use of biomarker-based disease activity scores such as MBDA may not be practical in resource-limited settings. In these settings validated composite disease activity indices that do not need laboratory markers, e.g., the CDAI, can suffice [5]. Additionally, in resource-limited settings with limited access to rheumatologists, rheumatology nurses can play a key role in patient education and monitoring. A randomized study of stable RA patients in Hong Kong found that nurse-led consultation was non-inferior to rheumatologist consultation and had high patient satisfaction [21].

3.2 | Use of csDMARDs

Statement 3. *Methotrexate should be initiated at a dose of 7.5–15.0 mg/week and rapidly escalated to the maximum tolerated and effective dose as needed. In the case of methotrexate intolerance or contraindication, other csDMARDs may be considered.*

Agreement: 95%; GRADE: B (Moderate); Strength: 2 (Conditional)

Methotrexate remains the first line of therapy for treatment-naïve patients in agreement with the APLAR 2015, APLAR 2018 and other guidelines [5, 6, 9, 22]. This statement merges statements 17 and 18 of the APLAR 2015 guidance which note MTX as an "anchor drug" [5]. Additionally this revised version is more detailed than a similar recommendation in Statement 1 of the 2018 update and now includes a suggested dose [6]. The utility of MTX monotherapy as an initial RA therapy is supported by a meta-analysis of studies comparing MTX monotherapy to MTX-containing DMARD combinations, that revealed that oral MTX monotherapy had a 40.5% response rate for achieving American College of Rheumatology 50% response (ACR50) in MTX-naïve patients, (vs. 61.2% for MTX + SSZ + HCQ) [23]. The expected radiographic progression for patients on MTX monotherapy was 2.34 points over 1 year (below the minimal clinically important difference of 5 units on the Sharp-van der Heijde scale), with a withdrawal rate due to AEs of 76 per 1000 patients within that time frame [23].

Evidence from systematic reviews supports the initiation of oral MTX at a dose of 15 mg/week and escalating to 25–30 mg/week (or the highest tolerated dose) [24, 25]. The efficacy and tolerability of MTX appear to be independent of the route of administration or whether the oral doses of MTX are split [26]. Furthermore, rapid dose escalation (5 mg every 2 weeks) from 15 to 25 mg/week is not associated with significant efficacy or tolerability differences compared with slower escalation (5 mg every 4 weeks), with the exception of more frequent gastrointestinal adverse events (AE) during the initial 8 weeks of rapid escalation (40% vs. 27%; $p = 0.048$) [27]. Parenteral administration is an option for patients with poor response or intolerance to oral MTX [24–26].

Statement 4. *Oral glucocorticoids may be considered for the control of active rheumatoid arthritis as a bridging therapy together with csDMARDs at a dose of less than 7.5 mg/day for prednisolone or equivalent and should be tapered and discontinued as soon as possible.*

Agreement: 95%; GRADE: B (Moderate); Strength: 1 (Strong)

This statement merges Statements 13, 14 and 15 of the 2015 APLAR guidance [5], and is in agreement with other expert groups [9, 28–30], we suggest oral glucocorticoids be considered as a bridging therapy in combination with a DMARD to manage disease. The recommendation against oral glucocorticoid monotherapy included in the 2015 APLAR recommendations has not been reiterated here [5], but is implicit in this statement. Glucocorticoids can delay both the onset and progression of joint damage [31]. Therefore, a short course of glucocorticoid therapy (i.e., 3–6 months) may be appropriate for managing disease flares in adults with recent onset or established disease. This approach can rapidly reduce inflammation while waiting for the effects of a newly initiated csDMARD regimen [31, 32]. However, a notable exception to this approach is that the 2021 ACR guidelines strongly recommend initiating csDMARDs without the use of longer-term (≥ 3 months) glucocorticoids in DMARD-naïve patients with moderate-to-high disease activity [22].

Different regimens and routes of administration can be employed for glucocorticoid therapy, but they should always be tapered and discontinued as soon as possible [9, 31]. The European Alliance of Associations for Rheumatology (EULAR) guidelines emphasize that csDMARDs and bDMARDs should be used to avoid chronic glucocorticoid therapy [9].

The efficacy of adding glucocorticoids to DMARDs is supported by multiple randomized studies [33, 34], with the GLORIA trial and CareRA being two notable examples [35]. The flexibility of glucocorticoid regimens is exemplified in CareRA, which included randomized groups representing all three COBRA (Combination therapy for early RA) regimens and a "tight step-up" regimen [36]. The COBRA-Slim regimen (MTX combined with glucocorticoid bridging) provided the best balance between efficacy and safety [36], but all regimens combining DMARDs with glucocorticoids proved effective for patients with early RA up to 2 years [36].

A post hoc analysis of phase 3 studies suggests that glucocorticoids should not be added to tofacitinib therapy due to a lack of efficacy [37], and emerging data from two small studies suggest that tofacitinib can be used as a steroid-sparing agent, allowing glucocorticoids to be discontinued in up to 30% of patients [38, 39].

Long-term use of glucocorticoids should be avoided due to their AE profiles, namely the risk of infections, fractures and cardiovascular (CV) events [9, 34, 40, 41]. The risk of infections associated with glucocorticoid use is influenced by both the dose and duration of use [34, 42], and is of particular relevance to rheumatologists in the AP region, given the high prevalence of tuberculosis and hepatitis in some countries [43, 44]. Although daily prednisone doses of ≤ 4 mg or with shorter cumulative doses and durations do not appear to be associated with increased CV risk, such risks are associated with daily doses ≥ 5 mg and increase with cumulative dose and duration of use [45]. Results from a multicenter, double-blind, placebo-controlled RCT compared the effects of high (60 mg/day) and low (10 mg/day) doses of prednisolone as short-term bridging strategies in active early RA. This study showed no benefit from short-term glucocorticoid bridging therapy on the progression of radiographic damage after 1 year at either dose [46]. A retrospective observational study that compared daily and alternate-day dosing of adjunctive glucocorticoid treatment concluded that alternate-day dosing is preferable to daily dosing to minimize AEs [47].

Statement 5. *In patients who have an inadequate response to methotrexate monotherapy without poor prognostic factors, the addition of other csDMARDs such as sulfasalazine and/or hydroxychloroquine may be considered.*

Agreement: 100%; GRADE: B (Moderate); Strength: 2 (Conditional)

The addition of another csDMARD to MTX, namely SSZ and/or HCQ, in patients with inadequate response to MTX monotherapy is an evolution of the principles of Statement 18 of the 2015 and Statement 2 of the 2018 APLAR guidelines, which recommend switching patients who cannot tolerate MTX to other csDMARDs and is consistent with guidance from other expert groups [5, 6, 9, 22].

This approach is supported by an RCT comparing the addition of glucocorticoids to MTX + HCQ against the addition of placebo [33]. Although the glucocorticoid group experienced a more rapid decrease in the DAS28-ESR score, both groups achieved similar scores by month 12 [33]. Additionally, there was no statistically significant difference between the two groups, which were defined as a DAS28-ESR < 2.6 (62.5% remission in the glucocorticoid group vs. 55% in the placebo group) [33]. Further support for intensifying MTX therapy with the addition of csDMARDs comes from a meta-analysis of 158 RCTs that compared MTX monotherapy with MTX-containing DMARD combinations [23]. For patients with an inadequate response to MTX, the addition of HCQ, SSZ or both resulted in probabilities of achieving an ACR50 response of 56.6%, 26.7% and 60.5%, respectively, compared with 12.7% for MTX alone [23]. Moreover, a change in radiographic progression over 1 year was 0.70 points for the combination of MTX + HCQ and SSZ compared with 3.35 points for MTX alone [23].

3.3 | Use of Targeted Therapies

Statement 6. *A b/tsDMARD should be promptly considered without delay in patients with poor prognostic factors and inadequate response to csDMARDs, as well as in those with csDMARD intolerance.*

Agreement: 100%; GRADE: A (High); Strength: 1 (Strong)

This statement recapitulates Statement 7 of APLAR 2018 and Statement 26 of APLAR 2015, both of which recommend targeted b/tsDMARD initiation in patients with poor response or intolerance of csDMARDs and Statement 27 of APLAR 2015 which endorses "early" bDMARD use in patients with active disease and poor prognostic factors [5, 6]. Poor prognostic factors typically includes persistently high disease activity (after csDMARDs), autoantibody positivity, early presence of erosions, failure of ≥2 csDMARDs, among others [9, 48]. Initiating b/tsDMARD treatment in patients with an intolerance or poor response to csDMARD therapy, as defined by a treat-to-target goal, aligns with recommendations from other expert groups and may be preferable to triple csDMARD therapy [9, 22]. High-quality evidence for this statement comes from two systematic reviews and a meta-analysis that included only RCTs [49, 50].

The meta-analysis by Wang et al. reviewed 20 RCTs evaluating JAK inhibitors (tofacitinib, $n=12$, baricitinib $n=5$ or upadacitinib $n=3$) in patients with inadequate response to other DMARDs [49]. Compared with placebo, treatment with JAK inhibitors significantly increased the ACR20 response rate (relative risk [RR] 2.03; 95% confidence interval [CI] 1.87 to 2.20; $p<0.001$) and resulted in lower Health Assessment Questionnaire-Disability Index (HAQ-DI) scores (mean difference 0.31; 95% CI 0.34 to 0.28; $p<0.001$) [49]. Further support is provided by a network meta-analysis by Weng et al. that included 88 RCTs of RA patients who had an inadequate response to csDMARDs [50]. Patients in this analysis received targeted therapy, either JAK inhibitors or bDMARDs [50]. All targeted therapies assessed were found to be significantly superior to placebo for ACR20 response rates (odds ratios [ORs] from 3.05 to 5.61), and HAQ-DI scores (weighted mean differences from −0.34 to −0.21) [50].

Statement 7. *Patients who do not achieve remission or low disease activity with b/tsDMARD therapy are recommended to switch to another b/tsDMARD, preferably with a different mechanism of action.*

Agreement: 100%; GRADE: B (Moderate); Strength: 1 (Strong)

Switching from one targeted therapy to another with a different mechanism of action in patients who fail to respond is a concept endorsed in multiple guidelines [6, 9, 22, 28]. This statement is an evolution of Statement 33 of the 2015 APLAR guidance and Statement 12 of the APLAR 2018 guidance, but explicitly adds the preference for different mechanism of action [5, 6].

A systematic review informing the 2019 EULAR update reinforces that in patients with an inadequate response to TNF inhibitors or other bDMARDs, both tsDMARDs and bDMARDs (from the same or different class) generally result in a similar efficacy [51]. Some studies indicate moderate improvements in efficacy from switching within the same class—referred to as "cycling." For example, in the EXXELERATE study, patients with an inadequate response to MTX were randomized to certolizumab pegol or adalimumab, both in addition to MTX [52]. Patients had the option to cycle between these TNF inhibitors at week 12 if they had an inadequate response to the first treatment [52]. Among those who did so, 58% of those cycled to certolizumab pegol and 62% of patients cycled to adalimumab, showed a DAS28 ESR reduction of ≥1.2 points at 12 weeks [52]. Another positive example of cycling is EXTEND, an extension of the ASCERTAIN study, which evaluated switching from intravenous (IV) tocilizumab to subcutaneous (SC) sarilumab (both anti-IL-6 agents) [53]. Patients who cycled in this study maintained clinical efficacy to 96 weeks, and no new safety concerns were noted [53].

A broader evidence base, comprising multiple RCTs, supports the benefits of switching between different classes of targeted therapy. In an RCT involving 300 patients with inadequate response to TNF inhibitors, a higher proportion of patients achieved a good or moderate EULAR response when randomized to a non-TNF-targeted bDMARD compared with those who cycled to a second anti-TNF agent (odds ratio [OR] 2.06; 95% CI 1.27 to 3.37; $p=0.004$) [54] Similarly, the SARIL-RA-TARGET RCT confirmed that that switching to sarilumab after inadequate response to TNF inhibitors improved the signs and symptoms of RA and physical function [55]. In SELECT-COMPARE, switching from upadacitinib to adalimumab or vice versa helped patients achieve meaningful clinical responses after inadequate response to their first alternative [56]. In SELECT-CHOICE, patients with RA and inadequate response to bDMARDs were randomized to upadacitinib or abatacept, and greater improvements in 12-week DAS28-CRP at week 12 were seen with upadacitinib (−2.52 vs. −2.00), respectively (difference, −0.52; 95% CI −0.69 to −0.35; $p<0.001$ [superiority]) [57].

High-quality evidence for the timing of switching is lacking, but other guideline publications have suggested 6 months as an appropriate time point [6, 28]. Similarly, evidence on whether patients with inadequate response to JAK inhibitors should be switched within this class or to other classes of agents is limited to observational studies [58–60].

Statement 8. *b/tsDMARDs are most effective when combined with a csDMARD, particularly methotrexate. For patients intolerant to csDMARDs, an IL-6 pathway inhibitor or a tsDMARD may be preferred for monotherapy. Additionally, some TNF inhibitors are approved for monotherapy and may be considered.*

Agreement: 100%; GRADE: B (Moderate); Strength: 1 (Strong)

This statement is an evolution of Statement 8 of APLAR 2018, which noted that all targeted therapies are equally effective when combined with MTX or csDMARDs [6], and Statement 31 of APLAR 2015 that noted while bDMARD monotherapy is an option, bDMARDs are most effective when combined with MTX [5]. It is also similar to Statement 9 of the EULAR 2022 update which suggests the use of IL-6 inhibitors and tsDMARD in patients who cannot use csDMARDs as a comedication [9]. Core evidence for this guidance is found in three meta-analyses and five RCTs. Two of the meta-analyses assessed the effectiveness of bDMARDs or tofacitinib combined with csDMARDs (mostly MTX), with ACR50 as the primary outcome for both [61, 62].

The analysis of Donahue et al. included 22 studies that compared TNF inhibitors +MTX or non-TNF-directed biologics + MTX with biologic monotherapy in patients with early RA [61]. Combination therapy—either adalimumab +MTX or etanercept + MTX—consistently outperformed biologic monotherapy. Relative risks for ACR50 response were 1.52 (95% CI 1.28–1.80) for adalimumab + MTX versus adalimumab monotherapy and 1.57 (95% CI 1.23–2.02) for etanercept versus etanercept monotherapy [61]. Similar results were seen in comparisons of abatacept + MTX with abatacept monotherapy and tocilizumab + MTX with tocilizumab monotherapy [61].

In the second meta-analysis, the patient population had been treated with MTX or other DMARDs, and interventions included all bDMARDs + MTX/csDMARD vs. comparator (MTX/csDMARD/placebo) [62]. In this analysis, bDMARDs + MTX/csDMARD was associated with a significant and meaningful ACR50 improvement versus the comparator (RR 2.71; 95% CI 2.36 to 3.10) [62]. In a network meta-analysis of phase 3 RCTs that compared adalimumab to other targeted therapies in combination with MTX [63], surface under the cumulative ranking curve (SUCRA) analysis found that upadacitinib + MTX, baricitinib + MTX, and tofacitinib + MTX rated highest for the likelihood of ACR50 response [63].

Additional evidence for anti-IL-6 agents as monotherapy or in combination with csDMARDs can be found in four RCTs conducted in patients with inadequate response to MTX or TNF inhibitors [55, 64–66]. These studies included SARIL-RA-TARGET, which demonstrated that sarilumab + csDMARDs leads to a higher achievement of ACR20 compared with csDMARDs alone [55]; KAKEHASI, which reported improved ACR20 achievement with sarilumab than with placebo [66]; SURPRISE, which compared adding tocilizumab to MTX with switching from MTX to tocilizumab [67]; and CREDO 1 and CREDO 3 studies showed better ACR20 responses with olokizumab compared with MTX [64, 65].

Statement 9. *After achieving sustained remission for at least 6–12 months, tapering of cs/b/tsDMARDs may be considered following glucocorticoid withdrawal.*

Agreement: 100%; GRADE: A (High); Strength: 1 (Strong)

Statement 10. *cs/b/tsDMARDs may be tapered to the lowest effective dose.*

Agreement: 100%; GRADE B (Moderate); Strength: 1 (Strong)

This statement is a broader recommendation for tapering than those included in previous APLAR recommendations. Statement 10 of APLAR 2015 recommended gradual tapering of csDMARDs after 6–12 months of remission after discontinuation of non-steroidal anti-inflammatory drugs, corticosteroids and bDMARDs, and dose reduction or tapering of targeted therapy after > 12 months of remission of disease is suggested in the 2015 and 2018 APLAR guidelines (Statements 34 and 13, respectively) [5, 6] The ACR and EULAR guidelines also recommend tapering of cs/b/tsDMARDs after 6 months of sustained remission (or low disease activity in the ACR guidance) [9, 22]. The decision to taper should be based on a shared decision with the patient, following a clear discussion of the risk of relapse. In the systematic review informing the 2022 EULAR update, a review of 47 studies of cs/b/tsDMARDs concluded that tapering was feasible for some patients, provided that they remain in remission or low disease activity [68].

Several studies have evaluated dose reduction strategies in patients with RA. These include a single-center trial that enrolled patients with DAS28 remission for ≥ 6 months on etanercept 50 mg once weekly [69]. Patients were randomized to continue weekly treatment ($n = 34$) or change to etanercept 50 mg every other week (EOW, $n = 32$) [69]. After 6 months, 76% and 59% of patients in the weekly and EOW groups, respectively, maintained disease control, a difference that was not statistically significant ($p = 0.136$) [69]. A similar approach has been demonstrated in a study of patients with active RA despite csDMARD therapy or a single bDMARD who received tocilizumab 162 mg once weekly as monotherapy or with the csDMARD combination during a 24-week single-arm phase [70]. Patients achieving remission (DAS28 ≤ 2.8) at weeks 20 and 24 were then randomized to tocilizumab 162 mg weekly or Q2W for 24 weeks [70]. In the single-arm phase, 45% (n/N; 179/401) patients achieved remission, and of those randomized at week 24, 90% of patients in the weekly tocilizumab group and 73% in the Q2W group remained in remission at week 48 ($p = 0.004$) [70]. Although this difference was statistically significant, it demonstrated that some patients were able to sustain remission on a less frequent dose of tocilizumab [70]. Therefore, tocilizumab Q2W dosing may represent an option for selected patients who find weekly dosing impractical or unaffordable.

Evidence also supports dose reduction of rituximab. In the REDO RCT, patients with RA and good response to rituximab at standard doses were randomized to one dose of either 1000 mg ($n = 29$), 500 mg ($n = 58$) or 200 mg ($n = 55$) [71]. The per-protocol analysis found that the 500 mg dose was non-inferior to 100 mg at 3 months but not at 6 months, and intention-to-treat analysis at 6 months found that both 500 mg and 200 mg rituximab were non-inferior to 1000 mg [71]. The investigators concluded that a strategy of one ultra-low dose of rituximab with additional DMARDs in case of flare may be feasible in clinical practice.

For adalimumab, the phase 4 PREDICTRA study, in which patients were randomized from adalimumab Q2W to adalimumab tapering (Q3W, $n = 102$), or the withdrawal arms ($n = 20$) [72]. Disease flares were experienced by 36% of patients in the taper group compared with 45% in the withdrawal group, and rescue adalimumab could restore disease control in some, but not all cases [72]. A pooled analysis of two studies evaluating down-titration and discontinuation strategies for anti-TNF bDMARDs concluded that discontinuation slightly increased the mean DAS28 score after 28 to 52 weeks (mean difference 0.96; 95% CI 0.67 to 1.25), and in an analysis of 6 RCTs, the RR of persistent remission was between 0.16 and 0.77 [73].

In general, evidence suggests that a gradual tapering of the dose is a better approach than discontinuation in patients who are in remission. A meta-analysis of studies evaluating tapering of csDMARDs ($n = 4$ studies) or TNF inhibitor bDMARDs ($n = 15$) concluded that more than one-third of patients may

taper or stop treatment without experiencing a disease flare within the first year [74]. Notably, dose reduction of TNF inhibitor bDMARDs was associated with lower flare rates than discontinuation [74].

3.4 | Vaccination and Screening for Infections, Cardiovascular and Malignancy Risks

Statement 11. *If vaccination is required during treatment, temporary discontinuation of methotrexate and delayed administration of rituximab for 1–2 weeks after vaccination may be considered if disease activity allows.*

Agreement: 95%; GRADE: B (Moderate); Strength: 2 (Conditional)

Previous APLAR consensus statements have not considered the temporary suspension of therapies to permit vaccination. Statement 11 is similar to guidance from the ACR, which recommends holding MTX therapy for 1–2 weeks after influenza vaccination if disease activity allows [75]. Rituximab should ideally be administered at least 2 weeks after the influenza vaccine of other non-live vaccines.

This approach has demonstrated its utility with COVID-19 and influenza vaccines [76–79]. For example, in a randomized multicenter study in the UK, patients randomized to a 2-week suspension of MTX ($n = 191$) immediately prior to the administration of a SARS-CoV-2 booster vaccine showed a significantly higher antibody titer than those randomized to continuation of MTX ($n = 192$; Geometric mean ratio of antibody titer: 2.08; 95% CI 1.59 to 2.70; $p < 0.0001$) [76]. Similarly, a single-center randomized study in Brazil found that anti-SARS-CoV-2 S1/S2 IgG seroconversion rates were higher in RA patients who suspended MTX for 2 weeks ($n = 37$) after each vaccine dose compared with those who continued MTX ($n = 55$, 78.4% vs. 54.5%; $p = 0.019$) [77]. A randomized multicenter study has also demonstrated the effectiveness of a 2-week hold of MTX for improving vaccine responsiveness in RA patients receiving the seasonal influenza vaccine. Patients in the MTX-hold group ($n = 160$) achieved a higher rate of satisfactory vaccine response (assessed by increase in hemagglutination inhibition antibody titer at 4 weeks after vaccination) than those in the MTX continuation group ($n = 156$, 75.5% vs. 54.5%; $p < 0.001$) [78]. A subsequent randomized multicenter study by the same investigators found that a 1-week suspension of MTX after vaccination was non-inferior to a 2-week suspension for vaccine response as measured by hemagglutination assay ($N = 178$; 68.9% versus 75.0% with satisfactory response, respectively; $p = 0.364$) [79].

The administration of vaccines before rituximab treatment is supported by a study in Taiwan that found, compared with RA patients treated only with csDMARDs ($n = 86$), those receiving rituximab or abatacept ($n = 142$) exhibited significantly lower immune response to an mRNA SARS-CoV-2 vaccine ($p = 0.008$ and $p = 0.035$, respectively). This underscores the importance of completing vaccination prior to the initiation of rituximab to optimize immune response [80].

Statement 12. *Screening and management of tuberculosis, hepatitis B and hepatitis C infections are recommended before initiating any DMARD treatment, following national guidelines. Patients with active or chronic infections should be referred to the appropriate specialists.*

Agreement: 100%; GRADE: A (High); Strength: 1 (Strong)

Screening and management of tuberculosis (TB), hepatitis B virus (HBV) and hepatitis C virus (HCV) infections prior to initiation of DMARD treatment are endorsed in multiple guidelines including APLAR 2015 (Statements 35–37) and 2018 (Statement 5) [5, 6, 81].

Minimizing the risk of infections is a key consideration when using any DMARDs, and the evidence base for infection risk in patients treated with targeted therapy is expanding. A meta-analysis of 39 RCTs found that treatment of RA with bDMARDs, particularly TNF inhibitors, significantly increased the risk of TB compared to non-biologics (OR 3.86; 95% CI 2.36 to 6.32; $p < 0.001$) [82]. Trends towards increased risk with IL-6 inhibitors and JAK inhibitors were also noted but were not statistically significant [82]. Similarly, a nationwide cohort study in Taiwan reported a 1-year incidence rate of TB of 1.513% among RA patients initiating TNF inhibitor therapy, highlighting a significantly increased risk compared to patients treated with non-TNF inhibitors (adjusted hazard ratio [HR] 7.19; 95% CI 4.18 to 12.34) [83]. Cohort studies on TB risk in RA patients in South Africa and Brazil, showing increased risks of TB infections in patients treated with biologics, reinforce these findings [84, 85].

Data from cohort studies conducted in Taiwan and Korea provide additional insights into infection risk with TNF inhibitors or JAK inhibitors. In a nationwide Korean cohort, infliximab was associated with a higher risk of developing TB compared to etanercept, particularly in patients without evidence of latent TB infection [86]. Data on the risk of infection with JAK inhibitor use compared with bDMARDs is mixed. A cohort study from Korea found a significantly lower risk of active TB in JAK inhibitor users compared with bDMARD users, indicating potential differences in TB risk among targeted therapy classes [87]. Conversely, a different Korean cohort study compared infection risks in RA patients treated with JAK inhibitors or TNF inhibitors and found a higher incidence of opportunistic infections, including TB, in JAK inhibitor users [88].

The risk of HBV infection has also been assessed in this setting. A meta-analysis of 26 clinical and observational studies found an estimated HBV reactivation rate of 2.0% (95% CI 0.01 to 0.04) in patients treated with biologics or JAK inhibitors [89]. For HCV reactivation risk data are more reassuring. A retrospective study of 1548 patients with rheumatic diseases (35.3% with RA) treated with bDMARDs and csDMARDs reported that 25.5% tested positive for anti-HCV antibodies, but no hepatitis C reactivation was observed during biologic therapy [90]. Nonetheless, HCV screening is essential before initiation of DMARD treatment.

Overall, these studies underscore the importance of systematic screening patients for TB, HBV and HCV infection prior

to DMARD therapy. This is essential in the AP region where many countries have high endemicity [5, 6]. Patients with these infections should be referred to specialists for appropriate management to ensure their eligibility for treatment. More detailed discussion and guidance for screening and vaccination for infectious diseases including TB, HBV, HCV and herpes zoster in candidates for b/tsDMARD therapy can be found in the 2015 and 2018 updates to the APLAR guidelines [5, 6]. Additionally, physicians should refer to national vaccine recommendations for further guidance on this topic.

Statement 13. *Surveillance is necessary for detecting malignancy and assessing the risk of cardiovascular disease.*

Agreement: 90%; GRADE: B (Moderate); Strength: 2 (Conditional)

This statement is an evolution of our 2018 guidance to use targeted therapy with caution in patients with a history of solid tumors [6]. Reassuring data on these risks are found in a systematic review/meta-analysis of 20 RCTs in RA patients that assessed the safety of tofacitinib, baricitinib and upadacitinib, including trials of monotherapy and combination therapy [49]. Venous thromboembolic events were considered in three studies using only upadacitinib, and no increase in risk was detected [49]. Malignancies were considered in seven studies, and the overall incidence of serious malignancy was similar to placebo (RR 1.68; 95% CI 0.57 to 4.95; $p = 0.34$) [49]. This is in contrast to an analysis of the ORAL Surveillance RCT, in which 4362 patients with RA and ≥1 CV risk factor were randomized to receive tofacitinib 5 mg or 10 mg twice daily or TNF inhibitors [91]. Incidence rates for malignancies excluding non-melanoma skin cancer were higher with tofacitinib (individual doses and combined) than with TNF inhibitors (HR 1.48; 95% CI 1.04 to 2.09); this did not meet non-inferiority criteria (HR 95% CI upper limit < 1.8) for combined tofacitinib doses versus TNFi [91]. Furthermore, malignancy risk was highest in patients with a history of atherosclerotic CV disease risk factors, suggesting there may be shared risk factors for CV risks and cancer [91].

Screening of patients may help minimize risks associated with targeted therapy [92]. An analysis from an observational cohort study conducted in Japan found that computed tomography (CT) screening for malignancies before initiating targeted therapy was more effective than standard screening [92]. Among 2193 patients who underwent CT scans prior to b/ts/DMARD initiation, 33 patients (1.5%) were diagnosed with malignancy. This approach enabled earlier detection and treatment of malignancy compared with standard screening, ultimately improving the safety of targeted therapy [92].

Based on these studies we recommend that prior to the initiation of targeted therapy, patients should be thoroughly assessed for cardiovascular and malignancy risk factors. This is particularly relevant in the AP region where resources are limited in many countries. This should include a detailed clinical and family history, physical examination, blood tests and chest x-ray, with any abnormalities noted.

3.5 | Use of DMARDs During Pregnancy

Statement 14. *Patients with rheumatoid arthritis who are pregnant or planning pregnancy and require medical therapy should continue or switch to pregnancy compatible DMARDs to control disease activity.*

Agreement: 100%; GRADE: B (Moderate); Strength: 2 (Conditional)

Statement 16 of the 2018 APLAR update notes that TNF inhibitors (preferably etanercept or certolizumab) may be continued during pregnancy in patients whose disease cannot otherwise be controlled [6]. This updated statement is informed by a meta-analysis of 39 studies showed that an increased risk of preterm births (OR 1.45; 95% CI 1.16 to 1.82) and infections in newborns (OR 1.12; 95% CI 1.00 to 1.27) for women treated with TNF inhibitors for immune mediated inflammatory diseases, including inflammatory bowel disease ($n = 21$ studies), RA ($n = 5$), and psoriasis ($n = 1$) [93]. No significant differences were seen for caesarian sections, miscarriage, low birth weight, newborns small for gestational age and congenital malformations [93]. The binding affinity of an immunoglobulin G-based biologic to the neonatal Fc receptor (FcRn) is an important consideration as biologics are transferred across the placenta via the same mechanisms as maternal antibodies [94]. This binding affinity is highest for monoclonal IgG1 antibodies (infliximab, adalimumab, golimumab, rituximab), low for Fc fusion proteins (etanercept and abatacept), and insignificant for pegylated Fc-free molecules (e.g., certolizumab) [94].

The 2024 update from EULAR on the use of antirheumatic drugs in pregnancy notes that TNF inhibitors can be used throughout pregnancy [94]. Non-TNFi bDMARDs including abatacept, anakinra, belimumab, canakinumab, ixekizumab, rituximab, sarilumab, secukinumab, tocilizumab, and ustekinumab may be used if needed as current evidence suggests they do not increase the rate of adverse pregnancy outcomes [94].

4 | Discussion

This updated APLAR guideline intends to guide clinicians when choosing among the growing range of targeted therapies in clinical use in the AP region. The number of recommendations herein is decreased relative to the 2015 and 2018 APLAR updates [5, 6], as this report intends to complement rather than replace these earlier recommendations, and some statements have evolved due to expansion of the evidence base. The updated recommendation on baseline disease activity measurement before initiating any therapy has a clearer emphasis in this update, and we now include a precise dose of MTX in the statements, which was lacking in 2015 and 2018. In 2024, oral glucocorticoids are considered a bridging therapy and a dose and duration has been recommended (< 7.5 mg, for 3–6 months), whereas in 2015 the recommended dose was ≤ 7.5 mg and duration was up to 6 months [5]. In this update, tapering of any DMARD may be considered (following glucocorticoid withdrawal) after achieving sustained remission for at least 6–12 months, whereas in 2015

and 2018, the required duration for remission was 12 months [5, 6]. We also note in this update that csDMARDs may be tapered to the lowest effective dose, a topic not addressed in the 2015 and 2018 updates.

In the 2015 and 2018 update, initial combination csDMARDs were recommended for patients with moderate to high disease activity and poor prognostic factors [5, 6], whereas, whereas in 2024 this is recommended for only those without poor prognostic factors following inadequate response to MTX monotherapy. Our recommendations around the use of targeted therapies in patients with malignancy and CV risk have also evolved since the prior updates.

Although a substantial volume of new evidence has been published on therapy for RA in recent years, many questions remain. For example, head-to-head trials for many agents are unavailable, and although network meta-analyses provide some data, they must be interpreted with caution. Due to the cost of prospective randomized studies, other means of comparing agents must be considered, such as registries of patients treated with targeted therapies. The ANSWER cohort in Kansai, Japan is an example of this approach in the AP region [95].

Despite the growing range of targeted therapies, some patients remain refractory to treatment, and the growing range of therapeutic options may lead to the problem of "clinical inertia" where patients undergo disease progression while they switch between multiple targeted therapy options before identifying one that is effective. Studies that identify biomarkers or other predictors of response or refractoriness may help reduce this problem and may be of particular value in parts of the APAC region where some patients must self-fund therapy. There is also a need for additional safety data for all classes of DMARDs, particularly in special settings such as pregnancy.

The cost of newer agents such as bDMARDs and tsDMARDs remains a barrier in many parts of the AP region, where reimbursement is limited and many patients must self-fund these therapies. It is crucial that physicians can identify patients most likely to benefit from these therapies and optimize their use to ensure care is cost-effective. Data on generic csDMARDs and biosimilar DMARDs may help reduce cost barriers.

5 | Conclusions

This update to the APLAR guidelines revisited older evidence for recommendations and reviewed newer evidence, particularly for topics concerning targeted therapy. As always, these recommendations are general in nature and should always be individualized according to the judgment of the treating physician.

Author Contributions

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Ethics Statement

The authors have nothing to report.

Conflicts of Interest

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Data Availability Statement

This review draws solely on previously published sources. No new datasets were generated or discussed, and all referenced materials have been disclosed in the bibliography.

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ORIGINAL ARTICLE

Retention Rates of Biological Disease-Modifying Antirheumatic Drugs in Patients With Rheumatoid Arthritis and Reduced Kidney Function: Analysis From the IORRA Cohort

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ABSTRACT

Introduction: To compare the retention rate, hazard ratio of treatment discontinuation, and effectiveness of tumor necrosis factor inhibitor (TNFi), interleukin-6 inhibitor (IL-6i), and cytotoxic T lymphocyte-associated antigen-4-Ig (CTLA4-Ig) in patients with rheumatoid arthritis (RA) and reduced kidney function.

Methods: We analyzed data from patients with RA and reduced kidney function included in the large-scale, real-world observational cohort study in Japan. Patients who initiated treatment with biological disease-modifying antirheumatic drugs (bDMARDs) between 2003 and 2018 were selected. Reduced kidney function was defined as an estimated glomerular filtration rate of $<60\,mL/min/1.73\,m^2$. Drug retention, disease activity, and physical function were compared during the observational period using inverse probability of treatment weighting (IPTW).

Results: The study included 154 patients with 237 treatment courses. The overall drug retention rate was 54.6% at 3 years, while the individual rates of TNFi, IL-6i, and CTLA4-Ig were 54.9%, 61.1%, and 44.3%, respectively. Retention rates due to ineffectiveness were 72.4%, 67.7%, and 49.3%, and due to adverse drug reactions were 76.2%, 90.3%, and 89.9%, respectively. Adjusted hazard ratios of discontinuation were 0.85 (95% confidence interval [CI], 0.37–1.96) for IL-6i and 1.31 (95% CI, 0.63–2.73) for CTLA4-Ig compared to TNFi. After IPTW, mean scores for the clinical disease activity index and the Japanese version of the health assessment questionnaire at 3 years were similar across the three groups.

Conclusion: The drug retention rates and effectiveness of bDMARDs with different modes of action were comparable in patients with RA and reduced kidney function.

1 | Introduction

Advances in treatment strategies and development of targeted drugs have led to improved clinical outcomes in patients with rheumatoid arthritis (RA) [1]. Specific interest has been shown in optimizing the treatment for refractory RA, referred to as difficult-to-treat RA (D2TRA) [2]. D2TRA develops because of factors such as the ineffectiveness of drugs with multiple modes

of action, comorbidities, non-inflammatory pain, and financial issues of patients [3], and sometimes can be prevented through treatment optimization. This is particularly important for patients with comorbidities, primarily because the risks of disease-modifying antirheumatic drugs (DMARDs) in such patients are unclear, often leading to less ambitious treatment targets and inadequate intensity.

Chronic kidney disease (CKD) is one of the most common comorbidities among patients with RA. A Japanese multicenter registry demonstrated that 18.5% of patients with RA have reduced kidney function, equivalent to an estimated glomerular filtration rate (eGFR) of $<60\,mL/min/1.73\,m^2$ [4]. CKD is associated with various unfavorable clinical outcomes and patients with RA and reduced kidney function have an increased risk of mortality, cardiovascular events, and hospitalized infections [5–7]. Moreover, a vicious cycle exists in which high disease activity is linked to the deterioration of kidney function [8]. An anchor drug, methotrexate (MTX), is contraindicated or used with caution for patients with reduced kidney function, and the same applies to most conventional synthetic DMARDs and Janus kinase inhibitors [9]. Meanwhile, the pharmacokinetics of biological DMARDs (bDMARDs) are less affected by renal clearance and have been reported to reverse eGFR reduction [10]. This suggests that bDMARDs may be safe and effective for patients with RA and reduced kidney function [11]; however, evidence that supports the usefulness of bDMARDs in this patient population is insufficient.

High-quality evidence related to RA treatment has mostly been derived from the results of randomized controlled trials (RCTs). Patients meeting the inclusion criteria for RCTs represent a minority of real-world patients [12], and individuals with moderately to severely reduced kidney function are not typically included. Therefore, research involving such patients usually relies on observational studies using real-world data [11, 13].

The aim of this study was to compare bDMARDs with three different modes of action, namely tumor necrosis factor inhibitor (TNFi), interleukin-6 inhibitor (IL-6i), and cytotoxic T lymphocyte-associated antigen-4-Ig (CTLA4-Ig), in patients with RA and reduced kidney function. We analyzed the retention rates of bDMARDs and hazard ratios (HRs) for their discontinuation, along with the changes in disease activity and physical function 3 years after treatment initiation. Inverse probability of treatment weighting (IPTW) was used to balance the groups for the analysis.

2 | Methods

2.1 | Patients and Data Collection

This retrospective study used data from the Institute of Rheumatology, Rheumatoid Arthritis (IORRA) cohort. The IORRA cohort is a single-center, large-scale, longitudinal study conducted at the Institute of Rheumatology, Tokyo Women's Medical University, which has been enlisting eligible patients with RA since 2000 [1]. The IORRA cohort study was approved by the Ethics Committee of Tokyo Women's Medical University (approval no. 2922-R16) and performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from participants. Details regarding the methodology and purpose of the IORRA cohort have been previously reported [14, 15]. We enrolled patients with RA and reduced kidney function who commenced treatment with bDMARDs from April 2003 to October 2018. Use of bDMARD was identified based on the IORRA cohort data and confirmed using medical records. Data from the IORRA survey immediately before the initiation of bDMARDs were used as the baseline values. All patients met either the 1987 RA Classification Criteria of the American College of Rheumatology (ACR) [16] or the 2010 RA Classification Criteria of ACR/EULAR [17]. The decision to initiate bDMARDs was made by the attending physician. The following data were collected from the IORRA cohort: age, sex, disease duration, body mass index (BMI), rheumatoid factor (RF) positivity, anti-citrullinated peptide antibody (ACPA) positivity, disease activity score 28-joint count using erythrocyte sedimentation rate (DAS28-ESR), clinical disease activity index (CDAI), simplified disease activity index (SDAI), Japanese version of the health assessment questionnaire (J-HAQ) score, eGFR calculated using creatinine, MTX use and dose, glucocorticoid use and dose (converted to prednisolone [PSL]–equivalent dose), previous medical history, comorbidities, and frequency of previous bDMARD use. The index month was defined as the month of bDMARD initiation. The index and discontinuation months of bDMARDs were confirmed using medical records. The observation period was defined as the period from the index month to the early stage of bDMARD discontinuation or 36 months. The observational period was set at 36 months because the reasons for discontinuation in our study may differ before and after 36 months. The bDMARDs were categorized as TNFi, IL-6i, and CTLA4-Ig. Data that could not be collected from medical records at Tokyo Women's Medical University Hospital were not supplemented from other sources.

2.2 | eGFR Calculation and Definition of Reduced Kidney Function

eGFR was calculated using the Japanese equation {eGFR = 194× [serum creatinine levels (mg/dL)] − 1.094 × [age (years)] − 0.287 for men; eGFR = 194 × [serum creatinine levels (mg/dL)] − 1.094 × [age (years)] − 0.287 × 0.739 for women} [18]. Reduced kidney function was defined as eGFR $<60\,mL/min/1.73\,m^2$, calculated using data collected immediately before the initiation of bDMARDs. To avoid including patients with transient renal function decline, we excluded those for whom eGFR $<60\,mL/min/1.73\,m^2$ was not recorded at least once, in addition to the baseline measurement, within 6 months before or after baseline. Therefore, a subgroup analysis was conducted on the population with eGFR $<45\,mL/min/1.73\,m^2$.

2.3 | Outcomes

The primary outcome was the drug retention during 36 months. Reasons for discontinuation were categorized as ineffectiveness, adverse drug reactions, patient preference, remission, and others. Patient preference included discontinuation due to financial reasons or the desire to become pregnant. “Others” included reasons for discontinuation that were not included in the

previous categories, such as adverse events not directly related to bDMARDs or transfer to another hospital. The classification was performed by a rheumatologist (TH) based on medical records. Temporary discontinuation or re-treatment with the same bDMARDs was not defined as discontinuations. Overall drug retention rates were analyzed based on discontinuation owing to insufficient effectiveness, adverse drug reactions, or a combination of both, whereas discontinuations for other reasons were treated as censored. The secondary outcomes were CDAI and J-HAQ scores at the points of 1, 2, and 3 years after initiation of bDMARDs. These outcomes were compared among patients treated with TNFi, IL-6i, and CTLA4-Ig. We also conducted subgroup analyses. In general, patients with eGFR <45 mL/min/1.73 m^2 are considered to have an increased risk of mortality due to cardiovascular disease, infection, and progression to end-stage renal disease, compared to those with eGFR ≥ 45 mL/min/1.73 m^2 [7, 19, 20]. Additionally, concomitant MTX use and prior bDMARD failure may affect bDMARD retention. In the subgroup analyses, patients were stratified by eGFR <45 mL/min/1.73 m^2, MTX use, and prior bDMARD use, and the drug retention over 36 months was compared among the TNFi, IL-6i, and CTLA4-Ig groups.

2.4 | IPTW

To adjust for confounding factors in the baseline characteristics, we used IPTW to compare retention, disease activity, and physical function over 3 years among the TNFi, IL-6i, and CTLA4-Ig groups. For the analysis of disease activity and physical function, we enrolled patients who initiated bDMARDs from 2011 onward because CTLA4-Ig was approved in Japan in the fall of 2010. Generalized propensity scores for multi-category treatments were calculated using the covariate balancing propensity score method [21]. The following factors were used to model the propensity score: time period at enrollment, sex, age, disease duration, previous bDMARD use, history of lung disease, BMI, DAS28-ESR, SDAI, CDAI, J-HAQ score, RF positivity, ACPA positivity, eGFR, serum C-reactive protein levels, MTX use, and PSL use.

2.5 | Statistical Analysis

Continuous variables are expressed as mean ± standard deviation (SD). Categorical variables are expressed as numbers and percentages. HRs for drug retention with 95% confidence intervals (CI) were calculated using the Cox regression model after IPTW to balance baseline differences. To account for within-subject correlation arising from multiple observations per individual, robust standard errors were calculated using a sandwich estimator with clustering at the patient level. To assess the disease activity and physical function, we compared CDAI and J-HAQ scores at the point of 1, 2, and 3 years. An IPTW-adjusted mixed model for repeated measures was used to estimate and compare group differences, adjusted for baseline values. For the analysis of mixed model for repeated measures, missing values were not imputed under the assumption of missing at random. The balance of each covariate in each group was assessed using a standardized mean difference (SMD), and an SMD of <0.1 was considered acceptable. $p<0.05$ was considered statistically significant. Statistical analyses were performed using the JMP statistical software (Japanese version 14, SAS Institute Inc., Cary, NC, USA) and R software (The R Foundation for Statistical Computing, Vienna, Austria).

3 | Results

3.1 | Baseline Characteristics

In total, 154 patients with 237 treatment courses were included in this study (Figure 1). The baseline characteristics are shown in Table 1. The mean age was 67.1 ± 8.5 years. The mean DAS28-ESR, mean CDAI, and mean J-HAQ were 3.9 ± 1.3, 10.9 ± 8.5, 1.2 ± 0.9, respectively. Of the 237 treatment courses, TNFi was administered to 142 (59.9%), IL-6i to 59 (24.9%), and CTLA4-Ig to 36 (15.2%). The mean eGFR was 50 ± 11.0 mL/min/1.73 m^2, 70 treatment courses had an eGFR <45 mL/min/1.73 m^2, and none had an eGFR <15 mL/min/1.73 m^2 or underwent hemodialysis. A total of 145 (61.2%) treatment courses were combined with PSL, and 151 (63.7%) with MTX. In 91 (38.4%) treatment courses, patients had previously used bDMARDs. None of the patients were administered sarilumab. Baseline DAS28-ESR was similar across the three bDMARD groups. The IL-6i and CTLA4-Ig groups showed a higher proportion of previous bDMARD use and a lower proportion of MTX use than the TNFi group. Additionally, the mean eGFR was lower and the proportion of eGFR <45 mL/min/1.73 m^2 was higher in the IL-6i and CTLA4-Ig groups compared to the TNFi group.

3.2 | Drug Retention Rate

The observational period spanned 485 patient-years, during which, 108 (45.6%) treatment courses were discontinued (Table S1); 49 due to ineffectiveness, 33 due to adverse drug reactions, 10 due to patient preference, one due to remission,

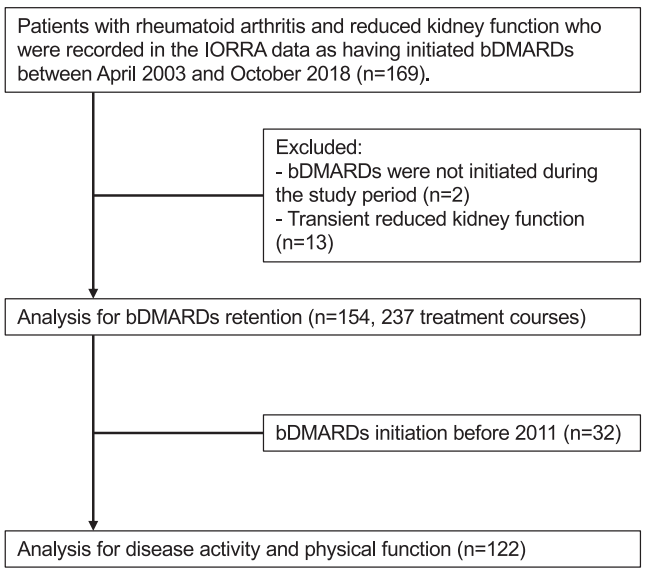

FIGURE 1 | Flow chart of patient inclusion. bDMARDs, biological disease-modifying antirheumatic drugs; IORRA, Institute of Rheumatology Rheumatoid Arthritis.

TABLE 1 | Baseline characteristics.

	Overall	TNFi	ADA	CZP	ETN	GLM	IFX	IL-6i	CTLA4-Ig
	N = 237	*N* = 142	*N* = 15	*N* = 5	*N* = 66	*N* = 30	*N* = 26	*N* = 59	*N* = 36
Age, years (SD)	67.1 (8.5)	67.3 (7.6)	66.9 (6.3)	66.0 (4.5)	66.8 (8.3)	70.3 (7.1)	65.6 (7.2)	64.6 (9.5)	70.3 (8.8)
Female, *n* (%)	204 (86.1)	121 (85.2)	13 (86.7)	5 (100)	54 (81.8)	26 (86.7)	23 (88.5)	52 (88.1)	31 (86.1)
Disease duration, years (SD)	17.6 (11.0)	16.6 (10.1)	14.7 (11.6)	14.5 (7.2)	16.6 (9.6)	19.4 (11.3)	14.6 (9.1)	19.9 (11.7)	18.3 (11.3)
RF positivity, *n* (%)	198/231 (85.7)	118/140 (84.3)	10/15 (66.7)	3/4 (75.0)	58/65 (89.2)	27/30 (90.0)	20/26 (76.9)	50/56 (89.3)	30/35 (85.7)
ACPA positivity, *n* (%)	198/220 (90.0)	114/130 (87.7)	11/15 (73.3)	5/5 (100)	54/59 (91.5)	27/30 (90.0)	17/21 (81.0)	53/55 (96.4)	31/35 (88.6)
DAS28-ESR (SD)	3.9 (1.3)	3.9 (1.4)	3.6 (1.1)	2.7 (0.7)	4.3 (1.4)	3.3 (1.1)	3.9 (1.5)	3.9 (1.2)	3.8 (1.1)
CDAI (SD)	10.9 (8.5)	11.2 (9.1)	10.3 (6.0)	1.6 (1.7)	12.9 (9.1)	8.2 (6.1)	12.2 (12.3)	10.9 (7.8)	10.1 (6.9)
J-HAQ (SD)	1.2 (0.9)	1.1 (0.9)	0.8 (0.8)	0.8 (1.2)	1.2 (0.9)	1.2 (0.9)	1.2 (0.9)	1.4 (0.8)	1.3 (0.9)
eGFR, mL/min/1.73 m^2 (SD)	50 (11.0)	51.4 (9.5)	54.5 (4.0)	53.5 (8.1)	50.6 (11.5)	50.2 (7.6)	52.9 (8.2)	47.4 (13.6)	48.6 (8.4)
eGFR < 45, *n* (%)	70 (29.5)	32 (22.5)	0 (0)	1 (20.0)	18 (27.3)	8 (26.7)	5 (19.2)	25 (42.4)	13 (36.1)
MTX use, *n* (%)	151 (63.7)	98 (69.0)	14 (93.3)	2 (40.0)	38 (57.6)	20 (66.7)	24 (92.3)	35 (59.3)	18 (50.0)
MTX dose, mg/week (SD)	7.6 (2.8)	7.5 (2.8)	7.2 (1.3)	7.3 (1.9)	7.4 (3.4)	7.8 (3.1)	7.8 (2.3)	7.3 (3.0)	8.4 (2.9)
PSL use, *n* (%)	145 (61.2)	87 (61.3)	8 (53.3)	3 (60.0)	41 (62.1)	16 (53.3)	19 (73.1)	36 (61.0)	22 (61.1)
PSL dose, mg/day (SD)	4.6 (2.6)	4.6 (2.6)	3.9 (1.2)	6.3 (5.9)	4.5 (2.7)	3.6 (1.7)	5.5 (2.5)	4.5 (2.8)	4.8 (2.4)
Previous bDMARDs use, *n* (%)									
0	146 (61.6)	103 (72.5)	12 (80.0)	1 (20.0)	55 (83.3)	15 (50.0)	20 (76.9)	25 (42.4)	18 (50.0)
1	65 (27.4)	33 (23.2)	3 (20.0)	2 (40.0)	10 (15.2)	13 (43.3)	5 (19.2)	22 (37.3)	10 (27.8)
2	19 (8.0)	5 (3.5)	0 (0)	2 (40)	1 (1.5)	2 (6.7)	0 (0)	8 (13.6)	6 (16.7)
3	7 (3.0)	1 (0.7)	0 (0)	0 (0)	0 (0)	0 (0)	1 (4)	4 (6.8)	2 (5.6)

Note: Data are expressed as mean (SD) or *n* (%).

Abbreviations: ACPA, anti-citrullinated peptide antibody; ADA, adalimumab; bDMARDs, biological disease-modifying antirheumatic drugs; CDAI, clinical disease activity index; CTLA4-Ig, cytotoxic T lymphocyte-associated antigen-4-Ig; CZP, certolizumab pegol; DAS28-ESR, disease activity score 28-joint count using erythrocyte sedimentation rate; eGFR, estimated glomerular filtration rate calculated using creatinine; ETN, etanercept; GLM, golimumab; IFX, infliximab; IL-6i, interleukin-6 inhibitor; J-HAQ, Japanese version of the health assessment questionnaire; MTX, methotrexate; PSL, prednisolone; SD, standard deviation; TNFi, tumor necrosis factor inhibitor.

and 15 due to other reasons. Among the 33 adverse drug reactions leading to discontinuation, infections ($n = 15$) were the most common, with the respiratory system and skin being the most frequently affected organs. Table 2 shows the baseline characteristics of patients before and after adjustment. Some variables of SMD were still > 0.10 after adjustment. Figure 2a,b show Kaplan–Meier curves for drug retention in the overall population and subgroups stratified by eGFR (45–60 or < 45 mL/min/1.73 m^2). The overall drug retention rate (i.e., discontinuation owing to insufficient effectiveness or adverse drug reactions; see the Methods section) was 54.6% at 3 years (Figure 2a). The drug retention rates were comparable between the two groups stratified by eGFR ($p = 0.27$) (Figure 2b). Regarding the modes of action, the drug retention rate at 3 years for TNFi, IL-6i, and CTLA4-Ig was 54.9%, 61.1%, and 44.3%, respectively ($p = 0.74$; Figure 2c). The drug retention rate due to ineffectiveness was 72.4%, 67.7%, and 49.3% ($p = 0.33$), and due to adverse drug reactions was 76.2%, 90.3%, and 89.9% ($p = 0.05$), respectively (Figure 2d,e). Adjusted HRs of overall drug discontinuation were 0.85 (95% CI, 0.37–1.96) for IL-6i and 1.31 (95% CI, 0.63–2.73) for CTLA4-Ig with TNFi as a reference.

TABLE 2 | Baseline characteristics before and after inverse probability of treatment weighting.

	Unweighted			Weighted			
	TNFi ($n = 128$)	IL-6i ($n = 51$)	CTLA4-Ig ($n = 34$)	TNFi ($n = 134.5$)	IL-6i ($n = 47.5$)	CTLA4-Ig ($n = 32.2$)	SMD
Year at enrolment, *n* (%)							0.257
2011–2012	9 (7.0)	0 (0.0)	0 (0.0)	5.4 (4.0)	0.0 (0.0)	0.0 (0.0)	
2013–2014	56 (43.8)	21 (41.2)	4 (11.8)	49.5 (36.8)	15.9 (33.4)	13.4 (41.5)	
2015–2017	63 (49.2)	30 (58.8)	30 (88.2)	79.6 (59.2)	31.6 (66.6)	18.9 (58.5)	
Female, *n* (%)	109 (85.2)	44 (86.3)	29 (85.3)	118.6 (88.2)	40.2 (84.7)	27.5 (85.5)	0.067
Age, years (SD)	67.4 (7.6)	64.5 (9.5)	70.2 (8.9)	67.2 (7.5)	68.4 (8.3)	65.2 (10.3)	0.239
Disease duration, years (SD)	16.5 (10.2)	19.8 (12.1)	18.1 (11.4)	17.1 (10.0)	18.0 (11.4)	17.0 (9.4)	0.064
Previous bDMARDs use, *n* (%)	34 (26.6)	30 (58.8)	17 (50.0)	56.3 (41.9)	18.3 (38.5)	16.2 (50.1)	0.156
Lung disease, *n* (%)	7 (5.5)	3 (5.9)	5 (14.7)	7.0 (5.2)	3.2 (6.6)	2.2 (6.8)	0.044
BMI, kg/m^2 (SD)	22.2 (2.6)	22.1 (3.3)	22.2 (3.1)	22.1 (2.5)	22.1 (2.8)	22.0 (2.4)	0.038
DAS28-ESR (SD)	3.8 (1.4)	3.8 (1.2)	3.8 (1.1)	3.9 (1.3)	3.7 (1.2)	3.6 (0.9)	0.156
SDAI (SD)	12.1 (9.9)	11.3 (8.1)	11.2 (7.8)	11.8 (9.3)	10.8 (8.3)	9.7 (6.8)	0.171
CDAI (SD)	11.0 (9.2)	10.4 (7.6)	10.2 (7.0)	10.7 (8.7)	10.0 (7.7)	8.6 (6.1)	0.187
J-HAQ (SD)	1.1 (0.9)	1.3 (0.8)	1.3 (0.9)	1.1 (0.9)	1.0 (0.8)	1.1 (0.9)	0.081
PSL use, *n* (%)	77 (60.2)	32 (62.7)	20 (58.8)	73.1 (54.4)	21.4 (45.0)	14.3 (44.4)	0.134
MTX use, *n* (%)	89 (69.5)	29 (56.9)	16 (47.1)	81.7 (60.8)	30.4 (64.0)	19.8 (61.5)	0.045
RF positivity, *n* (%)	107 (83.6)	45 (88.2)	30 (88.2)	113.8 (84.6)	38.9 (81.9)	29.7 (92.0)	0.204
ACPA positivity, *n* (%)	113 (88.3)	49 (96.1)	30 (88.2)	121.8 (90.5)	41.1 (86.6)	30.2 (93.7)	0.16
eGFR, mL/min/1.73 m^2 (SD)	51.6 (9.5)	48.2 (12.8)	48.2 (8.5)	49.3 (10.2)	49.8 (11.9)	48.9 (7.3)	0.064
CRP, mg/dL (SD)	1.2 (1.5)	1.0 (1.2)	1.1 (1.5)	1.0 (1.4)	0.8 (1.2)	1.0 (1.3)	0.111

Note: Data are expressed as mean (SD) or *n* (%).

Abbreviations: ACPA, anti-citrullinated peptide antibody; bDMARDs, biological disease-modifying antirheumatic drugs; BMI, body mass index; CDAI, clinical disease activity index; CRP, C-reactive protein; CTLA4-Ig, cytotoxic T lymphocyte-associated antigen-4-Ig; DAS28-ESR, disease activity score 28-joint count using erythrocyte sedimentation rate; eGFR, estimated glomerular filtration rate calculated using creatinine; IL-6i, interleukin-6 inhibitor; J-HAQ, Japanese version of the health assessment questionnaire; MTX, methotrexate; PSL, prednisolone; RF, rheumatoid factor; SD, standard deviation; SDAI, simplified disease activity index; SMD, standardized mean difference; TNFi, tumor necrosis factor inhibitor.

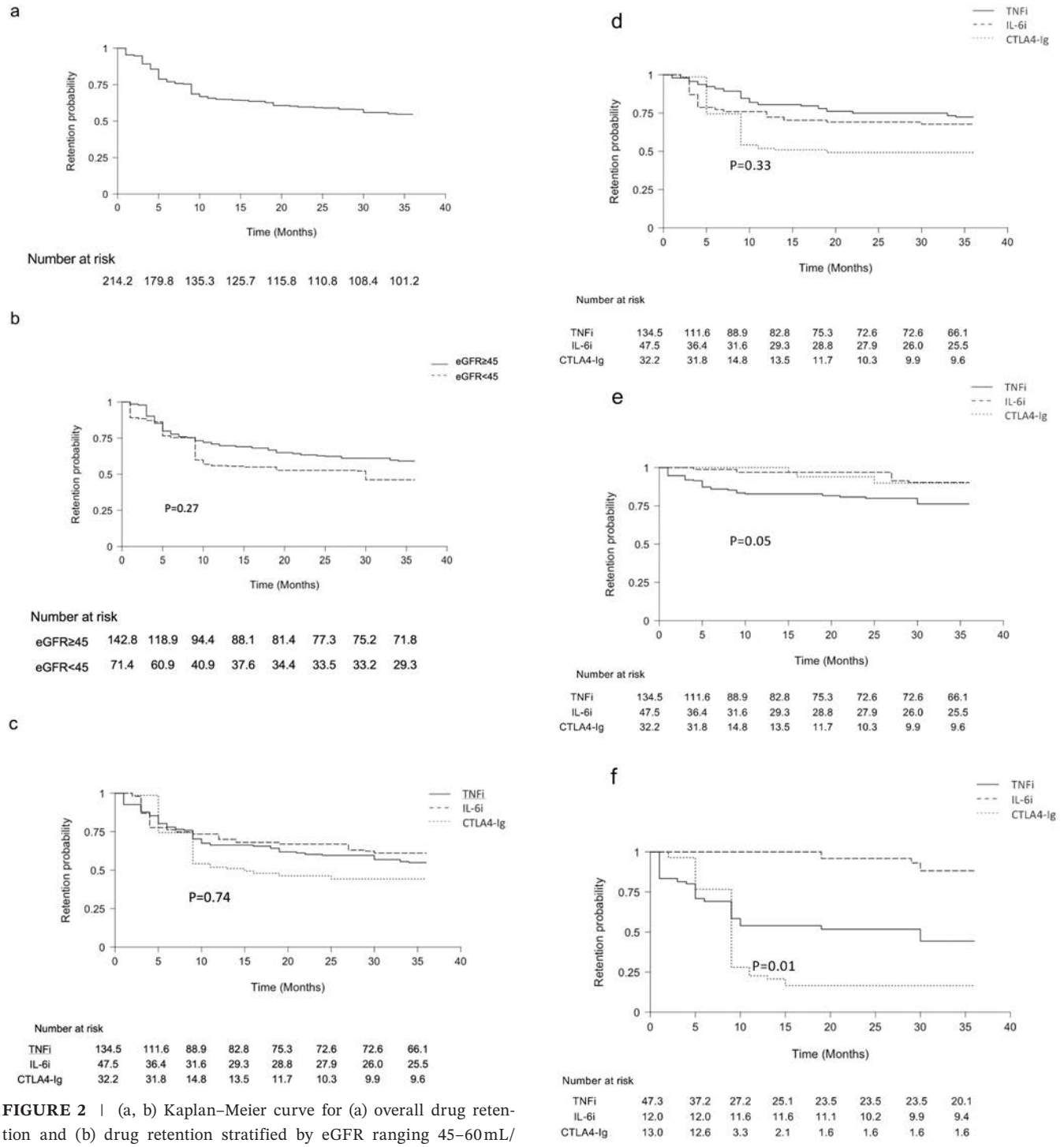

FIGURE 2 | (a, b) Kaplan–Meier curve for (a) overall drug retention and (b) drug retention stratified by eGFR ranging 45–60 mL/min/1.73 m^2 or <45 mL/min/1.73 m^2. (c–e) Kaplan–Meier curve stratified by the modes of action of bDMARDs for (c) overall drug retention, (d) drug retention with discontinuation due to ineffectiveness, and (e) drug retention with discontinuation due to adverse drug reactions. (f–h) Kaplan–Meier curve for patients with eGFR <45 mL/min/1.73 m^2 for (f) overall drug retention, (g) drug retention with discontinuation due to ineffectiveness, and (h) drug retention with discontinuation due to adverse drug reactions. Weighted numbers at risk are shown. bDMARDs, biological disease-modifying antirheumatic drugs; CTLA4-Ig, cytotoxic T lymphocyte-associated antigen-4-Ig; eGFR, estimated glomerular filtration rate (calculated using creatinine); IL-6i, interleukin-6 inhibitor; TNFi, tumor necrosis factor inhibitor.

FIGURE 2 | (Continued)

We also conducted a subgroup analysis of patients with eGFR <45 mL/min/1.73 m^2 ($n = 70$) using the Kaplan–Meier curve and log-rank test. At baseline, mean disease duration and seropositivity were comparable (Table S2). Regarding disease activity, TNFi values were higher compared to IL-6i and CTLA4-Ig values (DAS28-ESR: TNFi 4.4, IL-6i 3.7, CTLA4-Ig 3.8; CDAI: TNFi 12.5, IL-6i 9.5, CTLA4-Ig 9.6). The overall proportion of concomitant MTX use was 47.1% in this subgroup, with the lowest proportion observed in the CTLA4-Ig group (38.5%). The

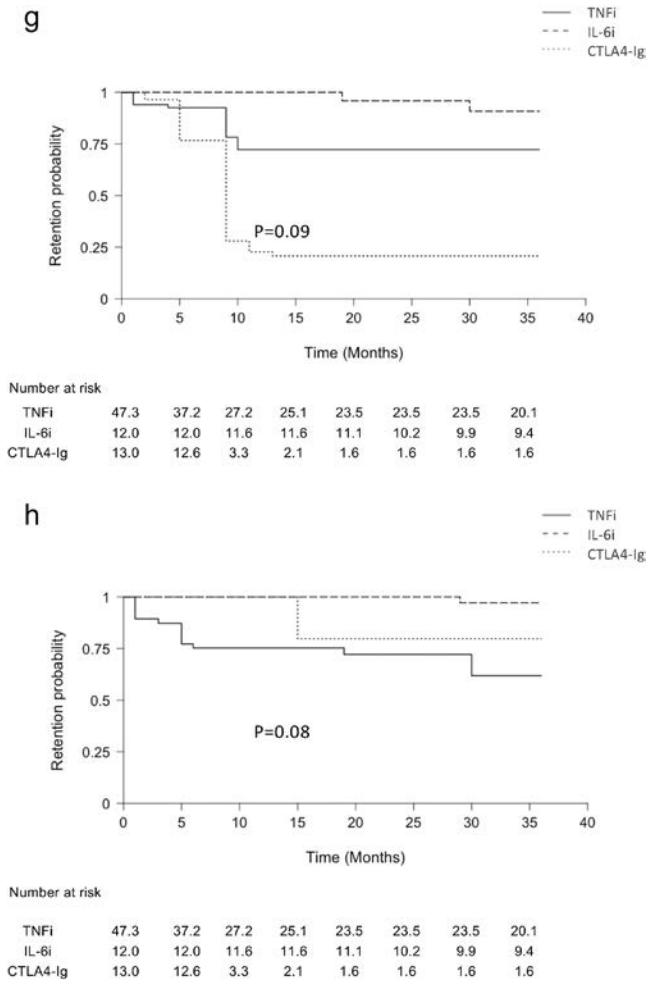

FIGURE 2 | (Continued)

drug retention rates for TNFi, IL-6i, and CTLA4-Ig were 44.4%, 88.3%, and 16.5% for overall reasons ($p=0.01$); 72.3%, 90.9%, and 20.7% for lack of effectiveness ($p=0.09$); and 71.9%, 97.1%, and 79.7% for adverse drug reactions ($p=0.08$), respectively (Figure 2f–h).

In the subgroup analyses of patients stratified according to concomitant MTX use and prior bDMARD use, drug retention over 36 months was compared among the TNFi, IL-6i, and CTLA4-Ig groups. In the subgroup of patients not receiving concomitant MTX, the IL-6i group had a lower HR for overall discontinuation than the TNFi group (HR, 0.32 [95% CI, 0.11–0.90]). The CTLA4-Ig group had higher HRs for discontinuation due to lack of effectiveness than the TNFi group in the subgroup of patients receiving concomitant MTX (HR, 2.72 [95% CI, 1.14–6.51]) and in the subgroup of patients with no prior bDMARD use (HR, 3.21 [95% CI, 1.15–8.97]) (Figure S1).

3.3 | Comparison of bDMARD Effectiveness

We further investigated whether the effectiveness differed between the modes of action of bDMARDs in patients with reduced kidney function using IPTW analysis. Table 3 shows the baseline characteristics of patients before and after adjustment. Some variables of SMD were still > 0.10 after adjustment.

Following adjustment using propensity score-based IPTW, the mean J-HAQ score (Figure 3b) at baseline was similar across the TNFi, IL-6i, and CTLA4-Ig groups, whereas the mean CDAI at baseline was lower in the CTLA4-Ig group (7.4) than in the TNFi (8.8) and IL-6i (9.3) groups (Figure 3a). The mean CDAI values for TNFi, IL-6i, and CTLA4-Ig were 6.3, 7.4, and 8.2 at 12 months; 5.7, 6.8, and 5.9 at 24 months; and 6.0, 6.5, and 6.6 at 36 months, respectively. The mean J-HAQ scores for TNFi, IL-6i, and CTLA4-Ig were 1.0, 1.0, and 1.2 at 12 months; 1.1, 1.0, and 1.2 at 24 months; and 1.1, 1.0, and 1.1 at 36 months, respectively. Disease activity at 36 months improved across all modes of action, with no increase in J-HAQ from baseline exceeding 0.13 (minimal important difference reported [22]).

4 | Discussion

This real-world observational study offers insights into drug retention and effectiveness of bDMARDs in patients with RA and reduced kidney function. The drug retention rates were comparable for patients with eGFR ranging 45–60 mL/min/1.73 m^2 and those with eGFR < 45 mL/min/1.73 m^2. Drug retention rates at 3 years due to ineffectiveness or adverse drug reactions of bDMARDs were 54.6% in patients with RA who had reduced kidney function, and this was similar across the three bDMARDs with different modes of action (TNFi, IL-6i, and CTLA4-Ig). The CDAI and J-HAQ at 3 years were similar across the bDMARDs.

Our findings suggest that reduced kidney function does not notably affect the retention rates of bDMARDs, a result consistent with a previous report [23]. In addition, the overall drug retention rate of 54.6% at 3 years was similar to that reported in previous studies, which included patients with normal kidney function [24–28]. Unlike conventional synthetic DMARDs and Janus kinase inhibitors, drug metabolism and bDMARD excretion are independent of kidney function; therefore, their pharmacokinetics are largely unaffected in patients with reduced renal function. Based on the overall drug retention rate and details of adverse drug reactions leading to drug discontinuation, our study suggests that bDMARD use may not significantly increase the safety risks affecting drug retention in patients with reduced kidney function. Previous studies have raised safety concerns about Janus kinase inhibitors [11, 29], particularly the potential for an increased incidence of herpes zoster and deep vein thrombosis in patients with severely reduced kidney function [29]. Therefore, the optimal use of bDMARDs and Janus kinase inhibitors in patients with moderate-to-severe reduced kidney function should be confirmed by studies with larger sample sizes.

Although we did not find statistically significant differences among the bDMARDs with three different modes of action, IL-6i demonstrated a numerically higher retention rate than TNFi and CTLA4-Ig, and a lower adjusted HR for discontinuation compared to TNFi. This is consistent with previous reports [30–32], including those focusing on patients with reduced renal function [11, 23]. One advantage of using IL-6i in patients with reduced renal function is that drug retention is likely to be maintained regardless of concomitant MTX use [30]. In this study, the overall rate of MTX use was 63.7% and the rate of MTX use

TABLE 3 | Baseline characteristics before and after inverse probability of treatment weighting for the analysis of disease activity and physical function.

	Unweighted			Weighted			
	TNFi ($n=68$)	IL-6i ($n=31$)	CTLA4-Ig ($n=23$)	TNFi ($n=123.1$)	IL-6i ($n=89.7$)	CTLA4-Ig ($n=103.3$)	SMD
Year at enrolment, *n* (%)							0.201
2011–2012	23 (33.8)	11 (35.5)	1 (4.3)	35.3 (28.7)	23.0 (25.7)	18.0 (17.4)	
2013–2014	25 (36.8)	12 (38.7)	12 (52.2)	54.9 (44.6)	37.9 (42.2)	50.5 (48.9)	
2015–2017	20 (29.4)	8 (25.8)	10 (43.5)	32.9 (26.7)	28.8 (32.1)	34.7 (33.6)	
Female, *n* (%)	55 (81)	30 (97)	21 (91)	107.9 (87.7)	85.7 (95.6)	89.7 (86.9)	0.209
Age, years (SD)	69.1 (7.9)	63.1 (9.9)	70.7 (9.2)	68.3 (7.7)	66.9 (8.6)	68.2 (8.1)	0.113
Disease duration, years (SD)	18.0 (10.3)	19.1 (11.6)	17.4 (12.0)	17.9 (10.4)	16.9 (10.3)	17.3 (9.9)	0.066
Previous bDMARDs use, *n* (%)	36 (52.9)	23 (74.2)	12 (52.2)	77.0 (62.6)	73.2 (81.7)	75.9 (73.6)	0.29
Lung disease, *n* (%)	10 (14.7)	4 (12.9)	8 (34.8)	21.7 (17.6)	10.9 (12.1)	20.0 (19.4)	0.133
BMI, kg/m^2 (SD)	21.9 (3.0)	22.0 (3.5)	21.8 (2.9)	21.9 (3.0)	22.2 (3.0)	22.3 (3.2)	0.085
DAS28-ESR (SD)	3.4 (1.2)	3.9 (1.2)	3.8 (1.1)	3.4 (1.3)	3.6 (1.2)	3.5 (1.1)	0.08
SDAI (SD)	9.1 (6.4)	13.0 (9.1)	10.7 (7.7)	9.8 (6.6)	10.1 (8.6)	8.2 (7.6)	0.163
CDAI (SD)	8.3 (5.9)	11.9 (8.5)	9.5 (6.5)	8.8 (5.9)	9.3 (7.9)	7.4 (6.8)	0.178
J-HAQ (SD)	1.0 (0.9)	1.3 (0.8)	1.3 (0.9)	1.1 (0.9)	1.0 (0.8)	1.0 (0.8)	0.08
PSL use, *n* (%)	37 (54.4)	19 (61.3)	13 (56.5)	67.8 (55.1)	39.9 (44.5)	50.7 (49.1)	0.087
MTX use, *n* (%)	47 (69.1)	17 (54.8)	11 (47.8)	76.0 (61.8)	58.1 (64.8)	54.9 (53.2)	0.158
RF positivity, *n* (%)	58 (85.3)	27 (87.1)	19 (82.6)	102.0 (82.9)	74.0 (82.6)	84.2 (81.5)	0.024
ACPA positivity, *n* (%)	59 (86.8)	30 (96.8)	20 (87.0)	111.3 (90.5)	79.3 (88.4)	90.3 (87.4)	0.066
eGFR, mL/min/1.73 m^2 (SD)	49.7 (9.1)	50.8 (10.1)	40.0 (7.5)	49.9 (8.9)	51.3 (9.0)	51.0 (6.6)	0.109
CRP, mg/dL (SD)	0.9 (1.3)	1.2 (1.6)	1.2 (1.7)	1.0 (1.6)	0.9 (1.5)	0.8 (1.2)	0.105

Note: Data are expressed as mean (SD) or *n* (%).

Abbreviations: ACPA, anti-citrullinated peptide antibody; bDMARDs, biological disease-modifying antirheumatic drugs; BMI, body mass index; CDAI, clinical disease activity index; CRP, C-reactive protein; CTLA4-Ig, cytotoxic T lymphocyte-associated antigen-4-Ig; DAS28-ESR, disease activity score 28-joint count using erythrocyte sedimentation rate; eGFR, estimated glomerular filtration rate calculated using creatinine; IL-6i, interleukin-6 inhibitor; J-HAQ, Japanese version of the health assessment questionnaire; MTX, methotrexate; PSL, prednisolone; RF, rheumatoid factor; SD, standard deviation; SDAI, simplified disease activity index; TNFi, tumor necrosis factor inhibitor.

in patients with eGFR <45 was 47.1%, which is lower than that in routine clinical practice at our institute (70%–80% of IORRA cohort participants during the same period). On the other hand, the discontinuation of IL-6i due to adverse effects, compared to other bDMARDs, is concerning. A previous study involving 19 registers and 31486 treatment courses revealed that, compared to TNFi, IL-6i was less frequently discontinued due to ineffectiveness (adjusted HR 0.76, 95% CI 0.67–0.85) and discontinuation due to adverse drug reactions was numerically higher (adjusted HR 1.09, 95% CI 0.85–1.03) [32]. A major adverse event associated with IL-6i treatment is severe infections. However, in our analysis, only three patients who used IL-6i developed infections leading to the discontinuation of bDMARDs, which is not numerically higher than the incidence of severe infections

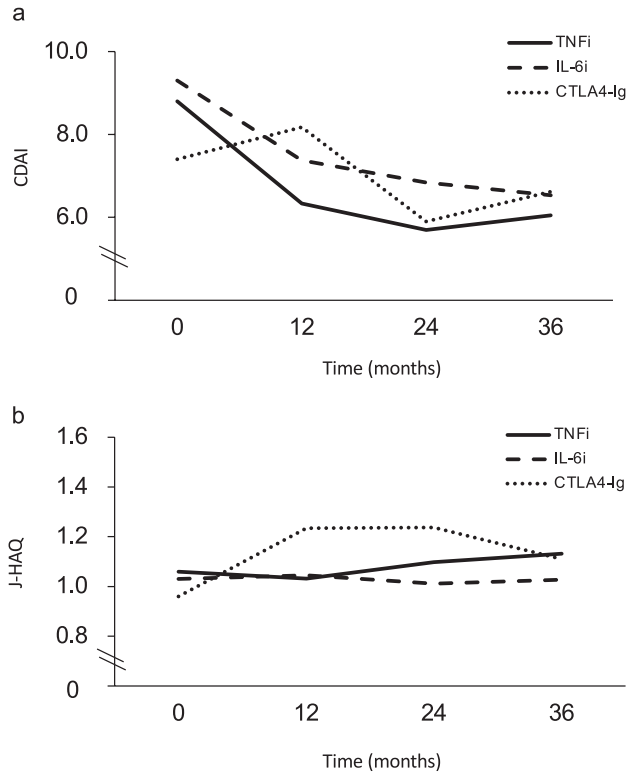

FIGURE 3 | Comparison of CDAI and J-HAQ scores across the TNFi, IL-6i, and CTLA4-Ig groups over 3 years. Baseline characteristics were balanced using propensity score-based IPTW analysis. CDAI, clinical disease activity index; CTLA4-Ig, cytotoxic T lymphocyte-associated antigen-4-Ig; IL-6i, interleukin-6 inhibitor; IPTW, inverse probability of treatment weighting; J-HAQ, Japanese version of the health assessment questionnaire; TNFi, tumor necrosis factor inhibitor.

reported in previous studies of bDMARD use (approximately 3–7/100 patient-years) [33]. Additionally, this study, along with others on reduced kidney function, did not show a significant increase in drug discontinuation because of infection or adverse drug reaction in the IL-6i group [11, 23].

Notably, the drug retention rate of CTLA4-Ig for discontinuation due to adverse drug reactions was comparable to that of other bDMARDs but was significantly lower in effectiveness than the other two bDMARDs in patients with eGFR <45 mL/min/1.73 m^2. This group was characterized by a lower proportion of MTX use. The additional efficacy of concomitant MTX use was not demonstrated in a phase III trial [34], and previous studies from Japan reported that the retention rate of CTLA4-Ig was comparable regardless of concomitant MTX use [35, 36]. However, in the AVERT trial, a numerical difference in efficacy was observed between the CTLA4-Ig monotherapy and MTX combination groups [37]. Moreover, a numerical increase in discontinuation rates due to ineffectiveness was observed in a retrospective study [35]. In the present study, among patients receiving concomitant MTX, the CTLA4-Ig group showed a higher HR for drug discontinuation due to ineffectiveness than the TNFi group. The insufficient sample size may have affected the result. Further studies are warranted to clarify whether the effectiveness of CTLA4-Ig and the additive effect of concomitant MTX use may vary depending on patient characteristics.

The strength of this study lies in its use of real-world data to present multiple long-term insights into drug retention and bDMARD effectiveness in patients with RA and reduced renal function over 3 years. The data included drug retention rates, breakdown of adverse drug reactions leading to drug discontinuation, disease activity, and functional indices. However, this study has several limitations. First, the small sample size limited the effectiveness of certain analyses. The results must be validated using larger sample sizes in future studies. Second, as this was a single-center cohort study, there is a possibility of selection bias and concerns regarding the generalizability of the results. Third, the results of the Cox regression analysis may have been influenced by unadjusted confounding factors. Data on the reasons for reduced renal function were missing, which may have been associated with the choice of bDMARDs or the occurrence of adverse drug reactions leading to drug discontinuation. Additionally, the effect of time-varying characteristics, which can sometimes have a stronger impact on discontinuation than baseline values, was not analyzed [38]. Fourth, differences in baseline data among the three groups, such as a higher proportion of previous use of bDMARDs in the IL-6i and CTLA4-Ig groups than in the TNFi group, may have affected the results of the IPTW-adjusted retention analyses. For example, restrictions on MTX co-administration and the higher proportion of patients with eGFR<45 mL/min/1.73 m^2 may have contributed to the selection of bDMARD monotherapy. This in turn, may have been associated with a higher drug retention rate, particularly if agents effective as monotherapy were preferentially used. In addition, patients at high risk of severe infection are likely to receive abatacept. The influence of these factors may remain even after adjustment by multivariable analysis. Therefore, our findings should be interpreted with caution, as they may vary according to the background characteristics of the study population. Fifth, we treated discontinuation for reasons other than ineffectiveness and adverse drug reactions as censored. However, as the reviewer pointed out, some of these cases may have led to informative censoring, which could have biased the comparison of drug retention among treatment groups. The direction and magnitude of this potential bias are difficult to determine. Sixth, compared with estimates that appropriately account for competing risks, cause-specific event-free probabilities may be underestimated [39]. Thus, the cause-specific drug retention rate in this study should be interpreted with caution. Seventh, some background factors remained unbalanced among the three groups after adjusting for propensity score-based IPTW.

5 | Conclusion

Our study indicates that the overall drug retention rates and their impact on disease activity and physical function are comparable across the three bDMARDs with different modes of action in patients with reduced renal function. Further investigation with larger sample sizes is necessary to confirm these results.

Author Contributions

T.H., E.T., E.I., and M.H. designed the study. T.H. and E.I. performed the data analysis. T.H. drafted the manuscript, and T.H., E.T., E.I., and M.H. revised it. All authors contributed to study preparation and

data collection, and have read and approved the final version of the manuscript.

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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:** Adjusted hazard ratios for bDMARD discontinuation stratified by concomitant MTX use and prior bDMARD use. **Table S1:** Reasons for discontinuation of bDMARDs. **Table S2:** Baseline characteristics of participants with eGFR <45 mL/min/1.73 m^2.

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LETTER TO THE EDITOR

Initial Nintedanib Dose and Treatment Continuation in Patients With Connective Tissue Disease-Associated Interstitial Lung Disease: A Retrospective Single-Center Observational Study in Japan

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Dear Editor,

Connective tissue disease-associated interstitial lung disease (CTD-ILD) is a frequent and often progressive complication of systemic autoimmune diseases [1, 2]. The extent of disease progression varies widely among patients, and in some cases, progressive lung fibrosis leads to irreversible decline in lung function with a poor long-term prognosis [3, 4]. Nintedanib has been shown to attenuate forced vital capacity (FVC) decline in patients with progressive fibrosing ILDs, including CTD-ILD [5, 6], and is widely used in the management of CTD-ILD. However, owing to gastrointestinal adverse drug reactions such as diarrhea, nausea, and elevations in hepatic enzymes [7], treatment discontinuation or dose reduction is frequently necessary. Recent real-world studies have reported that nintedanib dose reduction and interruption occurred in 26% and 42% of patients [8, 9]. Strategies to mitigate nintedanib-associated adverse events remain a high priority. Dose adjustment may represent one such strategy. A secondary analysis of the SENSCIS trial suggested that reducing the nintedanib dose from 300 mg/day to 200 mg/day after initiation of nintedanib did not diminish efficacy in patients with SSc-ILD [10]. Given that body weight is associated with nintedanib plasma concentration, and that Asian adults generally have lower body weight than other racial groups [11, 12], lower-dose initiation may improve treatment continuation while maintaining antifibrotic efficacy in Asian patients with CTD-ILD.

To explore this hypothesis, we conducted a retrospective cohort study at the University of Tsukuba Hospital (Tsukuba, Japan). We included CTD-ILD patients who became incident users of nintedanib between December 1, 2015, and February 1, 2025, and followed them from treatment initiation until the earliest of 1 year or the last recorded visit. The exposure of interest was the initial daily dose of nintedanib, determined based on the treating physician's judgment without predefined criteria. Patients were classified into a usual-dose group (200–300 mg/day) and a low-dose group (100–150 mg/day) in the primary analyses. Sensitivity analyses evaluated alternative dose categorizations of 300 mg/day versus $\leq$200 mg/day and 100 mg/day versus $>$100 mg/day. Cumulative nintedanib dose within 1 year of treatment initiation and reasons for nintedanib discontinuation were collected through electronic health record review. The primary outcome was time to nintedanib discontinuation, defined as a gap of 2 months or more without a new nintedanib prescription, beginning on the date when the patient would have run out of nintedanib based on the prior prescription. CT-documented progression of interstitial pneumonia within 1 year of nintedanib initiation was evaluated as an exploratory outcome. To address baseline confounding between the dose groups, we applied overlap weighting. Overlap weights were estimated from age, sex, body mass index (BMI), glucocorticoid dose, immunosuppressant or biologic use (mycophenolate mofetil (MMF), azathioprine (AZA), tacrolimus (TAC), and rituximab (RTX)), presence of

TABLE 1 | Baseline characteristics.

Characteristic	Usual dose (200–300 mg) *N* = 65	Low dose (100–150 mg) *N* = 31
	Mean (SD) except where noted	
Age, years	63 (12)	62 (12)
Female, *n* (%)	48 (74%)	20 (65%)
BMI, kg/m^2	22.8 (4.3)	24.5 (6.8)
Not measured	27	23
Pulmonary rehabilitation, *n* (%)	20 (31%)	5 (16%)
Any SSc, *n* (%)	32 (49%)	12 (39%)
Diffuse cutaneous SSc, *n* (%)	25 (38%)	6 (19%)
Limited cutaneous SSc, *n* (%)	7 (11%)	6 (19%)
Non-SSc, *n* (%)	33 (51%)	19 (61%)
Dermatomyositis, *n* (%)	5 (7.7%)	4 (13%)
Polymyositis, *n* (%)	5 (7.7%)	4 (13%)
Rheumatoid arthritis, *n* (%)	16 (25%)	9 (29%)
SLE, *n* (%)	3 (4.6%)	1 (3.2%)
Sjogren disease, *n* (%)	13 (20%)	4 (13%)
Polyarteritis nodosa, *n* (%)	1 (1.5%)	0 (0%)
Sarcoidosis, *n* (%)	0 (0%)	1 (3.2%)
Microscopic polyangiitis, *n* (%)	6 (9.2%)	3 (9.7%)
Mixed connective tissue disease, *n* (%)	0 (0%)	1 (3.2%)
LDH, U/L	212 (51)	213 (34)
Not measured	5	3
KL-6, U/mL	1183 (853)	926 (653)
Not measured	2	2
FVC, L	1.84 (0.71)	1.91 (0.78)
Not measured	30	20
% predicted FVC, %	64 (21)	62 (13)
Not measured	30	20
PSL, *n* (%)	46 (71%)	22 (71%)
PSL, mg/day	9 (11)	5 (4)
MMF, *n* (%)	15 (23%)	5 (16%)
AZA, *n* (%)	4 (6.2%)	3 (9.7%)
TAC, *n* (%)	15 (23%)	11 (35%)
RTX, *n* (%)	2 (3.1%)	0 (0%)

Abbreviations: AZA, azathioprine; BMI, body mass index; FVC, forced vital capacityKL-6, Krebs von den Lungen-6; LDH, lactate dehydrogenase; MCTD, mixed connective tissue disease; MMF, mycophenolate mofetil; PSL, prednisolone; RTX, rituximab; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; TAC, tacrolimus.

systemic sclerosis (SSc), lactate dehydrogenase (LDH), Krebs von den Lungen-6 (KL-6), and FVC using logistic regression models. The probability of treatment continuation was estimated using overlap-weighted Kaplan–Meier methods, and adjusted hazard ratios (aHRs) for discontinuation were estimated using overlap-weighted Cox proportional hazards models. Adjusted odds ratios (aORs) for CT-documented progression of interstitial pneumonia within 1 year of treatment initiation were estimated using overlap-weighted logistic regression models. Missing data were handled using multiple imputation with the mice package in R [13], generating 100 imputed datasets with 50 iterations each. This study was reviewed and approved by the ethics committee of the University of Tsukuba Hospital (approval no. R06-230).

A total of 96 incident users of nintedanib for CTD-ILD, identified through electronic health record review, were included, of whom 65 initiated a usual dose and 31 initiated a low dose. The mean age in both groups was in the sixth decade, and the mean BMI was higher in the low-dose group (Table 1). The underlying autoimmune diseases associated with CTD-ILD varied, with systemic sclerosis accounting for 39% of the patients in the low-dose group and 49% in the usual-dose group. The mean glucocorticoid dose was lower, and the use of MMF was less frequent in the low-dose group.

Mean cumulative nintedanib dose at 1 year was higher in the usual-dose group than in the low-dose group (59.0 g vs. 42.1 g). Diarrhea was the most common reason for nintedanib discontinuation (11% in the usual-dose group vs. 6.5% in the low-dose group), followed by hepatic enzyme elevations (7.7% vs. 3.2%) and other gastrointestinal symptoms excluding diarrhea (4.6% vs. 6.5%). Covariate balance was achieved after overlap weighting (Figure 1A). No deaths occurred during follow-up. The probability of treatment continuation was higher in the low-dose group than in the usual-dose group. The aHR for nintedanib discontinuation was 0.44 (robust 95% confidence interval (CI): 0.09–2.01) (Figure 1B). Similar trends were observed in the sensitivity analyses (Figure 1C,D). Follow-up CT within 1 year, together with baseline CT within the preceding year, was available in approximately one-third of patients, reflecting routine clinical practice. The aOR for CT-documented progression of interstitial pneumonia within 1 year was 3.88 (robust 95% CI: 0.68–22.0) in the low-dose group compared with the usual-dose group. Sensitivity analyses showed corresponding aORs of 5.67 (robust 95% CI:

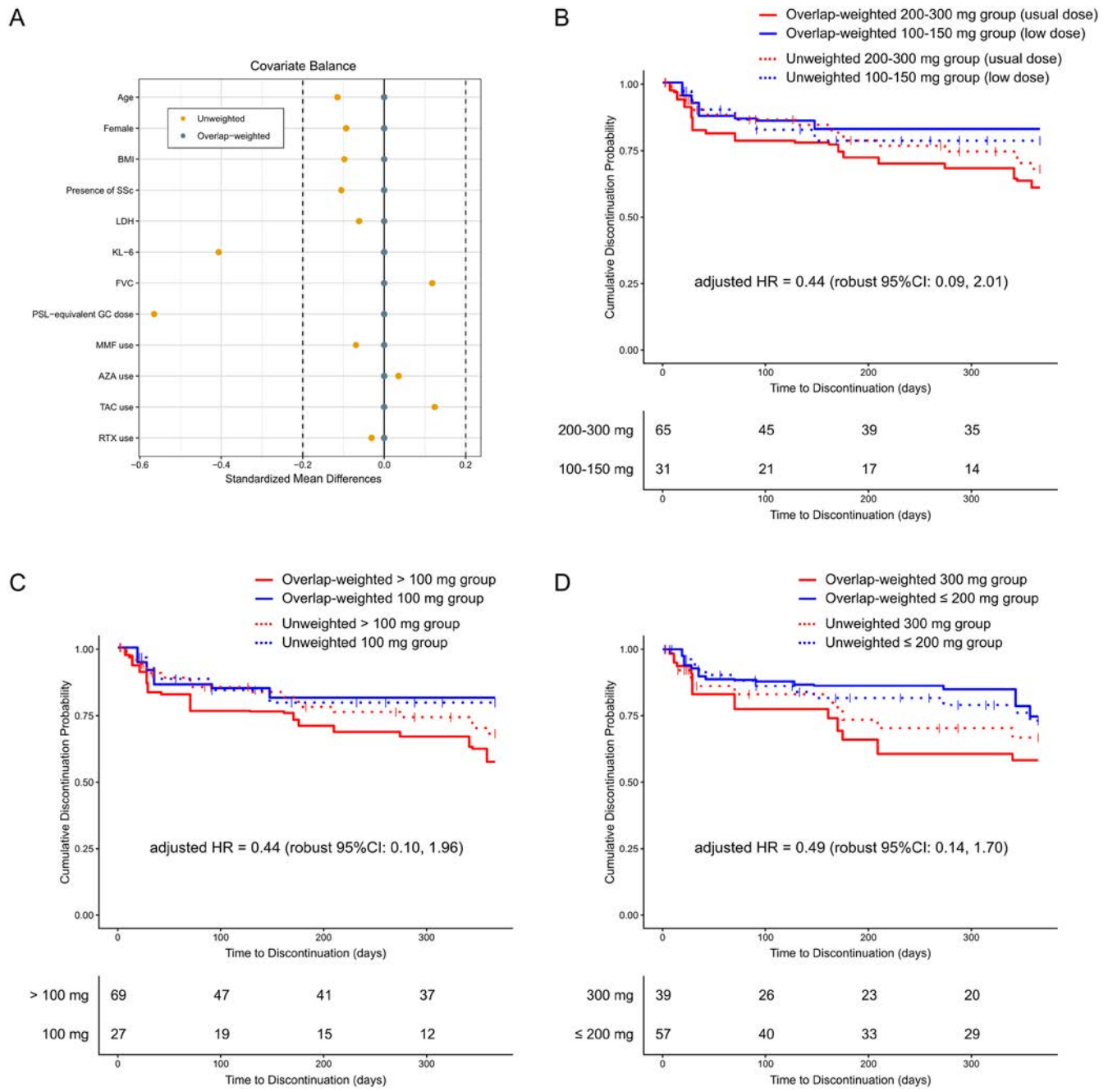

FIGURE 1 | Love plot and probabilities of nintedanib continuation by initial nintedanib dose Covariate balance in the unweighted and overlap-weighted populations is shown in (A). The probability of nintedanib continuation during the 1-year follow-up period was estimated using unweighted (dashed lines) and overlap-weighted (solid lines) Kaplan–Meier methods in the primary analysis (B) and sensitivity analyses (C, D). The 200–300 mg (usual dose), 300 mg, and > 100 mg groups are shown in red, whereas the 100–150 mg (low dose), < 200 mg and 100 mg groups are shown in blue. Vertical ticks indicate censoring events. Abbreviations in the (A) are as follows: AZA, azathioprine; BMI, body mass index; FVC, forced vital capacity; GC, glucocorticoid; KL-6, Krebs von den Lungen-6; LDH, lactate dehydrogenase; MMF, mycophenolate mofetil; PSL, prednisolone; SSc, systemic sclerosis; TAC, tacrolimus; RTX, rituximab.

0.77–41.5) for the 100 mg/day versus > 100 mg/day and 2.73 (robust 95% CI: 0.57–13.0) for the 300 mg/day versus ≤ 200 mg/day.

In this study, lower-dose initiation showed a numerically higher probability of treatment continuation and greater radiologic progression, although both estimates had wide confidence intervals. The proportions of nintedanib discontinuation due to diarrhea or hepatic enzyme elevations tended to be lower in the low-dose group. Previous Japanese studies evaluating lower-dose nintedanib initiation reported mixed findings, with improved tolerability and continuation reported in idiopathic pulmonary fibrosis (IPF) but not in CTD-ILD [14, 15]. Our findings provide additional insight into the potential clinical relevance of lower-dose initiation in patients with CTD-ILD.

Discontinuation due to diarrhea or hepatic enzyme elevations in the usual-dose group was more frequent than previously reported in patients receiving 300 mg/day, where 5%–7% discontinued

due to diarrhea and 1%–6% due to hepatic enzyme elevations [10, 16]. The differences could be attributed to patient characteristics in our cohort that are linked to increased nintedanib exposure, particularly the higher mean age (63.0 years in this study vs. 54.6 years in the SENSCIS study [5]) and the lower mean BMI (22.8 in this study vs. 26.7 in the INBUILD study [6]). Both advanced age and lower body weight are associated with higher nintedanib plasma concentration, which heightens the risk of diarrhea and liver damage [11, 17, 18]. The expected reduction in nintedanib exposure in the low-dose group may partly explain the lower proportion of nintedanib discontinuation due to these adverse events and the numerically lower hazard of treatment discontinuation.

In addition to the numerically higher probability of treatment continuation, our exploratory analysis showed numerically higher odds of CT-documented progression of interstitial pneumonia in the low-dose group. While a secondary analysis of the SENSCIS study showed that dose reduction after nintedanib initiation did not substantially compromise its efficacy in slowing FVC decline [10], nintedanib demonstrated a dose-dependent reduction in the incidence of acute exacerbation of IPF in the TOMORROW study [19]. Pharmacokinetic studies have suggested that plasma concentrations of nintedanib correlate with its effect on FVC decline [11, 20]. Collectively, lower-dose initiation might have led to suboptimal exposure and reduced efficacy in preventing CTD-ILD progression. The lower cumulative nintedanib exposure in the low-dose group supports this interpretation.

Strengths of our study include the use of detailed electronic health records reviewed by trained rheumatologists, enabling accurate assessment of both reasons for discontinuation and the timing of nintedanib discontinuation. We also employed robust epidemiological methods, including an incident user design and overlap weighting to account for a wide range of potential confounders. Consistency in findings between the primary and sensitivity analyses further supports the robustness of our results.

Several limitations of our study merit consideration. The sample size, although relatively large for CTD-ILD research, remains modest, resulting in wide confidence intervals. Residual confounding by indication remains possible, as uncaptured factors such as frailty, comorbidities, or physician perception of tolerability risk were not adjusted for. Thus, the signal toward greater radiologic progression may reflect these limitations rather than reduced efficacy. Potential selection bias and limited transportability of the CT-based assessment should also be considered, as follow-up CT imaging was not protocolized, resulting in substantial missingness that reflected routine clinical practice at a single institution. Additionally, longitudinal FVC assessment was not feasible because only five patients had pulmonary function test data available at both baseline and approximately 1 year. Our analysis focused on the initial dosing strategy and did not account for subsequent dose modifications or cumulative drug exposure, as these factors may lie on the causal pathway between the initial nintedanib dose and outcomes. Finally, cost-effectiveness analysis of nintedanib dosing strategy was not addressed in this study.

In conclusion, lower-dose initiation showed a numerically higher probability of treatment continuation in patients with CTD-ILD, although our exploratory analysis yielded numerically higher odds of radiologic progression, with wide confidence intervals. These real-world findings support the potential benefit of a lower initial dose for treatment continuation in Asian populations, in whom lower body weight may influence nintedanib exposure and tolerability. Individualized dosing strategies should therefore be considered when initiating antifibrotic therapy for CTD-ILD.

Author Contributions

K.M., H.A., and Y.K. conceived the study idea. M.S. designed the study. K.M. and H.A. collected the data. M.S. curated and analyzed the data. M.S. and H.A. drafted the original manuscript. I.M. supervised the overall research process. All authors reviewed and approved the final manuscript.

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Ethics Statement

Given its noninvasive, observational nature, the requirement for informed consent was waived by the ethics committee of the University of Tsukuba Hospital (Approval No. R06-230). In accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects issued by the Japanese government, patients were provided the opportunity to opt out via the hospital website (https://www.hosp.tsukuba.ac.jp/t-credo/researchers/ethics_guidelines/information).

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 from the corresponding author upon reasonable request.

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ORIGINAL ARTICLE

Specialty-Based Disparities in Biologic Use and Retention in Psoriatic Arthritis: A Nationwide Korean Claims Analysis

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ABSTRACT

Aim: Biologic agents play a pivotal role in controlling both articular and cutaneous manifestations of psoriatic arthritis (PsA). Although international guidelines emphasize the appropriate use of biologics, Korea lacks standardized treatment protocols tailored for PsA across specialties. We therefore aimed to examine specialty-specific prescription patterns and treatment retention using nationwide claims data.

Methods: Health Insurance Review and Assessment (HIRA) claims data from 2011 to 2022 were analyzed, including patients with PsA who initiated treatment with their first biologic agent. Patients with concurrent autoimmune diseases were excluded. Trends in diagnosis, prescription patterns, and retention were analyzed according to medical specialty.

Results: Of the 2406 patients with PsA, 63.0% were diagnosed in dermatology departments and 32.8% in internal medicine departments. Most biologics were prescribed in the dermatology department (80.2%), while 17.8% were prescribed in the internal medicine department. Since 2016, dermatology has exhibited a marked increase in both PsA diagnoses and biologic prescriptions. Interleukin-23 (IL-23) inhibitors were the most frequently prescribed class (62.0%), followed by IL-17 inhibitors (21.9%) and tumor necrosis factor inhibitors (TNFi) (16.1%). Drug retention analysis revealed that dermatology was associated with a significantly higher risk of biologic discontinuation than internal medicine (hazard ratio = 1.40, 95% confidence interval 1.11–1.78).

Conclusion: The predominance of PsA diagnosis and biologic initiation in dermatology indicates substantial specialty-specific differences in practice. This pattern warrants careful evaluation and supports the development of standardized, evidence-based guidelines across specialties to promote appropriate care.

1 | Introduction

Psoriatic arthritis (PsA) is a chronic inflammatory arthritis associated with psoriasis. It shares genetic and clinical characteristics with other forms of spondyloarthritis, situating it within the broader spondyloarthritis spectrum [1, 2]. Globally, the prevalence of PsA is approximately 112 per 100 000 adults, with higher prevalence rates in Europe and North America than in Asia or South America [3]. Although the prevalence of PsA in Korea has not been well established, the incidence among patients with psoriasis has steadily increased, reaching 5.01 cases per 1000 person-years in 2020 [4].

Approximately 30% of patients with psoriasis develop PsA, and up to 15% of those managed in dermatologic settings may have undiagnosed PsA [5]. This diagnostic gap underscores the risk of under-recognition, particularly when skin symptoms are mild or when clinical attention remains focused on cutaneous

manifestations [6]. Delayed diagnosis and undertreatment of joint involvement further exacerbate disease burden [7–9]. These challenges emphasize the need to enhance clinician awareness and promote interdisciplinary collaboration among dermatologists, rheumatologists, and other specialists in the diagnosis and management of PsA.

Biologic agents have demonstrated substantial therapeutic efficacy in both psoriasis and PsA. Since the introduction of tumor necrosis factor inhibitors (TNFi) in the early 2000s, followed by the approval of interleukin-17 (IL-17) and interleukin-23 (IL-23) inhibitors for PsA in Korea, treatment outcomes for these conditions have markedly improved [10]. However, concerns persist regarding the potential overutilization of biologics in PsA because of ambiguity in diagnostic criteria and biologic indications [6, 10].

Such ambiguity may result in inappropriate use of costly medications and hinder consistent monitoring of treatment response and long-term disease control. Variations in diagnostic approaches and therapeutic strategies across medical specialties, such as dermatology and rheumatology, can lead to patient confusion and complicate clinical decision-making. Ultimately, these disparities may strain national healthcare resources and adversely affect patients' quality of life.

A health services perspective on biologic prescription patterns in PsA is therefore warranted. We aimed to examine the real-world use of biologics in Korean patients with PsA by analyzing nationwide data from the Health Insurance Review and Assessment Service (HIRA), with an emphasis on variations by hospital type and medical specialty. Additionally, we analyzed biologic drug retention rates to gain insights into their long-term use in clinical practice.

2 | Materials and Methods

2.1 | Patients

This study utilized data obtained from the HIRA, which included patients aged 20–85 years who were newly diagnosed with PsA between January 1, 2011, and June 30, 2022. Patients who had been diagnosed with PsA within 1 year before their index date were excluded. Eligible cases were identified using the corresponding ICD-10 codes for PsA (M07.0, M07.2, and M07.3) and the rare disease registration code (V237). Patients with diagnostic codes for systemic lupus erythematosus, rheumatoid arthritis, Behçet's disease, ankylosing spondylitis, or inflammatory bowel disease were excluded. Additionally, patients who did not revisit the hospital within 3 months of their initial diagnosis were excluded (Table S1).

Analysis of biologic agents was restricted to the first biologic prescription for each patient. To assess biologic drug retention, continuation was defined as a prescription of the same biologic agent within 180 days of the last prescription, whereas discontinuation was defined as switching to a different biologic agent, absence of any biologic prescription for more than 180 days, or prescription of the same biologic agent beyond 180 days after the last prescription.

2.2 | Clinical Characteristics of Patients

Patient characteristics included age (categorized into 10-year intervals starting from 20 years), sex, year of diagnosis, and prescription of biologic agents. Prescription data for biologic agents approved and covered by health insurance in South Korea were collected, including TNFi (e.g., adalimumab, etanercept,

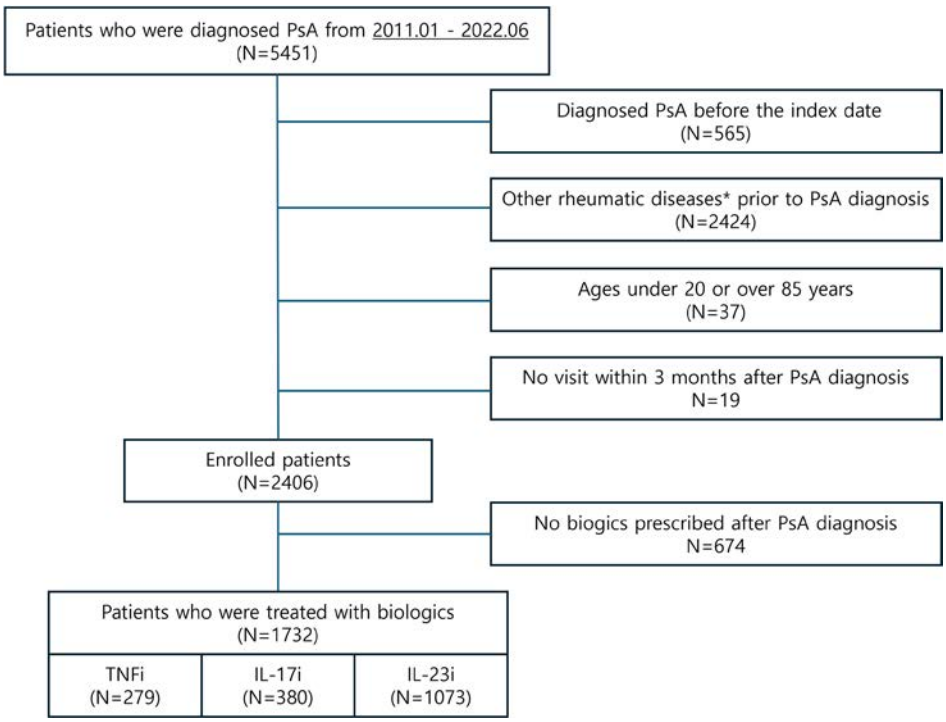

FIGURE 1 | Flowchart illustrating the process of patient selection. *Other rheumatic diseases as exclusion criteria include systemic lupus erythematosus, rheumatoid arthritis, Bechet's disease, ankylosing spondylitis, and inflammatory bowel disease.

TABLE 1 | Baseline characteristics of study participants diagnosed with PsA.

Variable	PsA diagnosis ($n = 2406$)	(%)	Prescribed biologics ($n = 1732$)	(%)
Age group (years)				
20–29	256	10.6	210	12.1
30–39	536	22.3	408	23.6
40–49	584	24.3	417	24.1
50–59	599	24.9	408	23.6
60–69	314	13.1	217	12.5
70–84	117	4.9	72	4.2
Sex				
Men	1533	63.7	1130	65.2
Women	873	36.3	602	34.8
Year of PsA diagnosis				
2012–2015	353	14.7	194	11.2
2016–2018	898	37.3	639	36.9
2019–2022.06	1155	48.0	899	51.9
Type of medical institution				
Tertiary hospital	1270	52.8	859	49.6
General hospital	1032	42.9	827	47.7
Hospital	19	0.8	8	0.5
Clinic	85	3.5	38	2.2
Clinical specialty				
Internal medicine	788	32.8	309	17.8
Dermatology	1515	63.0	1389	80.2
Orthopedics	74	3.1	32	1.8
Others	29	1.2	2	0.1
Comorbidities (1 year prior)				
Dyslipidemia	1128	46.9	817	47.2
Hypertension	656	27.3	455	26.3
Diabetes mellitus	399	16.6	271	15.6
Ischemic heart disease	147	6.1	96	5.5
Stroke	55	2.3	33	1.9
Asthma	206	8.6	146	8.4
COPD	16	0.7	9	0.5
Charlson comorbidity index				
0	1054	43.8	778	44.9
1	665	27.6	489	28.2
2+	687	28.6	465	26.8
Biologic agents used				
Adalimumab	226	9.4	226	13.0

(Continues)

TABLE 1 | (Continued)

Variable	PsA diagnosis ($n = 2406$)	(%)	Prescribed biologics ($n = 1732$)	(%)
Etanercept	44	1.8	44	2.5
Infliximab	26	1.1	26	1.5
Golimumab	31	1.3	31	1.8
Secukinumab	430	17.9	430	24.8
Ixekizumab	189	7.9	189	10.9
Ustekinumab	609	25.3	609	35.2
Guselkumab	671	27.9	671	38.7
Risankizumab	204	8.5	204	11.8

Abbreviations: CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease; PsA, psoriatic arthritis.

golimumab, and infliximab), IL-17i (e.g., secukinumab and ixekizumab), and IL-23i (e.g., ustekinumab, guselkumab, and risankizumab; Table S2). The hospital types and medical specialties responsible for diagnoses and prescriptions were also investigated. Comorbidities, including dyslipidemia, hypertension, ischemic heart disease, stroke, asthma, and chronic obstructive pulmonary disease (COPD), were identified using diagnostic codes from 1 year before the index date, and the Charlson Comorbidity Index (CCI) was calculated based on these data.

2.3 | Statistical Analysis

Continuous variables were expressed as means (standard deviations), whereas categorical variables were expressed as numbers (percentages). Statistical significance was set at $p < 0.05$, with all hazard ratios (HRs) reported alongside 95% confidence intervals (CIs). For basic statistical analyses, *t*-tests and chi-square tests were employed. Retention rates were analyzed using Kaplan–Meier survival curves, which were plotted for each biologic agent and stratified by specialty. The median survival time (in days), defined as the point at which 50% of the patients discontinued the biologic agent, was also calculated. To identify factors associated with the retention rate of biologic agents, HRs and adjusted HRs (aHRs) were calculated. The multivariate model for the aHRs included variables such as age, sex, and comorbidities.

Statistical analyses were conducted using SAS Enterprise Guide (version 6.1; SAS Institute Inc., Cary, NC, USA) and R (version 3.5.2; R Foundation for Statistical Computing, Vienna, Austria). Additional graphs were generated using Microsoft Excel.

3 | Results

From a total of 5451 patients with PsA-related diagnostic codes, 2406 newly diagnosed patients were enrolled. Among them, 674 did not receive a biologic agent prescription, whereas 1732 patients did. The distribution of biologic agent prescriptions was as follows: TNFi ($n = 279$), IL-17i ($n = 380$), and IL-23i ($n = 1073$) (Figure 1). As summarized in Table 1, the most common age group for both diagnosis and biologic agent prescription was 40–59 years (49.2% and 47.7%, respectively), and male patients comprised the majority of the cohort. Over 95% of the patients received both their PsA diagnosis and biologic agent prescription at a tertiary or general hospital. Notably, the majority of PsA diagnoses were made in the dermatology department (63.0%), followed by the internal medicine department (32.8%). For biologic prescriptions, the dermatology and internal medicine departments accounted for 80.2% and 17.8% of the prescriptions, respectively.

3.1 | Trends in Diagnosis and Prescription of PsA

Figure 2 illustrates longitudinal trends in PsA diagnoses and biologic prescriptions. As demonstrated in Figure 2A, the number of PsA diagnoses made by the internal medicine department remained relatively stable, whereas those made by the dermatology and other departments increased steadily after 2012.

As illustrated in Figure 2B, the number of prescriptions rose sharply in 2016 and thereafter stabilized, maintaining a trend comparable to the yearly incidence of newly diagnosed patients, indicating a trend toward early initiation of biologics. Figure 2C illustrates changes in the types of biologics prescribed. IL-23 inhibitor prescriptions rose sharply in 2016, followed by a gradual increase in IL-17 inhibitor prescriptions. These newer biologic classes were increasingly adopted over time, reflecting evolving real-world prescribing preferences. Overall, these findings indicate a significant shift not only in PsA diagnosis, with growing dermatology predominance, but also in its treatment, particularly in the early adoption of new biologic agents in dermatology practice.

3.2 | Characteristics of Biologic Agent Prescription

The median interval between PsA diagnosis and biologic agent prescription was 157 days (IQR: 17–448) (Table 2). Similarly, the median time for TNFi was 157 days (17–448), whereas it was substantially shorter for IL-17i (median 0 days [0–84]) and IL-23i (median 0 days [0–87]), indicating that these drugs were frequently prescribed immediately after diagnosis. Regarding hospital type, TNFi and IL-17i were most frequently prescribed

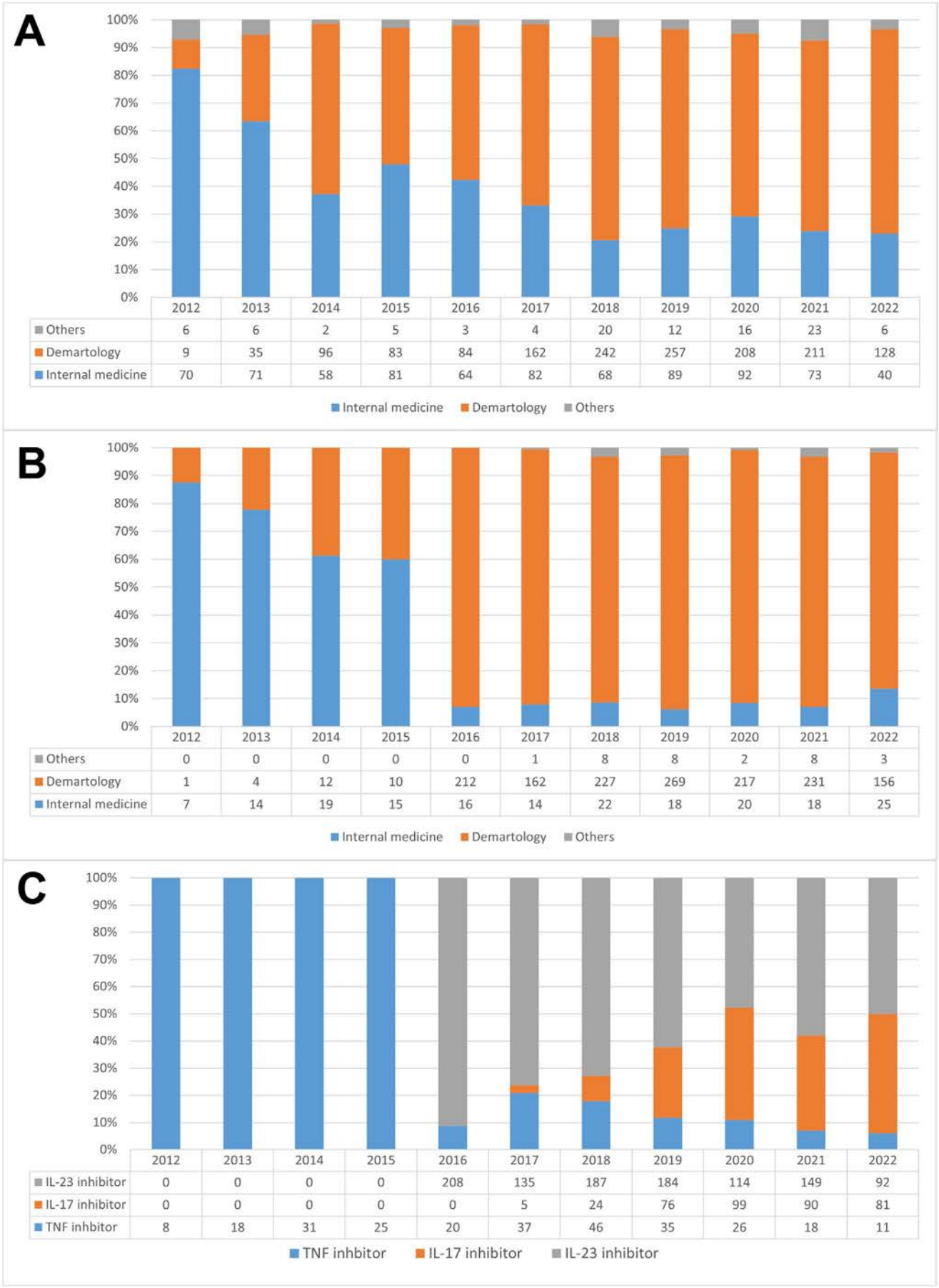

FIGURE 2 | Legend on next page.

FIGURE 2 | Trends in the diagnosis of psoriatic arthritis (PsA) and initiation of biologic agents. (A) Annual number of PsA diagnoses by department ($n = 2406$). (B) Annual number of patients with PsA initiating biologic agents by department ($n = 1732$). (C) Annual number of patients initiating each class of biologic agents ($n = 1732$).

at tertiary hospitals (68.5% and 52.6%, respectively), whereas IL-23i was most frequently prescribed at general hospitals (52.7%). Prescribing patterns also varied markedly by department: TNFi were primarily prescribed by the internal medicine department (60.2%), whereas IL-17i and IL-23i were almost exclusively prescribed by the dermatology department (94.5% and 96.8%, respectively). Differences in comorbidities were observed for dyslipidemia and asthma, and the CCI also differed across biologic treatment groups.

3.3 | Retention Rates of Biologic Agents

The retention rate of each biologic agent is illustrated in Figure 3. When all biologic agents were considered together, the time to 50% discontinuation was the longest in the dermatology department, followed by the internal medicine and other departments. However, as illustrated in Figure 3A, the retention curves for dermatology and internal medicine intersected around day 800, precluding definitive conclusions about which department achieved superior long-term persistence. The retention duration of TNFi was longer in the internal medicine department than in other departments, whereas for both IL-17i and IL-23i, it was longer in the dermatology department than in other departments (Figure 3B–D, respectively). The exact time to 50% discontinuation of each biologic agent by department is presented in Table S3. Notably, sample sizes were relatively balanced between internal medicine and dermatology for TNFi in Figure 3B, allowing meaningful comparison; conversely, sample sizes were substantially skewed toward dermatology for IL-17i and IL-23i in Figure 3C,D. This imbalance limits the interpretability of interdepartmental comparisons for these agents.

Figure S1A illustrates the comparison of biologic retention rates across departments, highlighting that IL-23 inhibitors exhibited the longest median time to discontinuation. However, the retention curves of IL-23i and TNFi intersect at approximately 1200 days, precluding a definitive conclusion regarding long-term persistence superiority between the two classes. Moreover, substantial differences in sample sizes among biologic agents hinder the direct comparison of retention superiority. Figure S1B,C illustrate department-specific retention patterns: in internal medicine, TNFi demonstrated the longest time to 50% discontinuation, whereas in dermatology, IL-23i demonstrated the longest time. However, because of unequal sample sizes and overlapping curves, it remains difficult to determine which treatment has superior persistence in either specialty.

3.4 | Hazard Ratios for Drug Retention

In the univariate analysis, IL-17 inhibitors were associated with a significantly higher risk of discontinuation than that observed with IL-23 inhibitors (HR = 1.39, 95% CI 1.24–1.57, $p < 0.001$), and this association remained consistent across all multivariable models (Table 3). Conversely, TNF inhibitors did not differ significantly in persistence compared with IL-23 inhibitors in any model. Older age (60–84 years) was associated with an increased risk of discontinuation.

Dermatology was associated with a significantly higher risk of discontinuation than that observed with internal medicine (multivariable 3: HR = 1.40, 95% CI 1.11–1.78, $p = 0.005$), a finding consistent across all models. However, given the substantial imbalance in sample sizes across biologic classes and specialties, and the presence of crossing Kaplan–Meier curves, these findings should be interpreted as descriptive associations rather than evidence of comparative superiority. Institution size also influenced retention outcomes, with higher discontinuation rates in smaller clinics and hospitals than in tertiary centers. These findings suggest specialty- and institution-level variation in real-world biologic prescribing and retention patterns. No comorbidities, including hypertension or diabetes, were significantly associated with the outcomes.

4 | Discussion

In Korea, PsA treatment with biologic agents involves multiple specialists. In this study, 63.0% of PsA diagnoses and 80.2% of biologic prescriptions originated from dermatology departments, demonstrating that dermatology plays a central role in the diagnosis and treatment of PsA in Korea. IL-17i and IL-23i constituted the majority of first-line biologic agents and were primarily prescribed by dermatologists, contrasting with internal medicine, where TNFi use was predominant. The risk of biologic discontinuation was significantly higher in dermatology than in internal medicine and higher in general hospitals, hospitals, and clinics than in tertiary hospitals. This study provides valuable insights into PsA management in Korea and underscores the need for standardized clinical guidelines across specialties to minimize specialty-driven variability in PsA management.

A key finding of this study is the pronounced disparity between dermatology and internal medicine departments in both diagnosis and treatment of PsA. Whereas PsA diagnoses and biologic prescriptions within internal medicine remained relatively stable throughout the study period, those in dermatology rose steadily and disproportionately. Between 2011 and 2020, only 309 out of 788 patients diagnosed with PsA in internal medicine (39.2%) received biologic therapy, a rate consistent with prior studies, in which biologic use rarely exceeded 60% [11–14]. Conversely, 1389 out of 1515 patients diagnosed in dermatology (91.7%) received biologics, indicating a substantially lower threshold for biologic initiation. This divergence indicates potential differences in diagnostic criteria, treatment decision-making, and policy adherence in dermatology-led PsA care [15, 16]. This divergence likely reflects differences in patient case-mix, diagnostic emphasis, and specialty-specific prescribing culture rather than simple non-adherence to guidelines. These findings highlight the complexity of real-world PsA management across specialties and

TABLE 2 | Distribution of biologic agents.

Variable	Total ($n=1732$)	TNFi ($n=279$)	IL-17i ($n=380$)	IL-23i ($n=1073$)	p
Days to biologic initiation, median (IQR)	157 (17–448)	157 (17–448)	0 (0–84)	0 (0–87)	—
Mean ± SD	188.3 ± 427.2	381.8 ± 620.3	149.9 ± 392.1	151.6 ± 359	
Min–max	0–3550	0–3550	0–2635	0–3062	
Year of biologic initiation, *n* (%)					
2012–2015	82 (4.7)	82 (29.4)	0 (0.0)	0 (0.0)	
2016–2018	662 (38.2)	103 (36.9)	29 (7.6)	530 (49.4)	
2019–2022.06	988 (57.0)	94 (33.7)	351 (92.4)	543 (50.6)	
Age group (years), *n* (%)					0.058
20–29	202 (11.7)	23 (8.2)	50 (13.2)	129 (12.0)	
30–39	395 (22.8)	78 (28.0)	83 (21.8)	234 (21.8)	
40–49	418 (24.1)	78 (28.0)	84 (22.1)	256 (23.9)	
50–59	411 (23.7)	65 (23.3)	89 (23.4)	257 (24.0)	
60–69	306 (17.7)	35 (12.5)	74 (19.5)	197 (18.4)	
Sex, *n* (%)					0.074
Men	1130 (65.2)	173 (62.0)	235 (61.8)	722 (67.3)	
Women	602 (34.8)	106 (38.0)	145 (38.2)	351 (32.7)	
Year of PsA diagnosis, *n* (%)					< 0.0001
2012–2015	194 (11.2)	91 (32.6)	1 (0.3)	102 (9.5)	
2016–2018	639 (36.9)	125 (44.8)	55 (14.5)	459 (42.8)	
2019–2022.06	899 (51.9)	63 (22.6)	324 (85.3)	512 (47.7)	
Type of medical institution, *n* (%)					< 0.0001
Tertiary hospital	860 (49.7)	191 (68.5)	200 (52.6)	469 (43.7)	
General hospital	826 (47.7)	83 (29.7)	178 (46.8)	565 (52.7)	
Hospital	9 (0.5)	4 (1.4)	2 (0.5)	3 (0.3)	
Clinic	37 (2.1)	1 (0.4)	0 (0.0)	36 (3.4)	
Clinical specialty, *n* (%)					< 0.0001
Internal medicine	192 (11.1)	168 (60.2)	20 (5.3)	4 (0.4)	
Dermatology	1509 (87.1)	111 (39.8)	359 (94.5)	1039 (96.8)	
Others	31 (1.8)	0 (0.0)	1 (0.3)	30 (2.8)	
Comorbidities (1 year prior), *n* (%)					
Dyslipidemia	873 (50.4)	136 (48.7)	166 (43.7)	571 (53.2)	0.005
Hypertension	481 (27.8)	90 (32.3)	98 (25.8)	293 (27.3)	0.160
Diabetes mellitus	297 (17.1)	49 (17.6)	67 (17.6)	181 (16.9)	0.925
Ischemic heart disease	93 (5.4)	14 (5.0)	24 (6.3)	55 (5.1)	0.650
Stroke	37 (2.1)	6 (2.2)	5 (1.3)	26 (2.4)	0.439
Asthma	154 (8.9)	36 (12.9)	25 (6.6)	93 (8.7)	0.017

(Continues)

TABLE 2 | (Continued)

Variable	Total ($n = 1732$)	TNFi ($n = 279$)	IL-17i ($n = 380$)	IL-23i ($n = 1073$)	p
COPD	12 (0.7)	4 (1.4)	4 (1.1)	4 (0.4)	0.103
Charlson comorbidity index, *n* (%)					0.016
0	705 (40.7)	90 (32.3)	158 (41.6)	457 (42.6)	
1	502 (29.0)	86 (30.8)	117 (30.8)	299 (27.9)	
2+	525 (30.3)	103 (36.9)	105 (27.6)	317 (29.5)	

Abbreviations: COPD, chronic obstructive pulmonary disease; IL-17i, interleukin-17 inhibitors; IL-23i, interleukin-23 inhibitors; IQR, interquartile range; PsA, psoriatic arthritis; SD, standard deviation; TNFi, tumor necrosis factor inhibitors.

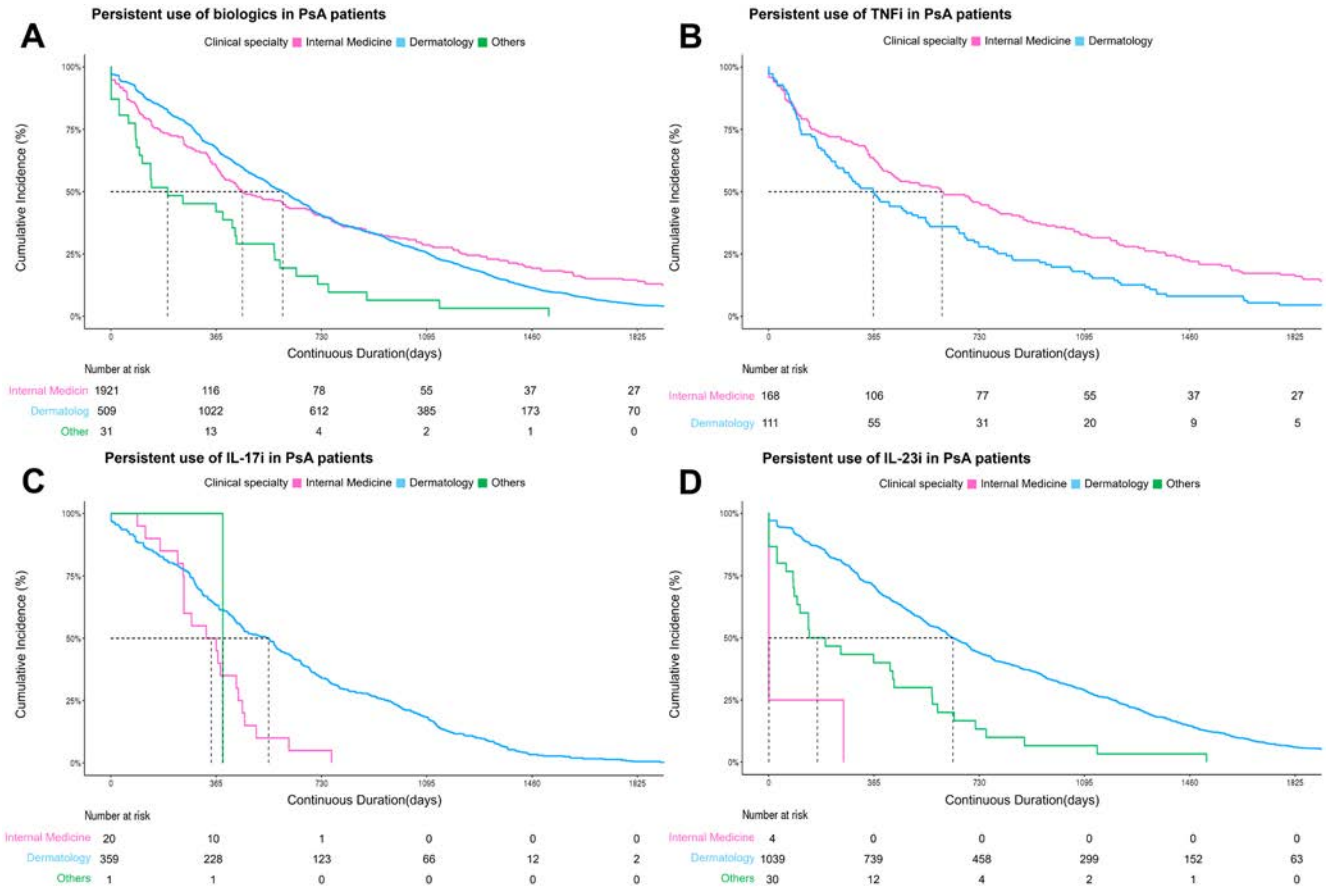

FIGURE 3 | Comparison of biologic drug retention rates by medical specialty. Kaplan–Meier survival curves illustrating retention rates of biologic agents by specialty. (A) Overall retention rates across all biologic classes. (B) Retention rates for tumor necrosis factor inhibitors (TNFi). (C) Retention rates for interleukin-17 inhibitors (IL-17i). (D) Retention rates for interleukin-23 inhibitors (IL-23i).

underscore the value of cross-specialty dialogue in developing consistent, context-appropriate treatment approaches.

Although PsA remains a rare intractable disease in Korea, its prevalence has increased over the past decade [4, 17]. Given that more than a decade has passed since nationwide health insurance coverage expanded access to biologic therapy for PsA [18], the rapid increase in prevalence is unlikely to be explained solely by epidemiological factors. Until the underlying causes of this trend are clarified, caution is warranted when interpreting findings based only on nationwide claims data. In large-scale cohort studies using health insurance databases, broad or nonspecific inclusion criteria are often applied to ensure adequate case numbers [19, 20]. However, if the clinical diagnosis of PsA is prone to variation or misclassification, for instance through inconsistent application of reimbursement indications, key epidemiological measures, including incidence, prevalence, and treatment rates, may be substantially biased. This limitation casts doubt on the reliability of national estimates regarding PsA burden, biologic prescription patterns, and downstream research on outcomes such as malignancy or comorbidities [21–24].

TABLE 3 | Cox proportional hazards models for biologic discontinuation among PsA patients initiating a first biologic agent.

	Univariate			Multivariable 1[a]			Multivariable 2[b]			Multivariable 3[c]			Multivariable 4[d]		
Variable	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***
Type of biologics															
TNFi	0.90	0.79–1.03	0.136	1.17	0.95–1.43	0.142	1.17	0.95–1.43	0.138	1.17	0.95–1.43	0.139	1.17	0.95–1.44	0.135
IL-17i	1.39	1.24–1.57	<0.001	1.47	1.31–1.66	<0.001	1.47	1.30–1.66	<0.001	1.45	1.29–1.64	<0.001	1.45	1.29–1.64	<0.001
IL-23i (ref)	1.00	—	—	1.00	—	—	1.00	—	—	1.00	—	—	1.00	—	—
Sex															
Male (ref)	1.00	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Female	1.05	0.95–1.16	0.299	—	—	—	—	—	—	—	—	—	—	—	—
Age group (years)															
20–59 (ref)	1.00	—	—	1.00	—	—	1.00	—	—	1.00	—	—	1.00	—	—
60–84	1.25	1.10–1.41	<0.001	1.17	1.03–1.34	0.019	1.17	1.03–1.34	0.018	1.24	1.10–1.41	0.001	1.24	1.10–1.41	0.001
Medical institution															
Tertiary hospital (ref)	1.00	—	—	1.00	—	—	1.00	—	—	1.00	—	—	1.00	—	—
General hospital	1.13	1.03–1.25	0.011	1.12	1.01–1.23	0.027	1.12	1.01–1.23	0.026	1.13	1.02–1.24	0.017	1.13	1.02–1.24	0.016
Hospital	1.98	1.02–3.81	0.042	2.64	1.34–5.21	0.005	2.42	1.25–4.71	0.009	2.52	1.28–4.96	0.008	2.33	1.20–4.53	0.012
Clinic	2.64	1.89–3.67	<0.001	3.98	2.04–7.77	<0.001	2.89	2.07–4.04	<0.001	3.90	2.00–7.61	<0.001	2.89	2.07–4.04	<0.001
Specialty															
Internal medicine (ref)	1.00	—	—	1.00	—	—	—	—	—	1.00	—	—	—	—	—
Dermatology	1.30	1.11–1.52	0.001	1.42	1.12–1.81	0.004	—	—	—	1.40	1.11–1.78	0.005	—	—	—
Others	2.92	1.99–4.29	<0.001	0.97	0.46–2.05	0.929	—	—	—	0.98	0.46–2.08	0.952	—	—	—
Department															
Internal medicine (ref)	—	—	—	—	—	—	1.00	—	—	—	—	—	1.00	—	—
Non-internal medicine	—	—	—	—	—	—	1.41	1.11–1.79	0.004	—	—	—	1.40	1.10–1.77	0.006

(Continues)

TABLE 3 | (Continued)

	Univariate			Multivariable 1[a]			Multivariable 2[b]			Multivariable 3[c]			Multivariable 4[d]		
Variable	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***
Comorbidities (1 year prior)															
Dyslipidemia	1.12	1.02–1.23	0.020	1.08	0.98–1.21	0.135	1.08	0.98–1.21	0.134	—	—	—	—	—	—
Hypertension	1.13	1.02–1.26	0.021	1.07	0.95–1.21	0.277	1.07	0.94–1.20	0.314	—	—	—	—	—	—
Diabetes mellitus	1.12	0.99–1.27	0.084	1.00	0.87–1.15	0.987	1.00	0.87–1.15	0.975	—	—	—	—	—	—
Ischemic heart disease	1.22	0.99–1.50	0.066	1.13	0.91–1.41	0.269	1.13	0.91–1.41	0.261	—	—	—	—	—	—
Stroke	1.02	0.74–1.41	0.912	—	—	—	—	—	—	—	—	—	—	—	—
Asthma	1.01	0.85–1.19	0.923	—	—	—	—	—	—	—	—	—	—	—	—
COPD	1.60	0.91–2.82	0.106	—	—	—	—	—	—	—	—	—	—	—	—
Charlson comorbidity index															
0 (ref)	1.00	—	—	—	—	—	—	—	—	—	—	—	—	—	—
1	1.01	0.90–1.13	0.892	—	—	—	—	—	—	—	—	—	—	—	—
2+	1.10	0.99–1.24	0.090	—	—	—	—	—	—	—	—	—	—	—	—

Note: Clinical specialty reflects the specialty code recorded in claims (internal medicine, dermatology, others). Department is a dichotomized variable (internal vs. non-internal medicine) used to account for potential misclassification of rheumatology-coded care within internal medicine in claims data.

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; IL-17i, interleukin-17 inhibitors; IL-23i, interleukin-23 inhibitors; PsA, psoriatic arthritis; TNFi, tumor necrosis factor inhibitors.

[a]Multivariable model 1 adjusted for age group, sex, type of medical institution, clinical specialty, and comorbidities (dyslipidemia, hypertension, diabetes mellitus, ischemic heart disease).

[b]Multivariable model 2 adjusted for age group, sex, type of medical institution, department (internal vs. non-internal), and the same comorbidities.

[c]Multivariable model 3 adjusted for age group, type of medical institution, and clinical specialty (parsimonious model).

[d]Multivariable model 4 adjusted for age group, type of medical institution, and department (parsimonious model).

Using cumulative national data, Bang et al. previously reported that only 11% of patients with PsA received biologics [4]. However, their analysis included patients diagnosed before biologic agents became widely accessible in Korea. Conversely, our study emphasized a more recently diagnosed cohort (2011–2022), a period characterized by substantial expansion in biologic use. Of the 2406 patients included, 1732 (71.9%) received biologic therapy, a proportion far exceeding previous reports. This pronounced increase indicates a substantial shift in treatment patterns, particularly after 2016, and may reflect both improved access and potential overutilization within current diagnostic and reimbursement systems. These patients likely represent a distinct treatment-era subgroup with unique therapeutic characteristics compared with earlier cohorts, underscoring the need for stratified analyses. To improve the validity of claims-based research, future studies must employ stricter inclusion criteria and foster cross-specialty collaboration in validating diagnostic definitions and treatment patterns.

Internal medicine departments demonstrated a significantly lower hazard ratio for biologic discontinuation than did dermatology departments, though the underlying reasons cannot be determined from claims data alone [17]. Notably, dermatologists predominantly prescribed IL-17 and IL-23 inhibitors and often initiated biologic therapy on the same day as PsA diagnosis (median time to initiation: 0 days), whereas TNF inhibitors were initiated much later (median: 157 days). This pattern may partly reflect prior dermatologic management of psoriasis rather than de novo biologic initiation for PsA, as psoriasis typically precedes joint involvement by several years [25–27]. Nevertheless, these specialty-related differences in treatment timing and drug selection highlight the potential value of multidisciplinary collaboration and consistent application of evidence-based criteria across specialties [25–27].

Drug retention reflects not only treatment efficacy and safety but also patient-related and external factors, including adherence, preferences, institutional formularies, and regional access [28, 29]. Accordingly, a higher retention rate does not necessarily imply a superior drug. Although IL-23i and IL-17i have demonstrated relatively longer retention times in several psoriasis-focused studies [28–30], findings have been inconsistent, warranting cautious interpretation. In our study, IL-23i also demonstrated the highest retention; however, this may partly reflect the disproportionately large number of prescriptions for this class, introducing potential bias. The primary aim of this analysis was not to determine the most effective biologic but to elucidate differences in prescribing patterns across specialties. From this perspective, retention patterns may reflect distinct specialty-specific preferences.

Tertiary hospitals demonstrated significantly higher biologic retention rates than other healthcare institutions, likely attributable to the concentration of PsA specialists, multidisciplinary care coordination, and streamlined administrative support for biologic use. Such centers typically provide timely treatment adjustments and patient education, both of which enhance long-term adherence. Conversely, smaller institutions may have limited clinical expertise or infrastructure capacity to support sustained disease management. These findings underscore the critical influence of institutional factors on biologic utilization and highlight the need to extend best practices across all tiers of care.

Some limitations should be considered. First, caution is warranted when interpreting drug retention rates, as both patient numbers and the preferred biologic classes vary considerably across medical specialties. Although TNFi were used with relative balance across departments, IL-17i and IL-23i prescriptions were predominantly concentrated in dermatology, with limited prescriptions in internal medicine. This imbalance complicates interdepartmental comparisons and warrants careful interpretation. Second, the analysis only included patients diagnosed with PsA after 2011, when biologics became more widely accessible in Korea. Consequently, patients diagnosed before this period were excluded, potentially limiting the generalizability of our findings. Third, the HIRA claims database does not capture biologic prescriptions issued outside the national insurance system (e.g., non-reimbursed or self-paid biologics), potentially resulting in underestimation of overall biologic use. Fourth, this study focused exclusively on the first biologic agent prescribed to each patient. Including second- or third-line biologic treatments could introduce additional complexity to the classification and interpretation. Fifth, because of the structure of claims data, prescriptions issued by rheumatologists are frequently categorized as internal medicine. However, considering the use of specific diagnostic and rare disease codes, it is reasonable to infer that most of these prescriptions originated from rheumatology specialists. Sixth, the 180-day gap criterion used to define discontinuation is consistent with prior Korean claims-based studies on biologic retention in inflammatory arthritis [31]. However, this threshold may influence retention estimates; a shorter gap would capture more discontinuation events, whereas a longer gap may overestimate persistence. These considerations should be borne in mind when interpreting the retention analyses. Finally, patients coded with M07.1 (arthritis mutilans) were excluded because its extremely low prevalence precluded a statistically meaningful subgroup analysis. Moreover, its markedly different clinical course and prognosis compared with other PsA subtypes could increase heterogeneity within the study population and potentially bias the interpretation of results.

5 | Conclusion

This nationwide analysis of the HIRA data revealed clear specialty-specific patterns in the diagnosis and biologic treatment of PsA in Korea. Dermatology accounted for the majority of PsA diagnoses and biologic prescriptions, with a strong preference for IL-17 and IL-23 inhibitors, whereas internal medicine demonstrated more conservative biologic use and lower hazard ratios for discontinuation in adjusted models. The marked differences in treatment timing, drug selection, and retention patterns across specialties reflect the heterogeneity of real-world PsA management and highlight the potential benefit of cross-specialty collaboration and consistent application of evidence-based approaches.

Author Contributions

Conceptualization: Bon San Koo. Methodology: Bon San Koo, Ye-Jee Kim. Data curation: Ye-Jee Kim. Formal analysis: Bon San Koo, Ye-Jee Kim, Yeo-Jin Lee. Investigation: Bon San Koo, Ye-Jee Kim, Yeo-Jin Lee. Validation: Bon San Koo, Ye-Jee Kim, Yeo-Jin Lee. Visualization: Bon San Koo, Ye-Jee Kim. Writing – original draft: Bon San Koo. Writing

– review and editing: All authors. Supervision: Bon San Koo, Yong-Gil Kim, Tae-Hwan Kim. Project administration: Bon San Koo, Yong-Gil Kim. Funding acquisition: Bon San Koo, Tae-Hwan Kim.

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Ethics Statement

This study was reviewed by the Institutional Review Board of Inje University Ilsan Paik Hospital (ISPAIK 2023-11-003-001) according to the ethical principles of the Declaration of Helsinki. All patient information was anonymized, and the processed data were provided by HIRA. Consequently, informed consent was not required.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The de-identified health insurance claims data that support the findings of this study are available from the Health Insurance Review and Assessment Service (HIRA) under license and with regulatory approval. Researchers seeking access for public-interest purposes must submit a formal application to HIRA via its designated data request form and pay the applicable processing fees. Data will be released only upon approval of the request. Please contact HIRA directly rather than the authors for all data access inquiries. Aggregate data outputs and the analytic code used in this study are available from the corresponding author upon reasonable request and are subject to HIRA's sharing policies.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** Specialty-based comparison of biologic drug classes using Kaplan–Meier curves (Overall, Internal Medicine, and Non-Internal Medicine departments). **Table S1:** Operational definitions of inclusion/exclusion criteria, outcome, and comorbidities (ICD-10 codes and HIRA definitions). **Table S2:** Medication codes for tumor necrosis factor α inhibitors, interleukin-17 inhibitors, and interleukin-23 inhibitors. **Table S3:** Median survival time of the persistence of biologics stratified by medical specialty.

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EDITORIAL

SGLT2 Inhibitors in Systemic Sclerosis–Associated Pulmonary Arterial Hypertension: A Translational Synthesis From Molecular Pathways to Clinical Potential

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Systemic sclerosis–associated pulmonary arterial hypertension (SSc-PAH) remains one of the most severe vascular complications of connective tissue disease, characterized by progressive pulmonary vascular remodeling, right ventricular (RV) dysfunction, and high mortality despite advances in targeted therapies [1, 2]. Current treatment strategies predominantly address vasoconstrictive pathways, including endothelin, nitric oxide, and prostacyclin signaling, yet fail to adequately target the underlying mechanisms of endothelial injury, fibrosis, inflammation, and metabolic dysregulation that drive disease progression.

Sodium–glucose cotransporter-2 (SGLT2) inhibitors have emerged as pleiotropic agents with established cardiovascular and renal benefits extending beyond glycemic control [3, 4]. Increasing evidence suggests that these agents modulate key biological pathways relevant to pulmonary vascular disease and RV dysfunction, supporting their potential relevance in SSc-PAH.

At a mechanistic level, SSc-PAH is characterized by endothelial dysfunction, impaired nitric oxide signaling, increased endothelin activity, and proliferation of pulmonary artery smooth muscle cells, accompanied by extracellular matrix deposition and fibrosis [5]. In parallel, metabolic reprogramming and mitochondrial dysfunction contribute to vascular remodeling and RV maladaptation, while chronic inflammation and immune activation further perpetuate vascular injury.

SGLT2 inhibitors appear to exert converging effects across these domains. These include improvement of myocardial and cellular energetics through enhanced mitochondrial efficiency [4], attenuation of profibrotic signaling and fibroblast activation [6], improvement of endothelial function and reduction of arterial stiffness [7], and modulation of inflammatory and oxidative pathways [8]. The proposed pathobiological mechanisms are summarized in Figure 1.

Although direct evidence in SSc-PAH is lacking, preclinical and clinical data from cardiovascular research provide indirect support for this concept. Experimental models have demonstrated attenuation of cardiac fibrosis and improved ventricular remodeling [9, 10]. In addition, large cardiovascular outcome trials have consistently shown reductions in heart failure hospitalization and improvements in cardiac structure and function [3, 4]. Given that RV dysfunction is the principal determinant of prognosis in pulmonary arterial hypertension, these observations are of particular relevance.

From a translational perspective, SGLT2 inhibitors may act on multiple interconnected mechanisms central to SSc-PAH, including metabolic dysfunction, fibrosis, inflammation, and RV maladaptation. This multimodal profile distinguishes them from current therapies and supports their potential role as adjunctive treatment. The key pathobiological domains and their potential modulation by SGLT2 inhibitors are summarized in Table 1.

Mislav Radić and Tina Bečić contributed equally to this work.

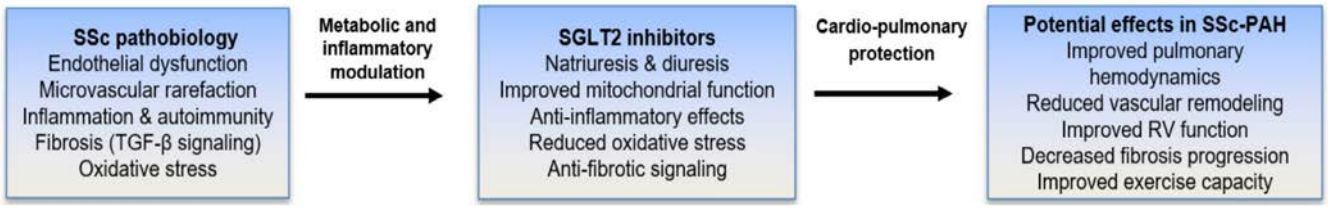

FIGURE 1 | Proposed pathobiological targets of sodium–glucose cotransporter-2 (SGLT2) inhibitors in systemic sclerosis–associated pulmonary arterial hypertension (SSc-PAH). SSc-PAH is characterized by endothelial dysfunction, inflammation, oxidative stress, fibrosis, and metabolic dysregulation, leading to pulmonary vascular remodeling and right ventricular (RV) dysfunction. SGLT2 inhibitors may exert pleiotropic effects across these pathways, including improvement of endothelial function, anti-inflammatory and antioxidative actions, attenuation of fibrotic signaling, and enhancement of myocardial energetics. PAH, pulmonary arterial hypertension; RV, right ventricle; SGLT2, sodium–glucose cotransporter-2; SSc, systemic sclerosis.

TABLE 1 | Translational rationale for SGLT2 inhibitors in systemic sclerosis–associated pulmonary arterial hypertension.

Pathobiological domain	Key abnormalities in SSc-PAH	Potential SGLT2 inhibitor effect	Current evidence base	Translational relevance
Endothelial dysfunction	Reduced nitric oxide bioavailability, enhanced endothelin signaling, impaired vascular homeostasis	Improved endothelial function and reduced arterial stiffness	Indirect human cardiovascular data	May complement vasodilator therapy by targeting vascular dysfunction
Inflammation/ oxidative stress	Immune activation, cytokine-driven vascular injury, oxidative stress	Anti-inflammatory and antioxidative modulation	Mechanistic and preclinical evidence	Could attenuate ongoing vascular remodeling
Fibrosis/matrix remodeling	Fibroblast activation and extracellular matrix deposition	Antifibrotic signaling with attenuation of profibrotic pathways	Experimental cardiac fibrosis models	Relevant to fibrotic vasculopathy in SSc-PAH
Metabolic and mitochondrial dysfunction	Abnormal cellular energetics in pulmonary vasculature and RV	Improved substrate utilization and mitochondrial efficiency	Mechanistic and heart failure data	May support RV adaptation and energy efficiency
Right ventricular maladaptation	Progressive RV remodeling and dysfunction, the main determinant of prognosis	Favorable effects on ventricular remodeling and loading conditions	Robust heart failure outcome trials; no dedicated SSc-PAH trial	Provides the strongest clinical rationale for prospective testing

Abbreviations: PAH, pulmonary arterial hypertension; RV, right ventricular; SGLT2, sodium–glucose cotransporter-2; SSc, systemic sclerosis.

However, several important limitations must be acknowledged. The available evidence is largely indirect and derived from heart failure and metabolic disease populations. The heterogeneity of systemic sclerosis and the absence of dedicated clinical trials in SSc-PAH limit definitive conclusions. Critical questions remain regarding patient selection, optimal timing of therapy, and integration with established treatment strategies.

Nevertheless, the convergence of mechanistic plausibility and clinical signals from related cardiovascular conditions provides a mechanistic and translational rationale for further investigation. These observations support the potential role of SGLT2 inhibitors as an adjunctive therapeutic strategy in SSc-PAH, particularly through targeting pathways not addressed by conventional vasodilator therapies.

Future research should focus on prospective clinical trials incorporating detailed hemodynamic assessment, imaging of RV function, and biomarkers of fibrosis and metabolic dysfunction. Such studies are essential to determine whether the mechanistic promise of SGLT2 inhibition translates into meaningful clinical benefit in this high-risk population.

In conclusion, SGLT2 inhibitors represent a biologically plausible therapeutic approach in SSc-PAH. By targeting multiple pathophysiological pathways, these agents may address

important gaps in current treatment paradigms and warrant dedicated clinical evaluation.

Author Contributions

Mislav Radić: conceptualization, supervision, investigation, visualization, writing – original draft, writing – review and editing. **Tina Bečić:** conceptualization, project administration, investigation, visualization, writing – original draft, writing – review and editing. **Petra Šimac Prižmić:** investigation, writing – original draft, writing – review and editing. **Tina Đogaš:** investigation, writing – original draft, writing – review and editing. **Josipa Radić:** supervision, investigation, writing – original draft, writing – review and editing. All authors have read and agreed to the published version of the manuscript.

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 analysed during the current study.

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EDITORIAL

Recent Advancements on CAR-T Therapy for the Management of Rheumatoid Arthritis: Mechanisms, Challenges and Clinical Insights

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1 | Introduction

Rheumatoid arthritis (RA) is an autoimmune chronic inflammatory disease primarily affecting joints, causing discomfort, swelling, and halting the quality of life. It is characterized by persistent overexpression of inflammatory cytokines including TNF-α and IL-6, etc. [1]. The pathophysiology involves complex humoral and cellular responses and infiltration of the synovium, monocytes, and lymphocytes. Currently, the treatment of RA includes initially pain alleviation and symptomatic management through NSAIDs, followed by DMARDs and modern biologics. Long term administration of these intervention leads to several concerns owing to multidrug resistance and non-targeted distribution and dose deposition resulting majority of the patients remain uncured and experience severe side effects [2]. After multidrug treatment, only a few patients experience long-lasting recovery and some experience relapses. Studies suggest that focusing on a single pathway might not be effective, so multi-centric therapeutic approaches like gene genetically reprogrammed cell-based therapies are required for RA management [3]. Chimeric antigen receptor T cell (CAR-T) cell therapies have the potential to target and destroy CD19/BCMA-positive B cells driving inflammation in RA, while improving immunological tolerance and healing properties [4]. This editorial aimed to critically analyze and highlight the translational development of next-generation cell-based therapeutics beyond conventional therapies, including CAR-T cell, along with ongoing recent clinical trials focused on their immunomodulatory applications in RA.

2 | CAR-T Cell Therapy

CAR-T cell therapy is a recent complex immunotherapy involving the genetic modification of autologous T cells to produce artificial antigen-binding receptors, which target the recognition of antigens on target cells. CAR-T therapy was initially used in hematological malignancies but has recently become the focus of attention in the context of autoimmune diseases, owing to its ability to selectively destroy pathogenic populations of immune cells and regulate dysregulated immune pathways [5]. CAR-T cells represent a novel therapy for RA through the recognition of B-cell-specific surface molecules. The B-cells activation and autoantibody generation indicate an epiphenomenon of T-cell-mediated autoimmunity, despite being the causative element of autoimmune diseases [6]. Even total depletion of B-cells may not effectively address autoreactive T cells that continue to sustain RA, and it remains unclear whether B-cells derived from plasma blasts or long-lived plasma cells are the predominant autoantibody sources in different autoimmune disorders [7]. Due to the antigens present on plasma cells compared to B cells and plasma blasts, they may evade therapy along with B-cell-targeted CAR T cells, hence perpetuating the RA process [8]. Resulting clinical manifestations such as persistent inflammation in RA

Abbreviations: CAAR-T, chimeric autoantibody-receptor T cells; CAR-T, chimeric antigen receptor T cell; COX, cyclooxygenase; CRS, cytokine release syndrome; DMARDs, disease-modifying antirheumatic drugs; IL, interleukin; NSAIDs, non-steroidal anti-inflammatory drugs; RA, rheumatoid arthritis; TNF, tumor necrosis factor.

lead to irreversible cartilage damage that may limit amelioration of symptoms even following effective CAR T therapies [8]. Along with antibody formation, B cells also regulate immune responses within the synovium by stimulating T cells, monocytes, and osteoclasts growth and proliferation through cytokine and mediator releases [9]. Temporary loss of CD20+ B cells is commonly associated with immunosuppression throughout the body, which leaves one more vulnerable to infections and even loss of the ability to respond to the recurring antigens [10]. Therefore, CAR-T therapy, through its ability to specifically target pathogenic B cells, can be considered a possible remedy to the shortcomings of the existing treatments of RA [9]. However, crucial issues concerning specificity in the treatment, drug-induced toxicity, and the reconstitution of the immune system in the long term are left without any solution. Additional streamlining of CAR design, patient selection, and dosing influences is hence necessary to be able to maximize therapeutic effects and reduce adverse events. Further translational studies and appropriately structured clinical trials are mandatory to determine the exact role of CAR-T therapy in the long-term treatment of rheumatoid arthritis [10].

2.1 | Inflammatory Toxicities of CAR-T Cell-Associated Cells: Mechanism to Prevention

The CAR-T cells identify the target antigens through their chimeric antigen receptors, which leads to selective destruction of disease-causing immune cells and autoimmune responses [11]. When it is activated, CAR-T cells release soluble inflammatory mediators that stimulate the surrounding myeloid cells to release pro-inflammatory cytokines including IL-6 and IL-1b, which further worsen systemic inflammation [12]. This cytokine cascade is the basis of cytokine release syndrome-driven inflammatory toxicities [12]. Treatment of the Chimeric Antigen Receptot T cell CAR-T-induced inflammatory toxicities is aimed via suppression of overproduction of cytokines. Widespread immune suppression by corticosteroids and specific interruption of specific inflammatory pathways by IL-6 block with tocilizumab and IL-1 block with anakinra were targeted [12]. These treatments decrease the cytokines and the activation of the myeloid cells, and hence reduce the toxicity. Preventive measures are meant to reduce the toxicities of inflammation both in terms of design and on molecular levels [13]. These are genetic alterations of CAR-T cells to trim inflammatory gene expression, multi-target CAR designs to maximize tumor specificity, and enhanced CAR designs that restrain hyper activation [13]. Other methods include cytokine binding, application of anti-inflammatory genes, receptor blocking, and transcriptional inhibitors to pre-emptively suppress cytokine relays and inflammatory amplification [13]. Figure 1 represents a summary of these processes and their matching management and prevention strategies.

2.2 | Clinical Trials of CAR-T Cell Therapies for the Management of RA

Clinical translation of CAR-T cell therapies is continuing at a rapid pace, with multiple phase I and II trials in autoimmune disorders. Examples include CD19-directed CAR-T cell therapy in antibody mediated autoimmune diseases for selective depletion of autoreactive B-cells with the aim of restoring immune tolerance (NCT06475495, NCT06428188) and CAR-T targeting B-cell antigens in refractory autoimmune diseases including RA (NCT07052565, NCT07100873). This represents a key step

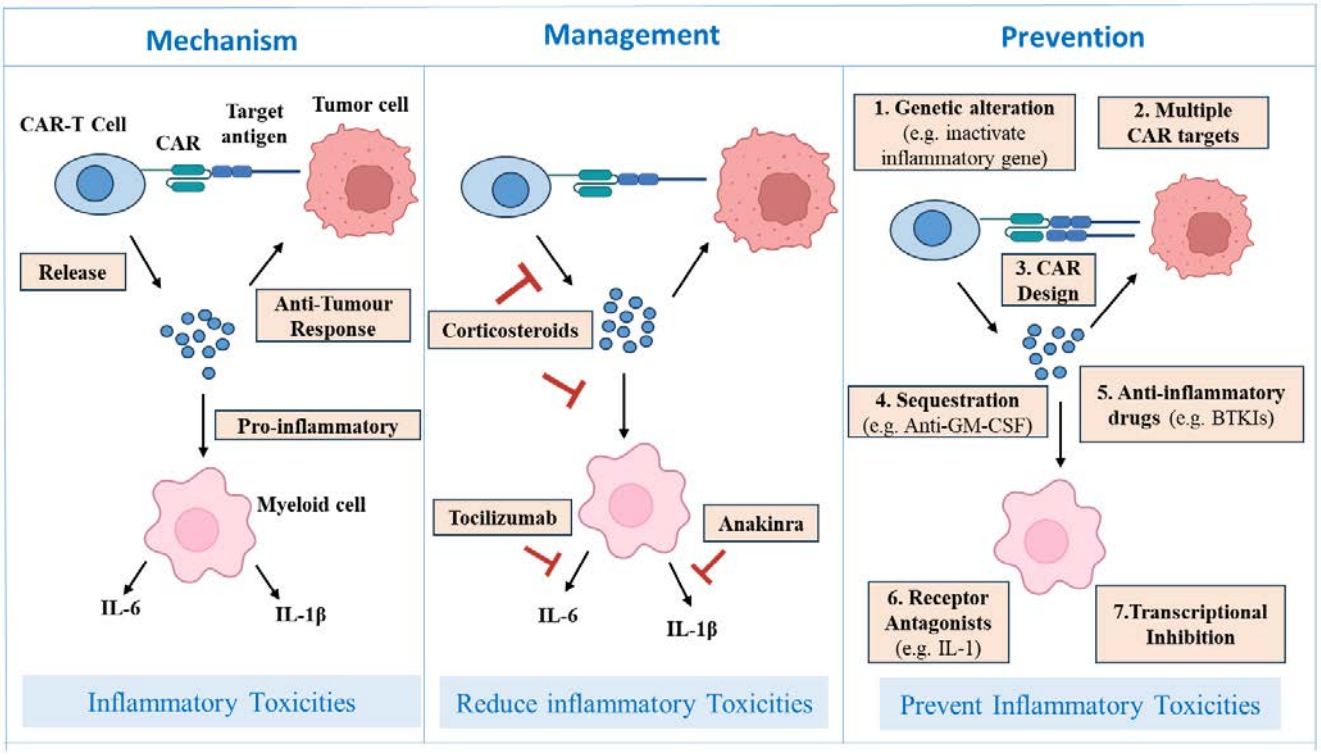

FIGURE 1 | Mechanisms, management, and prevention of CAR-T cell-associated inflammatory toxicities.

TABLE 1 | Clinical trials summary of CAR-T cell therapies.

ClinicalTrials.gov ID	Clinical phase	No of patients enrolled	Outcome measures (harmonized)	Interventions	References
NCT06475495	I/II	13	Primary: Safety and tolerability assessed by adverse events (NCI-CTCAE v5.0)	Drug: KYV101	[14]
NCT06428188	I/II	60	Primary: Maximum tolerated dose (MTD) and safety (NCI-CTCAE v4.03). Secondary: Clinical outcome assessment (COA)	BCMA/CD19 CAR-T cells, combined with chemotherapy	[15]
NCT07052565	NA	18	Primary: Safety assessed by adverse events, CRS grading (ASTCT), and NCI-CTCAE v5.0. Secondary: Disease activity assessment (DAS28) and SCAR02 evaluation	Drug: Anti-BCMA and CD19 CAR-T cell	[16]
NCT07100873	I	25	Primary: Safety and tolerability of AD1-001. Secondary: Clinical response and disease activity in rheumatoid arthritis	Drug: Anti-CD20 CAR-T	[17]
NCT05085431	Early phase I	9	Primary: Safety and tolerability assessed by NCI-CTCAE v5.0. Secondary: Preliminary clinical efficacy and feasibility	CD19/BCMA CAR T cells drug: CD19/BCMA CAR T-cells	[18]

toward clinical translation for rheumatology. CAR-T based therapies such as NCT05085431 are under investigation for organ-specific immune regulation, with favorable safety and tolerogenic potential in refractory Sjogren syndrome. An overview of ongoing clinical trials summary of CAR-T cell therapies is provided in Table 1.

3 | Novel CAR-T Cells in the Management of RA

CAR-T cell therapy is suggested as one of the immunomodulatory strategies to be used in the treatment of RA because this approach allows destroying pathogenic immune cells and retaining the immune homeostasis in a selective way [19]. The method can potentially confer remission in the long term because of the repurposing of the immune response partially. Short persistence in immune diseases, compared to oncological uses where long persistence is preferable, can help to decrease the risk of immune dysfunction and infection in the long term. Although it is necessary to mention that CAR-T products generated by the transient expression of mRNAs have demonstrated a promising therapeutic effect and reduced side effects. The recent CAR-T approaches in RA consider destroying autoreactive B cells that produce autoantibodies [20]. Chimeric autoantibody receptor T cells (CAAR-T) are selective in the recognition of disease-specific antigens and trigger cytotoxicity on pathogenic populations of B-cells. Regulatory CAR-T cells (CAR-Treg) are additionally being engineered as a way of increasing immune tolerance by reducing the overproduction of inflammatory reactions [21]. The proposed strategies are expected to lower the level of synovial inflammation, reduce the destruction of joints, and restore immune homeostasis, which illustrates the increasing therapeutic opportunities of CAR-T-based interventions in RA [22].

4 | Expert Opinion

Cell-based therapies, especially CAR-T, are a breakthrough in the cure of RA by the potential to induce sustained remission and restore immunological tolerance in case of failure of conventional medication. Present clinical trials, advances in cell sourcing and engineering, and growing insights into RA immunopathology will make these treatments more available, effective, and safer in the near future. In the meantime, its application must be exploratory and primarily based on strictly controlled clinical trials or compassionate use in refractory cases.

5 | Conclusion

Rheumatoid arthritis remains a complex autoimmune disease for which a substantial proportion of patients fail to achieve durable remission with currently available therapies. CAR-T cell–based immunotherapy offers a promising strategy to selectively eliminate pathogenic immune cell populations while potentially restoring long-term immune homeostasis. Beyond conventional CAR-T approaches, emerging platforms such as chimeric autoantibody receptor T cells (CAAR-T) and regulatory CAR-T cells (CAR-Treg) represent particularly attractive next-generation strategies because of their potential to provide antigen-specific

immune modulation and promote immune tolerance with reduced off-target effects. The ongoing CD19- and BCMA/CD19-directed clinical trials summarized in Table 1 are expected to provide important insights into the safety, feasibility, and therapeutic durability of CAR-T therapies in rheumatoid arthritis and related autoimmune disorders. Their outcomes may represent a critical translational milestone in determining whether engineered cellular immunotherapies can evolve from experimental interventions to disease-modifying treatments capable of achieving sustained remission in RA. Although challenges related to long-term safety, accessibility, and manufacturing remain, continued advances in CAR engineering are likely to accelerate the integration of precision cellular therapies into future rheumatoid arthritis management.

Author Contributions

Ravi Raj Pal: designed and supervised the manuscript; Bhawesh Kumar Mahato: drafted original manuscript; Ratnesh Kumar Yadav: edited; Vikas Kumar, Rajiv Ranjan: data collection and visualization.

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

Disease-Driven Versus Treatment-Driven Invisible Symptoms in Autoimmune Diseases: A Comparison of Systemic Lupus Erythematosus and Immune-Mediated Uveitis

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Dear Editor,

Patients with immune-mediated diseases frequently report fatigue, malaise, and other "invisible" symptoms that are often poorly correlated with laboratory findings yet significantly diminish quality of life (QoL) and psychological well-being [1, 2]. While the underlying disease primarily contributes to these issues, distinguishing between intrinsic disease manifestations and confounding adverse effects caused by immunosuppressive therapy remains a significant clinical challenge. In this study, we contrasted the burden of systemic lupus erythematosus (SLE), a prototypical multisystem disease, with that of immune-mediated uveitis. Uveitis was selected as a clinically relevant comparator because it represents an immune-mediated inflammatory condition that may require prolonged systemic immunosuppression, including classic immunosuppressants or biologic therapy, but can remain anatomically organ-limited. To better distinguish the impact of systemic disease burden from that of immune-mediated inflammation and its treatment, we limited the uveitis group to patients with immune-mediated uveitis without an identified systemic etiology. This allowed us to assess whether poorer quality of life and greater psychological distress were driven primarily by the multisystem nature of SLE rather than by immunosuppressive therapy alone.

We conducted a cross-sectional study recruiting 30 patients with stable SLE (SLEDAI-2K < 4) and 20 with immune-mediated uveitis from an outpatient autoimmune diseases clinic. Patients with uveitis associated with systemic inflammatory diseases, including Behçet's disease, sarcoidosis, or spondyloarthritis, were excluded. All patients had received active systemic treatment for over 6 months. QoL was assessed using the 36-item Short Form Health Survey (SF-36) and psychological distress with the Symptom Checklist-90 (SCL-90). Between-group comparisons used the Mann–Whitney *U* test. Stratified analyses by glucocorticoid and immunosuppressant use were performed to explore treatment confounding. The study was approved by our Ethics Committee (ref. PI-25-36-H-TFG).

The SLE group was older (median age 56 vs. 45) and had more females (100% vs. 80%) than the uveitis group. SLE patients used systemic glucocorticoids more often (60% vs. 25%), while uveitis patients favored methotrexate (65% vs. 9%). Both groups commonly received biologics, with SLE patients using belimumab (50%) and uveitis patients using adalimumab (70%).

SLE patients showed markedly worse SF-36 scores across physical and emotional domains, including role limitations due to physical or emotional problems, bodily pain, general health, and social functioning (all $p < 0.05$). The sole exception was the Mental Health scale ($p = 0.960$). Both Physical and Mental Component Summaries were significantly lower in SLE, with a more pronounced impairment in the physical component (Figure 1) [3]. On SCL-90, SLE patients scored significantly higher in somatization, obsessive-compulsive traits, interpersonal sensitivity, depression, phobic anxiety, and psychoticism, as well as in all three global indices (Global Severity Index, Positive Symptom Distress Index, and Positive Symptom Total). Dimensions of anxiety and hostility did not differ between groups. These differences persisted across treatment strata defined by glucocorticoid or immunosuppressant exposure,

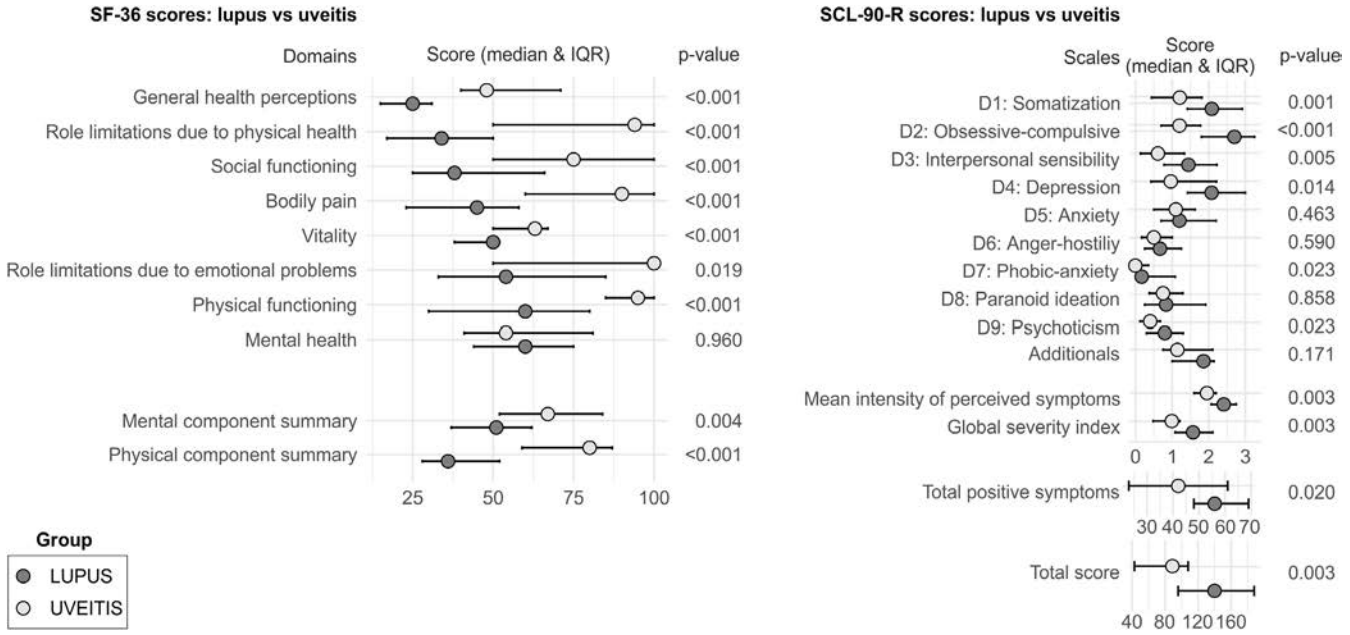

FIGURE 1 | SF-36 Physical Component Summary (PCS) and Mental Component Summary (MCS) scores, and SCL-90 Global Severity Index (GSI), in SLE versus immune-mediated uveitis patients. Bars represent medians with interquartile ranges. *$p < 0.05$, Mann–Whitney U test.

suggesting that pharmacological regimens alone are unlikely to fully explain the observed burden.

The results of this exploratory study suggest that the greater psycho-emotional burden observed in SLE patients may not be explained solely by treatment exposure. Instead, it appears to be a manifestation of the disease's multi-organ complexity and associated psychosocial variables [4, 5]. Despite uveitis patients receiving methotrexate, a drug associated with fatigue and malaise ("methotrexate hangover"), and similar rates of biologic therapy, their QoL and distress scores were substantially better than those of SLE patients [6]. Nevertheless, this interpretation should be considered cautiously. The small sample size, differences in age and sex distribution, and the lack of adjustment for cumulative glucocorticoid exposure, disease duration, comorbidities, and socioeconomic variables limit causal inference. Therefore, residual confounding cannot be ruled out.

Our study had several limitations. It was exploratory, used a convenience sample ($n = 50$), and lacked a formal power calculation. The two groups also differed in age, sex distribution, and treatment patterns, reflecting real-world clinical practice but limiting direct comparability. Glucocorticoids were more common in SLE, so their impact on mood and fatigue cannot be ruled out. Despite these factors, consistent between-group differences across treatments support systemic disease burden as the main cause [7]. Larger, matched cohorts with multivariable adjustment are needed to confirm whether systemic disease burden independently explains the poorer QoL and psychological distress observed in SLE.

Notably, uveitis patients also showed relevant psychological distress, particularly in anxiety, likely reflecting fear of vision loss and functional threat to sight [8, 9]. This underscores that organ-limited autoimmune conditions carry their own distinct psychological burden, distinct in quality from that of systemic disease. Together, these findings reinforce the need for multidisciplinary care integrating psychological support alongside immunosuppressive therapy in both disease contexts [10].

Author Contributions

Conception and design (C.A.-C., L.C.-G.), Acquisition of data (including patient recruitment and survey administration) (C.A.-C., L.C.-G.); Analysis and interpretation of data (C.A.-C., L.C.-G.); Drafting the article and revising it critically for important intellectual content (C.A.-C., L.C.-G.). Final approval of the version to be published (C.A.-C., L.C.-G.).

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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

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ORIGINAL ARTICLE

Longitudinal Frailty Status in Rheumatoid Arthritis and Its Association With Disease Activity and Glucocorticoid Use

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ABSTRACT

Objective: To examine factors associated with a higher long-term frailty status in patients with rheumatoid arthritis (RA).

Methods: We analyzed 313 patients who had complete annual Japanese version of the Cardiovascular Health Study (J-CHS) assessments from 2020 to 2025. Frailty status was evaluated using the mean J-CHS score across the study period, and patients were classified into two groups: mean J-CHS ≤ 2 ($n = 236$) and mean J-CHS > 2 ($n = 77$). Factors associated with mean J-CHS > 2 were examined using logistic regression analysis.

Results: Compared to patients with mean J-CHS ≤ 2, those with mean J-CHS > 2 were older (63.9 vs. 68.2 years) and had a longer disease duration (9.8 vs. 15.1 years), higher disease activity (mean DAS28-ESR: 2.44 vs. 3.17), higher rate of glucocorticoid use (23.3% vs. 36.4%), and worse physical function (mean HAQ-DI: 0.21 vs. 0.77). Logistic regression analysis identified longer disease duration (OR 1.06), higher DAS28-ESR (OR 2.38), and glucocorticoid use (OR 2.90) as independent factors associated with mean J-CHS > 2. In longitudinal analyses, patients with higher frailty status consistently exhibited higher glucocorticoid use over time. Among patients who achieved baseline remission, disease activity remained comparable between groups, whereas glucocorticoid use remained consistently higher in patients with mean J-CHS > 2.

Conclusions: Long-term frailty status in RA was associated with disease duration and treatment patterns, particularly continued glucocorticoid exposure. Even among patients in remission, those with mean J-CHS > 2 showed persistently higher glucocorticoid use despite comparable disease activity, without corresponding DMARD intensification, which may reflect differences in treatment patterns in this subgroup.

1 | Introduction

Frailty is a clinical syndrome characterized by age-related declines in physiological reserve, leading to an increased risk of adverse outcomes such as falls, fractures, physical disability, and mortality [1]. In patients with rheumatoid arthritis (RA), chronic inflammation, joint destruction, pain, and reduced physical activity interact and contribute to a higher prevalence of frailty compared with the general elderly population [2]. However, many patients with RA are not yet frail but belong to the preceding pre-frailty stage [3], and understanding transitions within this stage is essential for effective frailty prevention.

Recent advances in treatment, including methotrexate (MTX)-based therapy, biologic agents, and Janus kinase (JAK) inhibitors, have markedly improved disease control in RA [4].

Despite these therapeutic developments, some patients continue to experience progressive declines in muscle strength and physical performance, even when inflammation is well controlled, suggesting that frailty progresses independently of inflammatory activity [5, 6]. Multiple factors, such as a history of chronic inflammation, reduced physical activity, nutritional insufficiency, long-term glucocorticoid (GC) use, and aging, may contribute to this phenomenon, making frailty difficult to reverse even after disease remission. Therefore, comprehensive management of RA should include not only control of disease activity but also an evaluation of physical function and lifestyle factors [7].

To address this issue, a multicenter longitudinal observational cohort study was initiated in 2020 to continuously track frailty trajectories in patients with RA. Previous analyses have confirmed that a large proportion of these patients fall into the pre-frailty stage, and long-term observational data of this cohort provide a unique opportunity to evaluate temporal changes using pre-frailty as a central reference point (8).

Frailty is not a fixed condition but a reversible and dynamic concept influenced by physical and disease-related factors [8]. In patients with RA, pre-frailty represents the most prevalent state, as reported in previous studies and consistently observed in our cohort [9, 10]. From a clinical perspective, therefore, a realistic therapeutic goal is not a complete transition to robustness but instead maintaining patients within the pre-frailty–robust range, or allowing fluctuations within this favorable spectrum. In contrast, progression from pre-frailty toward frailty reflects increasing vulnerability and is more strongly influenced by declines in physical function and disease-related factors [11]. Accordingly, identifying the characteristics of patients who fluctuate within the pre-frailty–robust range, rather than those who progress toward frailty, is essential for preventing deterioration.

In this study, we aimed to characterize longitudinal patterns of frailty in patients with RA using repeated assessments of the J-CHS frailty score. By focusing on long-term frailty status and its temporal stability, rather than single time point measurements, we sought to better understand heterogeneity within the pre-frailty–robust range and to identify features associated with increased vulnerability to progression to frailty.

2 | Materials and Methods

2.1 | Patients

Patients with RA who fulfilled the 2010 American College of Rheumatology/European League Against Rheumatism classification criteria [12] and were followed at three participating institutions between June 1, 2020, and August 31, 2025, were considered for eligibility ($n = 662$). These individuals constituted the source population for the present longitudinal cohort analysis.

From this cohort, we identified patients who had undergone annual frailty assessments using J-CHS criteria throughout the 2020–2025 period. Patients without J-CHS data for any of the six assessment years were excluded ($n = 349$). After applying these exclusion criteria, 313 patients were included in the final analytic sample.

For each participant, the mean J-CHS score from 2020 to 2025 was calculated to represent overall frailty status during the six-year observation period. Participants were then categorized into two groups according to this mean score: those with a mean J-CHS score ≤ 2 and those with a mean J-CHS score > 2. The cutoff value of 2 points was selected because a J-CHS score of 1–2 corresponds to pre-frailty, whereas scores ≥ 3 indicate frailty. Thus, a mean J-CHS score > 2 reflects an overall higher frailty status during the study period. Although this approach does not describe year-to-year transitions, it allows comparison of relative frailty status between groups over time. Based on this classification, 236 patients were assigned to the mean J-CHS ≤ 2 group and 77 patients to the mean J-CHS > 2 group.

2.2 | Frailty Assessment

Frailty status was determined according to J-CHS criteria [13], an adaptation of the original CHS framework [14] that has been validated for its diagnostic reliability in Japanese individuals. The J-CHS assessment comprises five domains: unintentional weight loss, reduced muscle strength, self-reported exhaustion, slowed gait speed, and decreased physical activity.

Grip strength was measured using a Smedley-type hand dynamometer (TTM Smedley Dynamo Meter; Tsutsumi, Tokyo, Japan) with participants standing and their elbows fully extended. Each hand was tested twice, and the higher of the two values was used for analysis in accordance with recommendations of the Asian Working Group for Sarcopenia [15]. Based on total J-CHS scores, patients were categorized as robust (0 points), pre-frail (1–2 points), or frail (≥ 3 points).

2.3 | Clinical Assessment

Routine clinical evaluations were performed by board-certified rheumatologists. These evaluations included examinations of tender and swollen joint counts and determinations of Steinbrocker stage [16], along with a detailed review of current pharmacologic therapy. Standard laboratory testing was also conducted, including measurements of C-reactive protein (CRP), rheumatoid factor (RF), erythrocyte sedimentation rate (ESR), and matrix metalloproteinase-3 (MMP-3).

2.4 | Evaluation of Disease Activity and Physical Function

Disease activity was quantified using the DAS28-ESR, which integrates tender and swollen joint counts, the patient's global assessment, and the ESR value [3]. Disease activity was categorized according to established cutoffs: remission (< 2.6), low disease activity (2.6–3.2), moderate disease activity (3.2–5.1), and high disease activity (> 5.1) [17]. Physical function was evaluated using the Japanese version of the Health Assessment

Questionnaire Disability Index (HAQ-DI), with functional remission defined as a HAQ-DI score ≤0.5 [18, 19].

2.5 | Comorbidities

Information on comorbidities was obtained from electronic medical records. The presence of interstitial pneumonia was determined based on chest radiography and computed tomography findings documented in the charts. Renal function was assessed using the estimated glomerular filtration rate (eGFR), and patients with an eGFR $<60\,mL/min/1.73\,m^2$ were categorized as having decreased renal function [20]. In addition, a history of diabetes mellitus and any prior malignancy was extracted from the medical records.

2.6 | Missing Data

The breakdown of missing data is as follows: four for body mass index (BMI) (4/313, 1.3%), 14 for ACPA (14/313, 4.5%), two for RF (2/313, 0.6%), three for CRP (3/313, 1.0%), nine for ESR (9/313, 2.9%), eight for MMP3 (8/313, 2.6%), nine for DAS28-ESR (9/313, 2.9%), and one for HAQ-DI (1/313, 0.3%).

2.7 | Statistical Analysis

All statistical tests were two-sided, with the significance level set at $p<0.05$. Unless otherwise noted, values are presented as mean ± standard deviation. Patient characteristics between the mean J-CHS ≤2 and mean J-CHS >2 groups were compared using univariate analyses (Mann–Whitney *U* test and chi-square test). To identify factors associated with belonging to the mean J-CHS >2 group from 2020 to 2025, logistic regression analysis was performed, adjusting for age, disease duration, BMI, DAS28-ESR, MTX use, biologic/targeted synthetic DMARDs (b/tsDMARDs) use, and GC use.

In the longitudinal comparison of disease activity and GC use between the mean J-CHS ≤2 and mean J-CHS >2 groups (2020–2025), yearly DAS28-ESR values were compared using the Mann–Whitney U test. Annual proportions of GC users were assessed using Fisher's exact test, and GC dosages were compared using the Mann–Whitney U test. Dosage analyses were restricted to patients receiving glucocorticoids (GCs), and GC use was defined as systemic glucocorticoids (oral) at the time of each annual assessment, with doses expressed as prednisolone equivalents (mg/day).

Trajectories of DAS28-ESR from 2020 to 2025 were analyzed according to baseline remission status. Patients with missing baseline DAS28-ESR data ($n=2$) were excluded from this analysis, resulting in 173 patients in the baseline remission group and 138 in the non-remission group. Yearly DAS28-ESR values were compared between the two groups using the Mann–Whitney U test. In addition, annual proportions of GC users and GC dosages were evaluated in the same manner as described above. Furthermore, within the baseline remission group, annual proportions of MTX users and b/tsDMARDs users were assessed using Fisher's exact test, and MTX dosage was compared using the Mann–Whitney U test. Similar analyses were also performed in patients without baseline remission.

To assess potential selection bias, baseline characteristics were compared between included and excluded patients.

To further account for repeated measurements within individuals, generalized estimating equations (GEE) were performed using a logit link and binomial distribution. Frailty status (1 = frailty, 0 = non-frailty) was used as the dependent variable, and year, DAS28-ESR, MTX use, glucocorticoid use, and b/tsDMARDs use were included as independent variables, using all available repeated longitudinal measurements from 2020 to 2025.

To approximate cumulative glucocorticoid exposure, proxy measures were calculated, including the mean duration of GC use and the mean annual prednisolone-equivalent GC dose during the observation period (2020–2025). These variables were compared between groups using the Mann–Whitney *U* test.

To evaluate factors associated with progression to frailty, an additional multivariate logistic regression analysis was performed among patients who were non-frail at baseline (J-CHS <3). In addition, among patients without frailty at baseline (J-CHS <3), patients were further classified as robust (J-CHS = 0) or pre-frail (J-CHS = 1–2), and the proportion of patients who developed frailty during the observation period was compared between these groups using the chi-square test. The dependent variable was frailty status at the final assessment in 2025, and independent variables included age, sex, disease duration, DAS28-ESR, and glucocorticoid use.

All analyses were conducted using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical interface for R (The R Foundation for Statistical Computing, Vienna, Austria), modified explicitly from R Commander to include statistical functions commonly used in biostatistics [21].

3 | Results

3.1 | Baseline Characteristics According to Mean J-CHS Score

In the total cohort ($n=313$), mean age was 65.0 years, mean disease duration was 11.1 years, mean DAS28-ESR was 2.63, and mean HAQ-DI was 0.35. Compared to patients in the mean J-CHS ≤2 group, those in the mean J-CHS >2 group were older (63.9 vs. 68.2 years, $p=0.010$) and had a longer disease duration (9.8 vs. 15.1 years, $p<0.001$). The rate of GC use was higher in the mean J-CHS >2 group (23.3% vs. 36.4%, $p=0.027$), whereas that of MTX use was lower (73.6% vs. 60.8%, $p=0.041$). Patients in the mean J-CHS >2 group also showed more advanced disease status, with higher Steinbrocker stage and class (both $p<0.001$). In addition, disease activity and

TABLE 1 | Baseline characteristics according to mean J-CHS score.

Overall (2020 baseline data)		Total ($n=313$)	Mean J-CHS ≤2 ($n=236$)	Mean J-CHS >2 ($n=77$)	p
Age (years)	Mean (SD)	65.0 (12.8)	63.9 (13.1)	68.2 (11.3)	0.010
Duration of disease (years)	Mean (SD)	11.1 (9.5)	9.8 (8.3)	15.1 (11.7)	<0.001
Sex, female (%)		73.8	73.4	74.0	1
BMI (kg/m^2)	Mean (SD)	22.1 (3.9)	22.2 (3.8)	22.0 (4.0)	0.577
Steinbrocker stage (1/2/3/4) (%)		37.4/23.3/17.9/21.4	42.4/24.2/17.4/16.1	22.1/20.8/19.5/37.7	<0.001
Steinbrocker class (1/2/3/4) (%)		42.8/47.0/9.3/1.0	50.8/44.1/5.1/0	18.2/55.8/22.1/3.9	<0.001
Glucocorticoid use rate (%)		26.5	23.3	36.4	0.027
Methotrexate use rate (%)		70.5	73.6	60.8	0.041
b/tsDMARDs use rate (%)		39.6	36.9	48.1	0.107
Anti-CCP antibody (U/ml)		150.2 (286.3)	156.9 (292.7)	126.4 (152.1)	0.948
Rheumatoid factor (IU/ml)		108.0 (263.4)	106.2 (289.8)	113.2 (160.1)	0.377
CRP (mg/dl)	Mean (SD)	0.23 (0.44)	0.19 (0.30)	0.35 (0.70)	0.181
ESR 1 h (mm)	Mean (SD)	22.0 (18.4)	20.6 (18.0)	26.0 (19.2)	0.018
MMP-3 (ng/ml)	Mean (SD)	77.1 (61.4)	72.0 (57.2)	93.0 (71.2)	0.023
DAS28-ESR	Mean (SD)	2.63 (1.05)	2.44 (0.95)	3.17 (1.15)	<0.001
HAQ-DI	Mean (SD)	0.35 (0.53)	0.21 (0.39)	0.77 (0.66)	<0.001
Decreased renal function (eGFR <60 mL/min/1.73 m^2) (%)		34.5	30.8	42.5	0.101
Lung disease (%)		9.9	8.9	13.0	0.282
Diabetes mellitus (%)		9.6	7.2	16.9	0.023
Malignancy		10.9	10.2	13.0	0.528

Note: Data are presented as mean ± standard deviation or percentage.
Abbreviations: anti-CCP antibody, anti-cyclic citrullinated peptide antibody; BMI, body mass index; b/tsDMARDs, biological and targeted synthetic disease-modifying antirheumatic drugs; CRP, C-reactive protein; DAS28-ESR, disease activity score 28-erythrocyte sedimentation rate; eGFR, estimated-glomerular filtration rate; ESR, erythrocyte sedimentation rate; HAQ-DI, health assessment questionnaire-disability index; MMP3, matrix metalloproteinase 3; MTX, methotrexate.

functional impairment were more pronounced in the mean J-CHS >2 group, as indicated by higher DAS28-ESR scores (2.44 vs. 3.17, $p<0.001$) and higher HAQ-DI scores (0.21 vs. 0.77, $p<0.001$) (Table 1).

To assess potential selection bias, baseline characteristics were compared between included and excluded patients (File S1). No substantial differences were observed between the two groups, although patients included in the analysis had lower disease activity and a lower prevalence of lung disease.

3.2 | Factors Associated With Higher Frailty Status and Its Longitudinal Characteristics in Patients With RA

Factors associated with a higher mean J-CHS score (>2) included duration of disease (odds ratio [OR] 1.06, 95% confidence interval [CI] 1.03–1.10, $p<0.001$), DAS28-ESR (OR 2.38, 95% CI 1.71–3.30, $p<0.001$), and GC use (OR 2.90, 95% CI 1.49–5.63, $p=0.002$) (Table 2).

TABLE 2 | Predictors associated with mean J-CHS >2 from 2020 to 2025 in patients with rheumatoid arthritis.

Factor (Mean J-CHS >2)	Odds ratio	p
Intercept	0.01 (0.00–0.35)	0.009
Age (y.o.)	1.01 (0.98–1.04)	0.544
Sex, female	0.63 (0.30–1.32)	0.224
Disease duration	1.06 (1.03–1.10)	<0.001
BMI	0.98 (0.90–1.06)	0.605
DAS28-ESR	2.38 (1.71–3.30)	<0.001
MTX use	0.63 (0.31–1.26)	0.188
Glucocorticoid use	2.90 (1.49–5.63)	0.002
b/tsDMARDs use	1.39 (0.73–2.63)	0.317

Note: Data are presented as mean ± standard deviation.
Abbreviations: b/tsDMARDs, biological and targeted synthetic disease-modifying antirheumatic drugs; BMI, body mass index; DAS28-ESR, disease activity score 28-erythrocyte sedimentation rate; MTX, methotrexate.

In the GEE analysis, similar associations were observed between frailty status and DAS28-ESR, glucocorticoid use, and MTX use (File S2).

As a proxy for cumulative glucocorticoid exposure, both the mean duration of GC use and the mean annual GC dose were significantly higher in patients with mean J-CHS > 2 (File S3).

To further evaluate temporal changes in frailty status, an additional analysis focusing on progression to frailty was conducted. Among 264 patients without frailty at baseline, 48 progressed to frailty by 2025. In multivariate logistic regression analysis, disease duration (OR 1.04, 95% CI 1.00–1.08, $p = 0.035$) and glucocorticoid use (OR 2.47, 95% CI 1.22–5.02, $p = 0.012$) were independently associated with progression to frailty, while DAS28-ESR showed a trend toward association (OR 1.36, 95% CI 0.99–1.86, $p = 0.058$) (File S4).

In addition, among patients without frailty at baseline ($n = 264$), the proportion of patients who developed frailty during follow-up was significantly higher in the pre-frail group than in the robust group (41.9% vs. 21.8%, $p = 0.002$). Similarly, patients with a mean J-CHS score > 2 showed a higher frequency of progression to frailty than those with a mean J-CHS score ≤ 2 (File S5).

3.3 | Longitudinal Comparison of Disease Activity and GC Use Between Mean J-CHS ≤ 2 and J-CHS > 2 Groups

First, longitudinal trajectories of DAS28-ESR were examined in the mean J-CHS ≤ 2 and mean J-CHS > 2 groups. Across all years, the mean J-CHS > 2 group consistently demonstrated higher mean DAS28-ESR values compared to the mean J-CHS ≤ 2 group (mean J-CHS ≤ 2 vs. mean J-CHS > 2: 2020, 2.44 ± 0.95 vs. 3.17 ± 1.15, $p < 0.001$; 2021, 2.45 ± 0.94 vs. 3.05 ± 1.02, $p < 0.001$; 2022, 2.40 ± 0.92 vs. 3.33 ± 1.31, $p < 0.001$; 2023, 2.40 ± 0.95 vs. 3.11 ± 1.19, $p < 0.001$; 2024, 2.37 ± 0.97 vs. 3.24 ± 1.15, $p < 0.001$; 2025, 2.48 ± 1.04 vs. 3.32 ± 1.21, $p < 0.001$) (Figure 1A).

Next, GC use rates were compared between the two groups. In every year, the mean J-CHS > 2 group exhibited higher GC use rates than the mean J-CHS ≤ 2 group (mean J-CHS ≤ 2 vs. mean J-CHS > 2: 2020, 23.3% vs. 36.4%, $p = 0.027$; 2021, 22.0% vs. 29.9%, $p = 0.169$; 2022, 21.2% vs. 31.2%, $p = 0.089$; 2023, 20.0% vs. 32.9%, $p = 0.028$; 2024, 20.3% vs. 30.7%, $p = 0.081$; 2025, 18.2% vs. 29.9%, $p = 0.036$) (Figure 1B).

Finally, GC dosage was compared between the groups. No statistically significant differences in GC dosage were observed between the mean J-CHS ≤ 2 and mean J-CHS > 2 groups in any year during the study period (mean J-CHS ≤ 2 vs. mean J-CHS > 2: 2020, 3.7 ± 1.7 vs. 3.9 ± 2.4 mg, $p = 0.964$; 2021, 3.3 ± 1.9 vs. 3.7 ± 2.3 mg, $p = 0.496$; 2022, 3.0 ± 1.5 vs. 3.4 ± 1.9 mg, $p = 0.486$; 2023, 3.0 ± 1.4 vs. 3.4 ± 1.9 mg, $p = 0.521$; 2024, 3.0 ± 1.4 vs. 3.5 ± 1.7 mg, $p = 0.363$; 2025, 3.1 ± 1.8 vs. 3.6 ± 1.7 mg, $p = 0.244$) (Figure 1C).

3.4 | DAS28-ESR Trajectories According to Baseline Remission Status

To clarify the influence of baseline disease activity, DAS28-ESR trajectories over five years were examined separately in patients with and without baseline remission.

First, among patients without remission at baseline ($n = 138$), DAS28-ESR values did not differ significantly between the mean J-CHS ≤ 2 and mean J-CHS > 2 groups at baseline (mean J-CHS ≤ 2 vs. mean J-CHS > 2: 2020, 3.43 ± 0.70 vs. 3.71 ± 0.88, $p = 0.079$). In subsequent years, DAS28-ESR values in the mean J-CHS > 2 group were consistently higher than those in the mean J-CHS ≤ 2 group (2021, 3.15 ± 0.80 vs. 3.44 ± 0.79, $p = 0.056$; 2022, 3.00 ± 0.80 vs. 3.80 ± 1.21, $p < 0.001$; 2023, 3.01 ± 0.95 vs. 3.43 ± 1.10, $p = 0.008$; 2024, 2.97 ± 0.95 vs. 3.68 ± 0.91, $p < 0.001$; 2025, 3.10 ± 0.99 vs. 3.67 ± 1.10, $p = 0.002$) (Figure 2A).

Next, among patients with remission at baseline ($n = 173$), no significant differences in DAS28-ESR were observed between the mean J-CHS ≤ 2 and mean J-CHS > 2 groups throughout the study period (mean J-CHS ≤ 2 vs. mean J-CHS > 2: 2020, 1.90 ± 0.53 vs. 1.92 ± 0.59, $p = 0.667$; 2021, 2.05 ± 0.76 vs. 2.15 ± 0.91, $p = 0.264$; 2022, 2.08 ± 0.80 vs. 2.21 ± 0.72, $p = 0.436$; 2023, 2.08 ± 0.76 vs. 2.31 ± 1.03, $p = 0.127$; 2024, 2.07 ± 0.80 vs. 2.14 ± 0.95, $p = 0.518$; 2025, 2.15 ± 0.88 vs. 2.50 ± 1.05, $p = 0.056$) (Figure 2B).

3.5 | Trajectories of GC Use and Dosage According to Baseline Remission Status

Longitudinal changes in GC use were next examined among patients who achieved remission at baseline ($n = 173$) (Figure 3A). Across all years, the proportion of GC users was consistently higher in the mean J-CHS > 2 group than

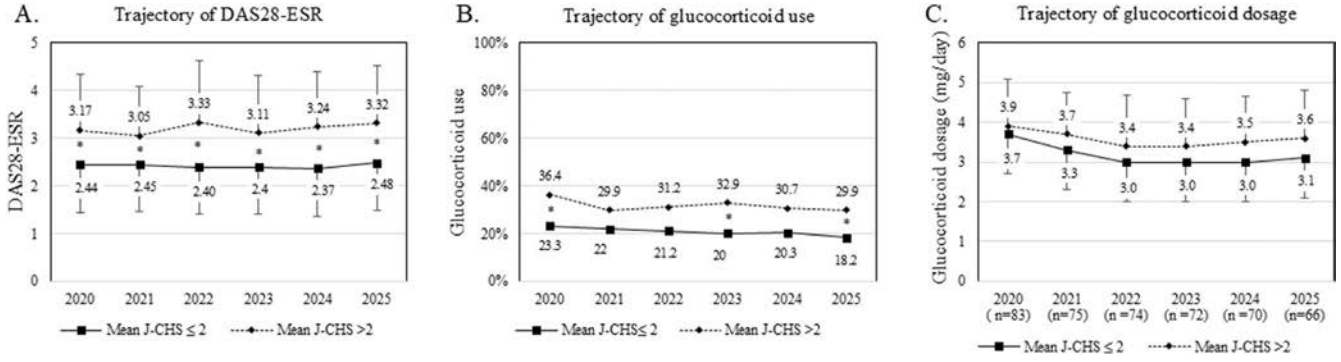

FIGURE 1 | Trajectories of disease activity, glucocorticoid use, and glucocorticoid dosage between mean J-CHS ≤ 2 and mean J-CHS > 2 groups.

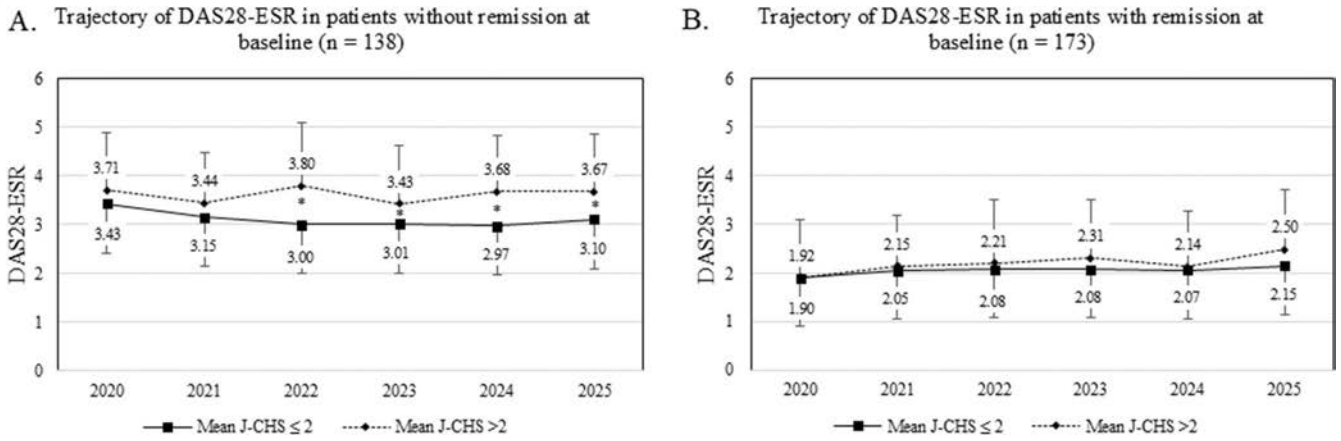

FIGURE 2 | DAS28-ESR trajectories according to baseline remission status.

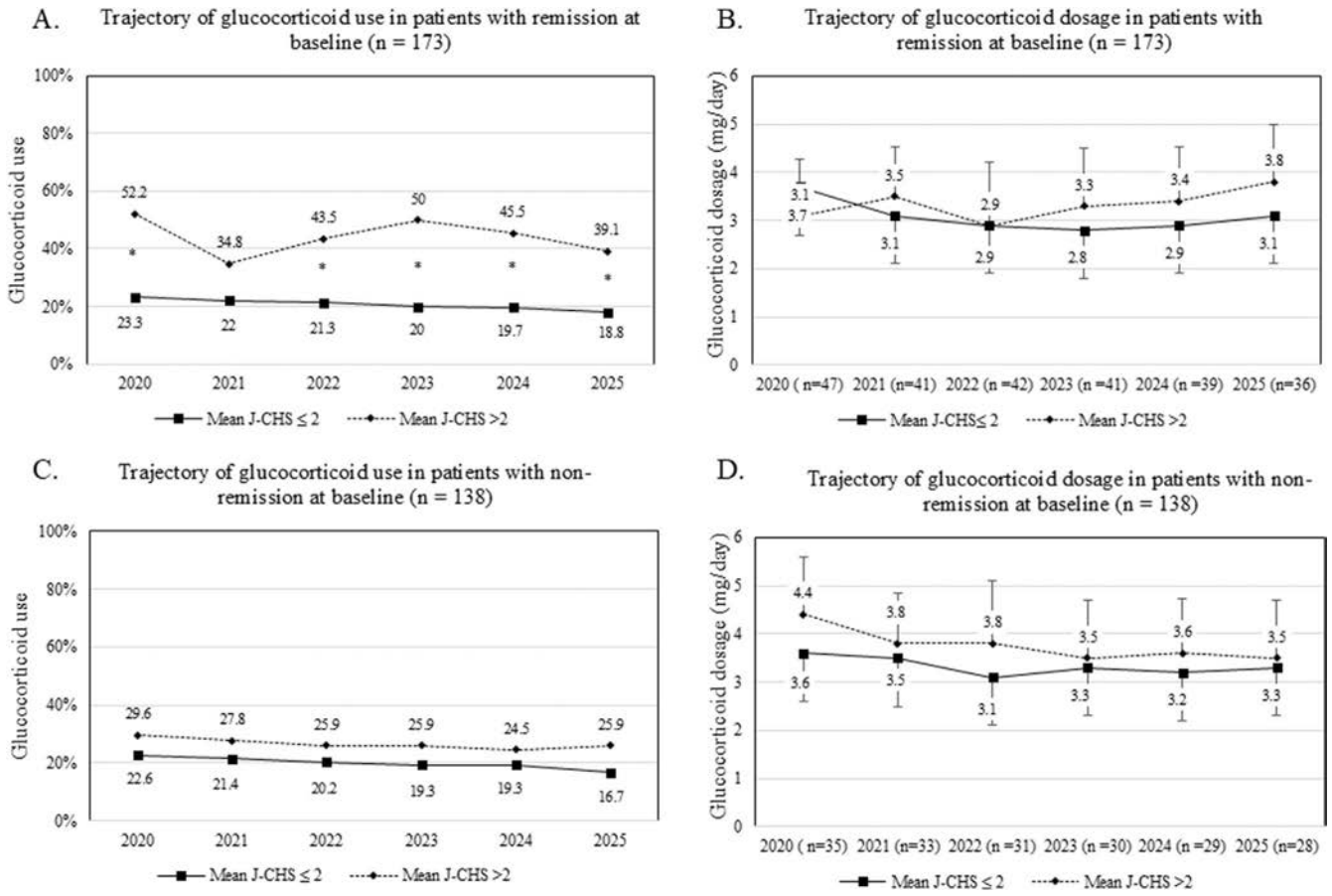

FIGURE 3 | Trajectories of glucocorticoid use and dosage according to baseline remission status.

in the mean J-CHS ≤2 group (mean J-CHS ≤2 vs. mean J-CHS >2: 2020, 23.3% vs. 52.2%, $p = 0.010$; 2021, 22.0% vs. 34.8%, $p = 0.193$; 2022, 21.3% vs. 43.5%, $p = 0.034$; 2023, 20.0% vs. 50.0%, $p = 0.005$; 2024, 19.7% vs. 45.5%, $p = 0.013$; 2025, 18.0% vs. 39.1%, $p = 0.028$). GC dosage was also compared between the two groups among patients with baseline remission (Figure 3B). Mean prednisolone-equivalent GC doses (mean J-CHS ≤2 vs. mean J-CHS >2) were 3.7 ± 1.8 vs. 3.1 ± 1.8 mg in 2020 ($p = 0.964$), 3.1 ± 2.1 vs. 3.5 ± 2.1 mg in 2021 ($p = 0.623$), 2.9 ± 1.5 vs. 2.9 ± 1.9 mg in 2022 ($p = 0.880$), 2.8 ± 1.4 vs. 3.3 ± 1.8 mg in 2023 ($p = 0.481$), 2.9 ± 1.4 vs. 3.4 ± 1.8 mg in 2024 ($p = 0.392$), and 3.1 ± 2.0 vs. 3.8 ± 1.6 mg in 2025 ($p = 0.195$). No statistically significant differences in GC dosage were observed in any year.

In patients without remission at baseline ($n = 138$), the proportion of GC users was consistently higher in the mean J-CHS >2 group than in the mean J-CHS ≤2 group throughout the observation period (Figure 3C), although the differences were not statistically significant in any year ($p = 0.200$–0.531).

Similarly, no statistically significant differences in GC dosage were observed between the two groups across all years (Figure 3D; $p = 0.437$–0.897).

3.6 | Trajectories of MTX Use, Dosage, and b/tsDMARDs Use According to Baseline Remission Status

Longitudinal changes in MTX use were also examined among patients who achieved remission at baseline ($n = 173$). At baseline, the proportion of MTX users did not differ substantially between the mean J-CHS ≤ 2 and mean J-CHS > 2 groups; however, over time, MTX use in the mean J-CHS > 2 group gradually declined relative to that in the mean J-CHS ≤ 2 group. Specifically, MTX use (mean J-CHS ≤ 2 vs. mean J-CHS > 2) was 73.8% vs. 66.7% in 2020 ($p = 0.600$), 73.3% vs. 56.5% in 2021 ($p = 0.136$), 72.7% vs. 47.8% in 2022 ($p = 0.027$), 74.7% vs. 45.5% in 2023 ($p = 0.010$), 74.1% vs. 50.0% in 2024 ($p = 0.025$), and 74.0% vs. 47.8% in 2025 ($p = 0.014$) (Figure 4A).

MTX dosage was also compared between the two groups among patients with baseline remission. Mean weekly MTX dosages (mean J-CHS ≤ 2 vs. mean J-CHS > 2) were 8.1 ± 2.6 vs. 10.3 ± 3.5 mg in 2020 ($p = 0.008$), 7.9 ± 2.4 vs. 10.0 ± 3.5 mg in 2021 ($p = 0.016$), 7.7 ± 2.3 vs. 9.6 ± 4.1 mg in 2022 ($p = 0.094$), 7.5 ± 2.4 vs. 9.6 ± 4.3 mg in 2023 ($p = 0.069$), 7.5 ± 2.5 vs. 9.3 ± 4.5 mg in 2024 ($p = 0.200$), and 7.5 ± 2.4 vs. 9.6 ± 4.4 mg in 2025 ($p = 0.087$). Although MTX dosage tended to be higher in the mean J-CHS > 2 group, statistically significant differences were observed only in the earlier years (Figure 4B).

Finally, the proportion of patients receiving b/tsDMARDs was compared between the two groups. No significant between-group differences were observed in b/tsDMARDs use throughout the study period (mean J-CHS ≤ 2 vs. mean J-CHS > 2: 2020, 35.3% vs. 47.8%, $p = 0.256$; 2021, 36.0% vs. 52.2%, $p = 0.168$; 2022, 36.0% vs. 52.2%, $p = 0.168$; 2023, 38.0% vs. 54.5%, $p = 0.165$; 2024, 35.4% vs. 45.5%, $p = 0.356$; 2025, 42.0% vs. 47.8%, $p = 0.654$) (Figure 4C).

In patients without remission at baseline ($n = 138$), MTX use was consistently lower in the mean J-CHS > 2 group than in the mean J-CHS ≤ 2 group, with statistically significant differences observed in all years except 2020 (Figure 4D). In contrast, no statistically significant differences were observed in MTX dosage or b/tsDMARDs use between the two groups throughout the observation period (Figure 4E,F).

4 | Discussion

4.1 | Study Focus and Conceptual Framework

This study was designed to include patients with RA across the entire frailty spectrum at baseline, while placing particular emphasis on the heterogeneity within the pre-frailty stage of RA. Rather than categorizing patients based solely on discrete frailty transitions, we evaluated longitudinal frailty status using continuous J-CHS scores from 2020 to 2025, capturing the persistence and status of vulnerability over time. By applying a cutoff value of J-CHS ≤ 2, corresponding to the upper boundary of pre-frailty, we aimed to distinguish patients who remained within a relatively favorable frailty range from those with a consistently higher frailty status. This approach allowed us to conceptualize frailty as a dynamic construct, without excluding patients based on predefined transition patterns, providing a clinically relevant framework for understanding vulnerability and resilience within the pre-frailty population in RA.

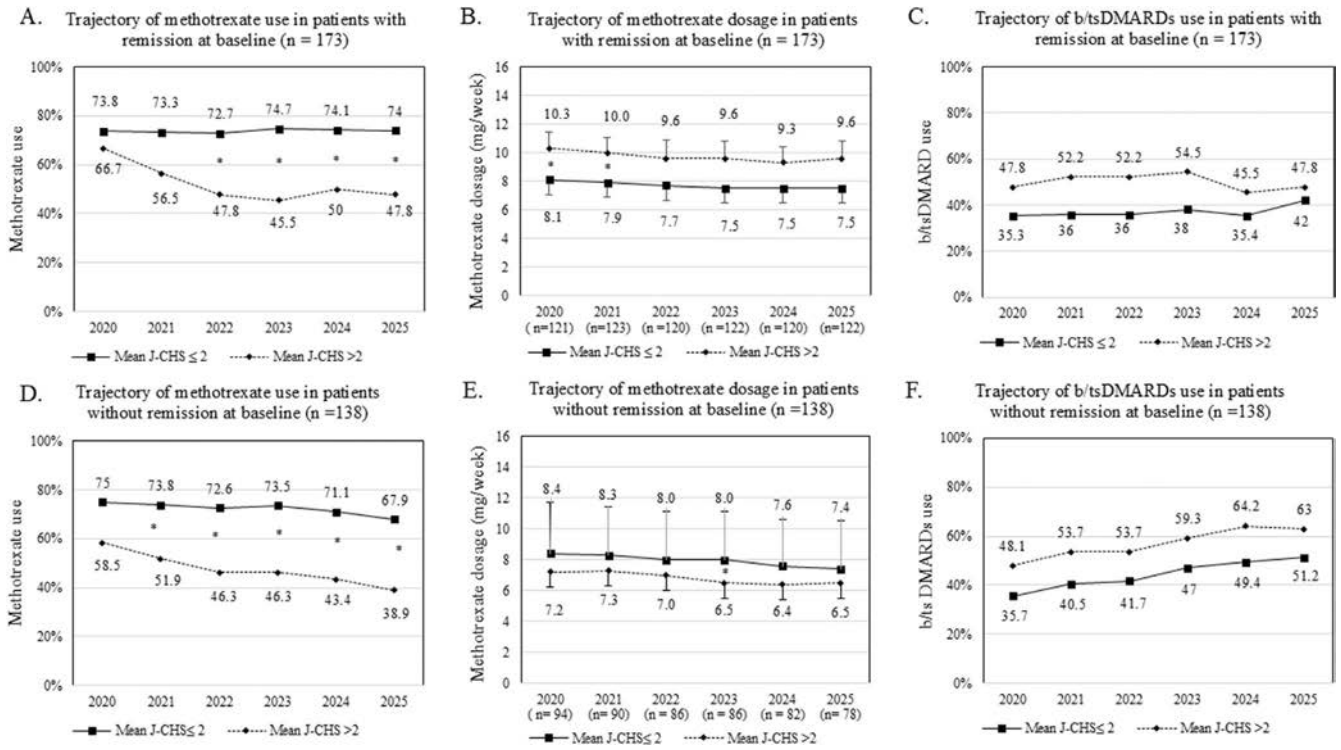

FIGURE 4 | Trajectories of methotrexate use, dosage, and b/tsDMARDs use according to baseline remission status.

4.2 | Impact of Disease Activity on Frailty Trajectory

The most notable finding of this study was that patients with a higher mean J-CHS score (>2) consistently demonstrated higher disease activity from 2020 to 2025, with DAS28-ESR values being significantly higher than those in the mean J-CHS ≤2 group every year. Patients with a mean J-CHS ≤2 remained in remission throughout the study period, whereas those with a mean J-CHS >2 consistently showed disease activity ranging from low to moderate levels.

Among patients who had not achieved remission at baseline, disease activity in the mean J-CHS ≤2 group improved rapidly starting the following year and was subsequently maintained, whereas differences between the two groups became evident over time. These findings suggest that lower disease activity was associated with a lower longitudinal frailty status, as reflected by a mean J-CHS score ≤2 [22]. In addition, among patients without frailty at baseline, the proportion of patients who developed frailty during follow-up was significantly higher in the pre-frail group than in the robust group, supporting the concept that pre-frailty represents a high-risk transitional state toward frailty [2]. Similarly, patients with a higher longitudinal frailty burden, reflected by a mean J-CHS score >2, also showed a higher frequency of progression to frailty during follow-up. These findings further support the clinical relevance of sustained frailty burden over time in patients with RA.

In contrast, even among patients who had achieved and maintained remission at baseline, a subset still exhibited a consistently higher frailty status, reflected by a mean J-CHS score >2. This suggests that control of disease activity alone may not fully account for differences in longitudinal frailty status, highlighting the need for additional interventions beyond further intensification of anti-rheumatic therapy [23].

4.3 | Role of GC Exposure in Frailty Progression

GC use was also more common in the mean J-CHS >2 group, with the proportion of GC users being significantly higher than that in the mean J-CHS ≤2 group, although statistically significant differences were observed only in some years. These findings are consistent with previous studies reporting an association between GC exposure and frailty progression [24]. Chronic GC use is known to induce muscle atrophy, decrease bone mineral density, and impair physical functioning [25, 26], which may be associated with frailty-related vulnerability.

In our longitudinal analysis, even among patients who had achieved remission at baseline, patients with a consistently higher frailty status exhibited higher GC use. Although GC dosage did not differ between the two groups in our analyses, this study was not designed to comprehensively evaluate cumulative GC exposure or duration of use. To partially address this limitation, we further examined proxy measures of cumulative GC exposure, including the mean duration of GC use and the mean annual GC dose. Both measures were significantly higher in patients with a persistently higher frailty status, suggesting that greater cumulative GC exposure may be associated with longitudinal frailty status. Therefore, the potential impact of long-term or cumulative GC use on longitudinal frailty status warrants further investigation. These findings emphasize the importance of minimizing GC dependence as part of the frailty prevention strategy in RA management [27].

4.4 | Clinical Inertia After Remission and Its Impact on Frailty Progression

The observation that some patients with a persistently higher frailty status showed worsening physical vulnerability despite achieving remission at baseline raises an important clinical implication. In these individuals, DAS28-ESR levels remained comparable to those of patients with a lower frailty status throughout follow-up, yet physical vulnerability continued to worsen. This pattern suggests that remission status alone may not fully reflect underlying inflammatory control or the adequacy of treatment [28]. Long-term GC use, which was more prevalent in patients with a persistently higher frailty status, was observed despite comparable DAS28-ESR levels and no clear differences in b/tsDMARDs use. This pattern may reflect differences in treatment reliance rather than differences in inflammatory control.

Taken together, among patients who achieved baseline remission, the absence of differences in DAS28-ESR and b/tsDMARDs use between frailty status groups across all years, combined with consistently higher GC use, suggests that disease activity in patients with a persistently higher frailty status may have been more frequently managed with continued GC exposure rather than with optimization of DMARD therapy. This pattern may be interpreted as being consistent with the concept of clinical inertia, although this construct was not directly measured in the present study [29]. In this context, continued GC use may be associated with sustained vulnerability despite comparable disease activity levels.

Notably, MTX use gradually declined over time in patients with a persistently higher frailty status, without a compensatory increase in b/tsDMARDs use. Although MTX dosage tended to be higher in the mean J-CHS >2 group, no consistent differences were observed, which may reflect treatment de-escalation related to aging, comorbidities, or tolerability concerns and may further contribute to reliance on GCs in this population [30].

In contrast, among patients without baseline remission, differences in GC use and dosage between frailty status groups were modest and not consistently significant, as confirmed in the present longitudinal analyses. In this subgroup, MTX use was consistently lower in patients with a persistently higher frailty status, with statistically significant differences observed in all years except baseline. However, no consistent differences were observed in MTX dosage or b/tsDMARDs use between groups. These findings suggest that differences in MTX exposure in this subgroup may reflect treatment initiation or continuation rather than dose intensity. The lower MTX use observed in this subgroup may reflect clinical decision-making influenced by factors such as comorbidities, polypharmacy, or concerns about adverse events. This contrast indicates that, in active disease states, treatment strategies are primarily driven by the need to achieve remission through DMARD-based therapy, whereas

issues related to treatment optimization and clinical inertia become more apparent after remission is achieved [31].

4.5 | Study Limitations

This study has several limitations. First, due to its observational design, causal relationships could not be directly inferred. Second, we were unable to fully evaluate important frailty-related factors such as physical activity levels and nutritional indices [32, 33]. Furthermore, J-CHS primarily captures physical frailty and does not assess psychosocial or cognitive domains of frailty.

Although selection bias cannot be completely ruled out, baseline characteristics were generally comparable between included and excluded patients (File S1). Third, although MTX use gradually declined over time in patients with a persistently higher frailty status in the remission subgroup, the reasons for treatment de-escalation—such as adverse events, comorbidities, aging-related considerations, or patient preference—could not be systematically assessed. Future research incorporating objective measures of muscle mass, physical activity, and lifestyle factors, as well as interventional studies targeting pre-frailty reversal, will be essential. Finally, the number of patients who progressed to frailty was relatively limited, which restricted the number of variables that could be included in the multivariate model. Therefore, the results of this analysis should be interpreted with caution. In addition, glucocorticoid use and dosage were assessed only at annual time points; therefore, detailed information on cumulative exposure or dose changes between assessments or exact initiation dates was not available.

4.6 | Strengths of the Longitudinal Multicenter Cohort

Although the findings of this study may appear clinically intuitive—namely, that older age, longer disease duration, higher disease activity, and GC exposure contribute to frailty progression—the strength of our results lies in the longitudinal design of the present multicenter cohort. Most previous studies have relied on cross-sectional or short-term observations [34], making it difficult to distinguish transient fluctuations from true transitions in frailty status. By obtaining complete frailty assessments over six consecutive years, our analysis demonstrates longitudinal evidence that pre-frailty trajectories in RA follow consistent and biologically plausible patterns. Importantly, this longitudinal framework allowed us to differentiate disease activity-driven changes in frailty status from treatment-related influences emerging after remission, which cannot be adequately addressed in cross-sectional analyses. Thus, the value of this study rests not only in identifying relevant risk factors but also in longitudinally confirming their sustained impact over time, particularly in relation to differential treatment exposure and disease activity control.

In addition, to account for repeated measurements, we performed additional analyses using generalized estimating equations (GEE). These analyses yielded results consistent with the primary findings, further supporting the robustness of the observed associations.

5 | Conclusion and Clinical Implications

This study highlights the importance of evaluating frailty as a long-term condition in patients with RA using longitudinal J-CHS assessments. Our findings indicate that functional decline may progress even when disease activity appears well controlled, particularly in patients receiving prolonged GC therapy, which may be consistent with the concept of clinical inertia in treatment optimization; however, this interpretation should be considered hypothesis-generating. These results underscore the need for comprehensive management strategies that address not only inflammatory control but also physical vulnerability to maintain long-term robustness in RA.

Author Contributions

Yoshifumi Ohashi, Nobunori Takahashi, Yasumori Sobue and Mochihito Suzuki contributed to the development of the study concept and design, carried out data acquisition, and were responsible for data analysis and interpretation. They also prepared the initial draft of the manuscript and provided substantial critical revisions. Kenya Terabe and Shuji Asai supported the analytical processes, assisted with data interpretation, and were involved in revising the manuscript to enhance its intellectual rigor. Kenya Terabe and Shiro Imagama additionally participated in formulating the study design, collecting study data, and performing critical revisions to refine the manuscript. All authors reviewed and approved the final version of the manuscript.

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Ethics Statement

This study drew on data from a prospective multicenter observational cohort and was approved by the institutional review board(s) of the participating institutions. Instead of individual written consent, an opt-out approach was employed in accordance with institutional guidelines. All procedures were conducted in compliance with the ethical standards of the Declaration of Helsinki, and patient information was anonymized to ensure confidentiality.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **File S1:** Comparison of baseline characteristics between included and excluded patients **File S2:** Factors associated with frailty based on generalized estimating equations (GEE) **File S3:** Proxy measures of cumulative glucocorticoid exposure according to mean J-CHS group **File S4:** Multivariate logistic regression analysis for progression to frailty **File S5:** Progression to frailty among patients without frailty at baseline.

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REVIEW

The Asia Pacific League of Associations for Rheumatology (APLAR) Consensus Statements for the Management of Reproductive Issues in Autoimmune Rheumatic Diseases

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ABSTRACT

Background: The management of reproductive health in individuals with autoimmune rheumatic diseases (AIRDs) has evolved into a primary clinical priority. Wide variations in clinical practice and drug availability in the Asia-Pacific regions necessitate localized frameworks. These consensus statements, developed by the Asia Pacific League of Associations for Rheumatology (APLAR) Special Interest Group for Women's Health & Reproductive Issues in Rheumatic and Musculoskeletal Diseases, aim to bridge the gaps within the region, foster multidisciplinary collaboration, and address regional knowledge deficits.

Methods: An expert panel comprising 16 members of the 13 APLAR member nation organizations formulated 23 research questions using the PICO framework. A systematic review of English-language literature up to July 2025 was conducted across the MEDLINE, Scopus, Google Scholar, and Cochrane Library databases, supplemented by a manual search of journals from the APLAR regions. Evidence from the APLAR region was appraised using the GRADE system. A modified Delphi online voting process was employed to reach consensus, pre-defined as ≥75% agreement.

Results: The panel approved four overarching principles and 86 statements, organized into 16 broad categories. These statements cover all three phases of pregnancy in AIRDs, the safety of medications during pregnancy and lactation, contraception, assisted reproductive techniques, fertility preservation, and hormonal replacement therapy, covering both female and male aspects as relevant.

Conclusion: In a field often lacking high-quality data, these consensus statements from APLAR provide expert opinion-based guidance to support clinical decision-making. It is envisaged that it will assist in educational and training purposes and help shape future research priorities.

1 | Introduction

The management of reproductive health in individuals with autoimmune rheumatic diseases (AIRDs) has shifted from a peripheral concern to a primary area of interest, driven by recent advances in rheumatology. Several international societies, including the European Alliance of Associations for Rheumatology (EULAR), the American College of Rheumatology (ACR), and the British Society for Rheumatology (BSR), have published guidelines in this area [1–4].

The aforementioned available guidelines have been largely derived from Western populations (1–4). In contrast, the Asia–Pacific region is characterized by substantial heterogeneity in health-care infrastructure, the availability of specialist services, socioeconomic conditions, and cultural contexts, which impact many aspects of the management of reproductive issues in AIRDs. Due to a shortage of sufficient manpower in rheumatology in many Asia-Pacific countries, such care is often provided by other healthcare practitioners, resulting in variations in practice and a lack of standardized treatment. Furthermore, there is a paucity of region-specific data to adequately support evidence-based recommendations in this regard. Within the Asia Pacific League of Associations for Rheumatology (APLAR) nations, only Australia has comprehensive guidelines (based on the aforementioned guidelines) for managing reproductive issues in AIRDs [5]. In contrast, China and Saudi Arabia have limited them to systemic lupus erythematosus (SLE) only [6, 7]. Therefore, there is a felt need to develop customized guidelines to address regional gaps, bearing local and regional factors into account.

In this context, the objective of this exercise by the APLAR's Special Interest Group (SIG) for Women's Health & Reproductive Issues in Rheumatic and Musculoskeletal Diseases was to examine the multiple aspects of reproductive health management to develop a comprehensive set of evidence-based consensus statements on managing reproductive issues in AIRDs with an intent to have appropriate relevance and applicability to the APLAR regions covering all three phases of pregnancy, contraception, assisted reproductive techniques (ART), fertility preservation, and hormonal replacement therapy (HRT) covering both female and male aspects as relevant (Table 1).

The present report describes the methodology, summary of evidence, and consensus statements on the management of reproductive health issues in people with AIRDs. We envisage that these statements will help establish standardized local pathways and optimize reproductive health care. Further, these will also foster multidisciplinary care, including rheumatologists and obstetricians, thus potentially reducing inconsistent advice and addressing the knowledge gaps among healthcare providers.

TABLE 1 | The scope of the APLAR consensus statements for the management of reproductive health in autoimmune rheumatic diseases.

Diseases	Antiphospholipid antibody syndrome, inflammatory myositis, primary systemic vasculitis, rheumatoid arthritis, Sjögren's syndrome, spondyloarthritis, systemic lupus erythematosus, systemic sclerosis
Key areas	The preconceptional phase, risk assessment and counseling, the safety of medications in the preconceptional, pregnancy, and lactational period, the safety of medications in men with AIRDs planning to become fathers, pregnancy monitoring, specifically the monitoring of Systemic Lupus Erythematosus with and without renal involvement, the management of Anti phospholipid antibody syndrome pregnancy, the postpartum phase, contraception, fertility preservation, hormone replacement therapy, and Human papilloma virus vaccination
Medications	Apremilast, avacopan, azathioprine, bosentan, colchicine, cyclophosphamide, cyclosporine, hydroxychloroquine, glucocorticoids, IL-1 inhibitors (anakinra, canakinumab), IL-6 inhibitors (tocilizumab, sarilumab), IL-17 inhibitors (secukinumab, ixekizumab), IL-12/23 inhibitors (ustekinumab), abatacept, B-cell depleting agents (rituximab, and belimumab), Immunoglobulins, Janus kinase inhibitors (such as tofacitinib, baricitinib, or Upadacitinib), sildenafil, leflunomide, methotrexate, mycophenolate mofetil, Nonsteroidal anti-inflammatory agents, sulfasalazine, tacrolimus, and Tumor Necrosis Factor (TNF) inhibitors (certolizumab, infliximab, etanercept, adalimumab and golimumab), voclosporin

2 | Methods

2.1 | Expert Panel

All members of the aforementioned APLAR SIG with expertise in reproductive rheumatology, as well as two additional rheumatologists (MR and SK), were invited. Those willing to participate in this exercise and declaring no relevant conflicts of interest formed the expert panel, comprising 16 members from 13 APLAR member nation organizations (MNOs).

A working group (VR, MR, and SK) identified key domains relevant to the management of pregnancy in AIRDs to develop

23 clinically relevant questions using the PICO (Population, Intervention, Comparison, and Outcome) framework [8]. The draft version was shared with the panelists, and based on their feedback, these research questions were revised and further refined (Supporting Information S1).

2.2 | Search Strategy

These research questions formed the basis for the keywords used to search four major databases: MEDLINE (from 1946), Scopus (from 1970), the Cochrane Library (from 1995), and Google Scholar (from 2004) until July 31, 2025 (Supporting Information S2). The search was limited to English-language publications focusing on relevant literature from the Asia-Pacific region (Figure 1). This was supplemented by a manual search of relevant journals from the Asia-Pacific region, including the *Indian Journal of Rheumatology*, *Modern Rheumatology*, *Journal of Rheumatic Diseases*, and the *International Journal of Rheumatic Diseases*. This systematic literature review (SLR) ultimately yielded 152 original articles from the Asia-Pacific region.

Subsequently, the working group carried out data extraction. The articles were matched for relevance to each research question, with some providing information for multiple questions. For each PICO, the working group prepared a summary of evidence from the APLAR regions, appraised relevant available guidelines (1–7), and tabulated findings from each relevant study (Supporting Information S3).

2.3 | Quality of Evidence and the Strength of Recommendations

The quality of evidence (which refers to the robustness of the available data, i.e., RCTs vs. non-RCTs, and is categorized as high, moderate, low, or very low quality) and strength of recommendation (which reflects the extent to which we can be confident that the desirable effects of an intervention outweigh the undesirable effects) for each statement was evaluated using the evidence-assessment frameworks prescribed by the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) system [9].

Overall, data from the APLAR regions were limited, comprising only 152 original articles (Figure 1). Generally, the quality of evidence as per the GRADE approach was low, and in many domains, due to the absence of any relevant studies, the GRADE system for assessing the level of evidence was not applied (Table 2) [9]. However, for determining the strength of recommendations, the panel considered, in each scenario, the balance between desirable and undesirable effects, the quality of available evidence, the costs and accessibility of resources, and, in some instances, panelists' individual values and preferences (Table 2) [9]. The strength of recommendation reflects the confidence that benefits outweigh harms; thus, strong recommendations may be issued despite low-quality evidence based on expert consensus, with the expectation that they may be revised based on relevant evidence in the future (Table 2) [9]. Consequently, the strength of recommendation was not determined solely by the quality of evidence but also by clinical necessity, indirect evidence, clinical judgment, feasibility, safety considerations, ethical imperatives, and regional applicability.

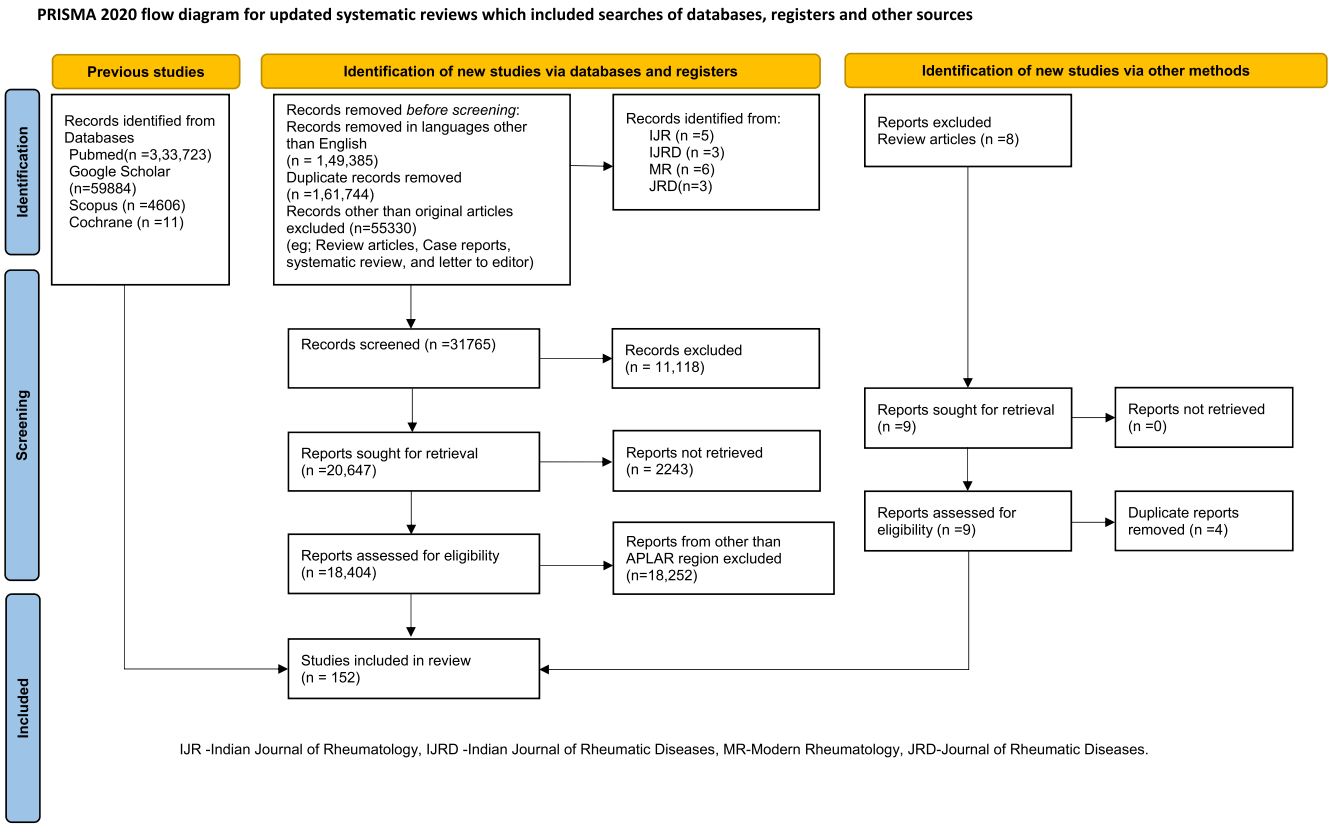

FIGURE 1 | PRISMA 2020 flow diagram of study selection.

TABLE 2 | The APLAR consensus statements for the management of reproductive health in autoimmune rheumatic disease.

Area/phase/ indication	No.	Consensus statements	Quality of evidence±	Percentage agreement	Strength of recommendations[a]
Overarching principles	I	Rheumatologists should take the initiative in discussing reproductive health-related issues with their patients	NA	100%	Strong
	II	A multidisciplinary approach, including but not limited to collaboration with obstetricians, physicians, and midwives, is essential in managing pregnancy in a woman with AIRDs	NA	100%	Strong
	III	The reproductive health goals of the patient should be acknowledged, and concerns should be addressed while discussing the clinical evidence	NA	100%	Strong
	IV	Shared decision-making is essential to assist patients in deciding about their reproductive health-related issues	NA	100%	Strong
I. Preconceptional phase	1	Every patient in the reproductive age group should be asked about their plans for pregnancy, and offered pre-conceptional counseling and evaluation	Low	100%	Strong
	2	Preconceptional evaluation should include a review of disease activity, organ damage, comorbidities, and medications	Low	100%	Strong
	3	In women with AIRDs, pregnancy should be planned after a period of remission or low disease activity for a minimum of 6 months	Low	100%	Strong
	4	In women with AIRDs, testing for anti-Ro/SSA and anti-La/SSB antibodies should be performed ideally in the pre-conceptional period or early pregnancy, but it may be done even later during the pregnancy	Low	100%	Strong
	5	Every woman with SLE should be tested for the antiphospholipid antibodies (anticardiolipin antibodies-IgG & IgM, lupus anticoagulant, and beta2 glycoprotein 1 antibodies-IgG & IgM). In women with other AIRDs, antiphospholipid antibodies should be tested if they have clinical features suggestive of APS. If not done before conception, they may be tested during pregnancy	Low	100%	Strong
II. Medications in the pre-conception phase	6	Hydroxychloroquine, sulfasalazine, azathioprine, colchicine, cyclosporine, tacrolimus, and TNF inhibitors (such as certolizumab, infliximab, etanercept, adalimumab and golimumab) may be safely continued during the preconception phase without modification	Low	100%	Strong
	7	Prednisolone may be used in the pre-conceptional period, but should be maintained at the lowest effective dose	Low	100%	Strong
	8	Methotrexate should be discontinued 1–3 months before, mycophenolate 1.5 months before, and CYC at least 3 months before planning conception	Low	100%	Strong
	9	Women planning pregnancy who are on leflunomide should undergo testing of the drug levels and, if the levels are detectable, undergo a cholestyramine washout procedure. If the testing for the levels of leflunomide is not available then pregnancy may be planned after a period of discontinuation of at least 3.5 months or after the cholestyramine washout procedure	NA	81%	Strong
	10	Other biologics (rituximab, belimumab, abatacept, IL-1 inhibitors, IL-6 inhibitors, IL-17 inhibitors, and IL 12/23 inhibitors) may be used in the pre-conceptional period, after carefully evaluating the benefits and risks for both mother and the fetus	Low	100%	Weak
	11	NSAIDs may be discontinued in women experiencing difficulty in conceiving	NA	100%	Weak

(Continues)

TABLE 2 | (Continued)

Area/phase/indication	No.	Consensus statements	Quality of evidence±	Percentage agreement	Strength of recommendations[a]
	12	Janus kinase inhibitors (such as tofacitinib, baricitinib, or upadacitinib) should be discontinued at least 2 weeks before planning conception	NA	81%	Strong
	13	Apremilast, avacopan, bosentan, and voclosporin should be replaced by pregnancy-compatible medication, when possible, before planning a pregnancy	NA	100%	Strong
III. Paternal medication	14	In men with AIRDs planning to be fathers, CYC should be discontinued 3 months before, and thalidomide a month before planning conception	NA	94%	Strong
	15	In men with AIRDs planning to be fathers who are experiencing a delay in conception, sulfasalazine may be discontinued, and additional tests for infertility must be offered	NA	100%	Strong
	16	In men with AIRDs planning to be fathers, NSAIDs, glucocorticoids, hydroxychloroquine, azathioprine, methotrexate < 25mg weekly, mycophenolate mofetil, leflunomide, cyclosporine, tacrolimus, anakinra, sildenafil, colchicine, rituximab, and TNF inhibitors (certolizumab, infliximab, etanercept, adalimumab, golimumab) may be safely continued without modification	NA	100%	Strong
	17	In men with AIRDs planning to be fathers, there is insufficient data on the use of apremilast, avacopan, bosentan, voclosporin, belimumab, abatacept, IL-6 inhibitors, IL-17 inhibitors, IL-12/23 inhibitors and JAK inhibitors (such as tofacitinib, baricitinib, and upadacitinib)	NA	94%	Weak
IV. Pregnancy in women with SLE without renal involvement	18	Pregnant women with SLE without renal involvement should undergo regular monitoring with relevant clinical assessment, including laboratory tests at least once every trimester. However, the frequency of clinical evaluations and laboratory monitoring may vary with an individual patient's clinical status and medications. Recommended laboratory investigations include a complete blood cell count, complete urine examination, urinary protein-to-creatinine ratio/24-hour urine protein estimation, anti-dsDNA, C3, and C4 levels	NA	100%	Strong
	19	Women with SLE should undergo supplementary fetal surveillance with Doppler ultrasonography and biometric parameters, particularly in the third trimester, to screen for placental insufficiency and small for gestational age fetuses	NA	100%	Strong
	20	Women with SLE and positive anti-Ro/SSA and/or anti-La/SSB antibodies should undergo appropriate fetal cardiac monitoring	NA	100%	Strong
	21	Every pregnant woman with SLE should be prescribed hydroxychloroquine throughout the pregnancy unless contraindicated	Moderate	100%	Strong
	22	Every pregnant woman with SLE should be prescribed low-dose aspirin unless contraindicated	Moderate	88%	Strong
	23	Non-fluorinated glucocorticoids (Prednisolone, methylprednisolone, and hydrocortisone) can be given for mild flares of SLE during pregnancy	Low	100%	Strong
	24	Moderate to high doses of non-fluorinated glucocorticoids (prednisolone, methylprednisolone, and hydrocortisone) or pulses of intravenous methylprednisolone can be used for moderate and severe flares of SLE, respectively. As relevant, glucocorticoid doses should be tapered, and steroid-sparing medication should be started	NA	100%	Strong

(Continues)

TABLE 2 | (Continued)

Area/phase/indication	No.	Consensus statements	Quality of evidence±	Percentage agreement	Strength of recommendations[a]
	25	Intravenous Immunoglobulin (IVIg) may be considered as an adjunct therapy in selected situations of severe maternal disease in SLE	NA	100%	Weak
	26	Azathioprine, tacrolimus, and cyclosporine can be used in pregnant women with SLE	NA	100%	Strong
	27	Cyclophosphamide (during the 2nd and 3rd trimester), rituximab (throughout pregnancy), and belimumab (throughout pregnancy) may be used for life or organ threatening maternal disease in pregnant women with SLE	NA	100%	Weak
	28	Anifrolumab may be considered only if other pregnancy-compatible medications are unable to control the maternal disease	NA	100%	Weak
V. Pregnancy in women with SLE with nephritis	29	Women with SLE should be advised to plan for conception when the nephritis has been in remission for at least 6 months, and they are on pregnancy-compatible medications	Low	100%	Strong
	30	Blood pressure should be closely monitored in all pregnant women with current or pre-existing lupus nephritis	Low	100%	Strong
	31	Women with lupus nephritis should be prescribed low-dose aspirin during pregnancy	Low	100%	Strong
	32	Mild to moderate doses of non-fluorinated glucocorticoids (prednisolone, methylprednisolone, hydrocortisone), hydroxychloroquine, azathioprine, tacrolimus, and cyclosporine can be used to treat lupus nephritis throughout pregnancy	Low	100%	Strong
	33	High-dose glucocorticoids (prednisolone, methylprednisolone, hydrocortisone) and intravenous methyl prednisolone may be used to treat severe renal flares	Low	100%	Weak
VI. Pregnancy in women with positive antiphospholipid antibodies and obstetric or thrombotic APS	34	In women with positive antiphospholipid antibodies without clinical features of APS, low-dose aspirin may be considered in the pre-conceptional period and during pregnancy	NA	100%	Weak
	35	For women with recurrent pregnancy loss with low-titer antiphospholipid antibody positivity, the decision of low-dose aspirin or a combination with low molecular weight heparin should be made based on the individual patient's clinical status	Low	100%	Weak
	36	Women with obstetric APS should be given a combination of prophylactic doses of low molecular weight heparin and low-dose aspirin starting from conception until 6–12 weeks postpartum	Moderate	100%	Strong
	37	In women with obstetric APS, adding hydroxychloroquine to the combination of aspirin and prophylactic LMWH may be considered	NA	94%	Weak
	38	For women with obstetric APS that is refractory to the combination therapy of aspirin and low molecular weight heparin, there is insufficient data to support the use of IVIg or prednisolone	NA	100%	Weak
	39	Women with thrombotic APS should receive a therapeutic dose of low molecular weight heparin along with aspirin starting from conception until 6–12 weeks postpartum	NA	100%	Strong
	40	In women with thrombotic APS, adding hydroxychloroquine to the combination therapy of aspirin and therapeutic LMWH may be considered	NA	100%	Weak

(Continues)

TABLE 2 | (Continued)

Area/phase/indication	No.	Consensus statements	Quality of evidence±	Percentage agreement	Strength of recommendations[a]
VII. Pregnancy in Anti-Ro/SSA and/or Anti-La/SSB positivity	41	Hydroxychloroquine can be considered for pregnant women with anti-Ro/SSA and/or anti-La/SSB positive antibodies	NA	94%	Strong
	42	In pregnant women with anti-Ro/SSA and/or anti-La/SSB positivity, without previous fetal cardiac involvement, fetal cardiac monitoring may be considered from the 16th week of gestational age up to the 26th week at fortnightly intervals. Weekly monitoring may be performed when there is a history of prior fetal cardiac involvement	NA	100%	Weak
	43	For pregnant women with anti-Ro/SSA and/or anti-La/SSB antibodies and fetal first- or second-degree heart block, treatment with oral dexamethasone 4 mg can be initiated. Treatment with dexamethasone is not advisable in fetal 3rd degree (i.e., complete) heart block	Low	94%	Weak
	44	IVIg or plasmapheresis may be considered when there is no response to dexamethasone	Very low	100%	Weak
VIII. Management of other conditions during pregnancy	45	In women with other AIRDs, including rheumatoid arthritis, systemic sclerosis, idiopathic inflammatory myositis and vasculitis, disease activity should be optimally controlled before pregnancy	Low	100%	Strong
	46	In pregnant women with systemic sclerosis (scleroderma) renal crisis, angiotensin-converting enzyme inhibitors can be used	Very low	88%	Weak
	47	In pregnant women with idiopathic inflammatory myositis, careful monitoring of disease activity and creatinine phosphokinase levels should be carried out	Low	100%	Strong
	48	In pregnant women with vasculitis, careful monitoring of hypertension and disease activity should be carried out	Low	100%	Strong
IX. Postpartum period	49	To monitor for potential postpartum flares in women with AIRDs, history, examination, and laboratory tests should be undertaken. Medication should be continued and optimized as required	NA	100%	Strong
X. Medications during Pregnancy	50	Glucocorticoids should be used to maintain disease remission during pregnancy at the lowest possible dose. The dose of glucocorticoids should be tapered and kept at a minimum (preferably ≤ 5 mg per day) and discontinued where possible	Low	100%	Strong
	51	In women on long-term glucocorticoid therapy, stress doses may be considered at the time of cesarean section and may not be needed for a normal vaginal delivery	NA	94%	Weak
	52	NSAIDs may be used intermittently until 28 weeks of gestation for disease control. Short-acting, non-selective NSAIDs with short half-lives are preferred	NA	100%	Weak
	53	Hydroxychloroquine, azathioprine, sulfasalazine, colchicine, tacrolimus, and cyclosporin are safe to use during pregnancy in women with AIRDs	Low	100%	Strong
	54	Methotrexate should be avoided throughout the pregnancy	NA	100%	Strong
	55	Cyclophosphamide, and mycophenolate mofetil may be considered in the second and third trimesters for the management of life-threatening disease, if there is no alternative	NA	100%	Weak
	56	TNF inhibitors are safe to continue throughout pregnancy	Very low	94%	Strong
	57	If the TNF inhibitor is continued throughout pregnancy, BCG vaccination should be deferred until the infant is at least 6 months old	NA	100%	Strong

(Continues)

TABLE 2 | (Continued)

Area/phase/ indication	No.	Consensus statements	Quality of evidence±	Percentage agreement	Strength of recommendations[a]
	58	Non-TNF bDMARDs, such as rituximab, belimumab, IL-6 inhibitors (tocilizumab), sarilumab IL-1 inhibitors (anakinra, canakinumab), IL-17 inhibitors (secukinumab, ixekizumab), IL-12/23 inhibitors (ustekinumab) and abatacept, sildenafil, intravenous methylprednisolone pulses and Intravenous immunoglobulin may be used in pregnant women in cases of severe maternal disease	NA	100%	Weak
	59	Due to insufficient evidence, Janus kinase inhibitors (such as tofacitinib, baricitinib, or upadicitinib), leflunomide, apremilast, bosentan, avacopan, and voclosporin should not be used in pregnant women with AIRDs	NA	88%	Strong
XI. Drugs during lactation	60	Women with AIRDs should be encouraged to breastfeed	NA	88%	Strong
	61	Nonselective NSAIDs, glucocorticoids, hydroxychloroquine, azathioprine, sulfasalazine, colchicine, cyclosporine, and tacrolimus can be safely continued during the lactational period. In those women receiving IV methylprednisolone pulses (1000 mg), a delay of 2 to 4 h before breastfeeding is advisable	Low	94%	Strong
	62	TNF inhibitors (etanercept, adalimumab, certolizumab, golimumab, and infliximab), IL-6 inhibitors (tocilizumab, sarilumab), IL-1 inhibitors (anakinra, canakinumab), IL-17 inhibitors (secukinumab, ixekizumab), IL-12/23 inhibitors (ustekinumab), abatacept, rituximab and belimumab may be used during the lactational period	NA	100%	Weak
	63	Methotrexate < 25 mg weekly, bosentan, and sildenafil may be considered during the lactational period if no alternative drug compatible with breastfeeding can be used	NA	100%	Weak
	64	Janus kinase inhibitors (such as tofacitinib, baricitinib, and upadacitinib), apremilast, avacopan, voclosporin, leflunomide, cyclophosphamide, and mycophenolate mofetil should not be used during the lactational period	NA	100%	Strong
XII. Contraception	65	Rheumatologists should have discussions regarding safe and effective contraception with women with AIRDs who are of reproductive age	Low	100%	Strong
	66	When choosing the contraception, the safety and efficacy of the contraceptive method, comorbidities, and antiphospholipid antibody status should be considered	NA	100%	Strong
	67	Emergency contraception should be offered to all women with AIRDs, including those with SLE and positive antiphospholipid antibody status. Women should be supported in making an informed choice based on their individual circumstances	NA	100%	Strong
	68	Unless contraindicated, both IUDs and progestin-only pills can be safely offered to women with AIRDs; intrauterine devices (IUDs) provide superior contraceptive efficacy	NA	100%	Strong
	69	Depot medroxyprogesterone acetate is not advisable for those women with positive antiphospholipid antibodies and thrombotic risks or those at a high risk of osteoporosis	NA	100%	Strong
	70	For women with SLE with stable disease/low disease activity and negative antiphospholipid antibodies, hormonal contraceptives, IUDs, and progestin implants can be advised as a contraceptive choice	NA	94%	Strong
	71	For women with SLE with moderate and high disease activity with negative antiphospholipid antibodies IUDs and progestin-only pills are preferable	NA	100%	Strong

(Continues)

TABLE 2 | (Continued)

Area/phase/ indication	No.	Consensus statements	Quality of evidence±	Percentage agreement	Strength of recommendations[a]
	72	For women with definite APS or positive antiphospholipid antibodies, combined estrogen–progestin contraceptives are not advisable. They may be offered IUDs or progestin-only pills	NA	100%	Strong
XIII. Assisted Reproductive Techniques	73	In women with AIRDs who have stable/ inactive disease and negative antiphospholipid antibodies, ART is safe and effective	Low	94%	Strong
	74	In patients with SLE, ART may be planned when the disease is quiescent	Low	100%	Strong
	75	Prednisolone and other disease-modifying medications (except CYC) and biological agents required for disease control can be continued throughout the process. Careful monitoring for disease flare is recommended	NA	94%	Strong
	76	For women undergoing ART, who have AIRDs and asymptomatic antiphospholipid antibody positivity, prophylactic anticoagulation with heparin or low molecular weight heparin and/or aspirin may be considered	NA	100%	Weak
	77	For women undergoing ART who have obstetric APS, prophylactic anticoagulation may be considered	NA	100%	Weak
	78	For women undergoing ART who have thrombotic APS, therapeutic anticoagulation may be considered	NA	94%	Weak
	79	The induction protocol for ART may be modified as relevant, by using milder hormonal stimulation or a GnRH antagonist protocol to decrease the risk of ovarian hyperstimulation syndrome	NA	100%	Weak
XIV. Fertility preservation	80	GnRH agonists can be offered to pre-menopausal women with SLE and other AIRDs who need cyclophosphamide for their disease control	Low	100%	Strong
	81	In men with AIRDs requiring CYC, sperm cryopreservation should be done before beginning CYC or 3 months after the last dose	Low	100%	Strong
XV. Hormone Replacement Therapy	82	Hormone Replacement Therapy may be offered to women with AIRDs without antiphospholipid antibody positivity, who have severe postmenopausal vasomotor symptoms	Low	100%	Strong
	83	In women with antiphospholipid antibody positivity with or without obstetric or thrombotic APS, the risk of thrombotic events should be carefully weighed against the benefits of hormone replacement therapy	NA	100%	Strong
	84	Women with AIRDs requiring hormone replacement therapy may additionally benefit from the protective effect on osteoporosis/osteopenia	Low	100%	Strong
XVI. HPV Vaccination	85	HPV vaccination is reasonably safe and efficacious in women with AIRDs	Low	94%	Strong
	86	For optimal effectiveness, HPV vaccination can be scheduled for women with AIRDs, especially those with SLE, when the disease is stable, and the patient is on a minimum dose of glucocorticoids	Low	100%	Strong

Note: ± For categorizing the quality of evidence as per GRADE, only studies from the Asia-Pacific region (Supporting Information S3: SLR) were appraised [9].
Abbreviations: AIRDs, autoimmune rheumatic diseases; APS, Anti-Phospholipid Syndrome; ART, assisted reproductive techniques; CYC, cyclophosphamide; GnRH, gonadotropin-releasing hormone; GPS, good practice statements; HPV, human papilloma virus; IUD, intra-uterine contraceptive devices; IVIg, intravenous immunoglobulins; NA, not applied; NSAIDs, non-steroidal anti-inflammatory drugs; SLE, systemic lupus erythematosus; TNF, tumor necrosis factor.
[a]In line with GRADE approach, strong recommendations may be based on expert consensus despite low-quality evidence, incorporating clinical judgment, particularly when data are limited, and considering stakeholder values and other preferences and other parameters such as safety, feasibility, and resource use [9].

2.4 | Use of Existing Guidelines

The panel decided to use the international guidelines (EULAR 2017 and 2024, ACR 2020, BSR 2023) as the starting point for developing the current statements, based on their reputation and relevance [1–4]. The published evidence based on the aforementioned SLR (Supporting Information S3: SLR) and guidelines from the APLAR region [5–7] further informed the panel and helped

generate evidence-based statements on managing reproductive issues in AIRDs, considering both the evidence and its applicability to real-world practice [5–7]. For the appraisal and adaptation of the relevant guidelines, established resources (the ADAPTE process—www.nccmt.ca and AGREE II—www.agreeturst.org) were used.

2.5 | Conesus Development

The initial 94 statements, including four overarching principles, were circulated to the expert panel for online review. Statements were retained, modified, or removed based on the feedback. A first round of voting was then conducted using a modified Delphi method via Google Forms; voting was not anonymized, and consensus was predefined as > 75% agreement.

In round one, 58 statements achieved 100% agreement, twenty-one 94%, ten 88%, four 81%, and one 67%. Explanations for disagreements were shared with all panelists, and statements were further refined for clarity and brevity, and some were merged or removed, resulting in 90 statements. A second, final round of voting yielded 100% agreement on 73 statements and 81%–94% agreement on the remaining 17 (Table 2). All statements exceeded the predefined consensus threshold. These consensus statements were duly approved by the APLAR board of directors.

3 | Results

3.1 | General

The panel finally approved 4 overarching principles and 86 consensus statements, grouped into 16 broad categories. The statements, along with the quality of evidence and strength of recommendations using the GRADE system and percentage agreement for each statement, have been provided in Table 2. For each domain, a summary of evidence and the details of relevant studies have been provided in Supporting Information S3: SLR.

A brief discussion of the relevant rationale and pertinent literature of each statement is provided below.

3.2 | Overarching Principles (Table 2)

These foundational principles capture critical elements for counseling patients with AIRDs on reproductive health. Designed to reflect best practices, these statements were formulated through expert consensus to supplement the consensus statements.

Rheumatologists play a pivotal role in managing AIRDs in the context of reproductive health. Given the complexity of AIRDs, medication safety, and pregnancy-related risks, reliance on patient-initiated conversations may lead to missed opportunities for timely counseling and risk mitigation. Patients also prefer that the discussion be led by the rheumatologist [10].

Optimal management of pregnancy in women with AIRDs necessitates a multidisciplinary approach. Such coordinated care facilitates individualized risk assessment, ensures optimal disease control, improves patient confidence and compliance, and ultimately better pregnancy outcomes [11].

Recognition of the patient's individual reproductive goals is critical, as is an open discussion of patient concerns to facilitate trust and support informed decision-making. Counseling should integrate patients' values and preferences, with transparent communication of available clinical evidence, including acknowledgment of uncertainties when data are limited, and should lead to shared decision-making [1].

3.3 | Consensus Statements (Table 2)

3.3.1 | Preconception Phase

The management of pregnancy in patients with AIRDs requires proactive planning and evaluation to ensure optimal maternal and fetal outcomes [12].

Pre-pregnancy planning provides a window of opportunity to make the appropriate adjustments in medications, investigate possible risks to the mother and fetus, and ensure an adequate period of the disease being in remission to minimize the risks of pregnancy and ensure optimal outcomes. By evaluating disease activity, existing organ damage, and comorbidities before conception, healthcare teams can implement a systematic approach to manage them, which significantly reduces the risk of flares and adverse pregnancy outcomes (APOs) [13].

Active disease at the time and during pregnancy is associated with poor outcomes in SLE. Testing for antiphospholipid antibodies should be undertaken in women with SLE who have clinical features suggestive of Antiphospholipid Syndrome (APS) [14]. To assess the risk of neonatal SLE and fetal cardiac involvement, testing for Anti-Ro/SSA and Anti-La/SSB antibodies is recommended in the pre-conceptional phase. If not done before, testing may be performed early in pregnancy; repeat testing is not warranted.

3.3.2 | Medications in the Preconceptional Phase

Use of medications in the preconceptional period was categorized as those compatible with pregnancy, teratogenic drugs that should be avoided, those with limited data to support their use, and specific considerations in individual medications.

Preconceptional glucocorticoid (GC) therapy requires careful clinical oversight due to potential links with adverse effects such as orofacial clefts, gestational diabetes, and APOs such as preterm birth and pre-eclampsia. However, since poorly managed maternal AIRDs can also cause APOs, prednisolone may be used for preconceptional stabilization using the least effective dose [15].

Cyclophosphamide is a known teratogen associated with pregnancy loss, congenital anomalies (including limb and skeletal deformities and cleft palate), and fetal cytopenias when administered during organogenesis, particularly in the first trimester. Due to their teratogenicity, cyclophosphamide (CYC) should be

discontinued at least 3 months before, methotrexate 1–3 months before, and mycophenolate 1.5 months before planning a pregnancy.

Leflunomide is teratogenic in animal studies. Data from case series suggest that the teratogenic potential may not be significant in humans [16]. The recent EULAR guidelines recommend that patients either discontinue leflunomide at least 3.5 months (equivalent to 5 half-lives) before conception or undergo a cholestyramine drug-elimination procedure [3]. The panel debated whether the earlier recommended 1-year period was more appropriate, but resolved that real-world data enabled by the latest EULAR guidelines would further strengthen these recommendations in due course.

The use of B-cell depleting agents (Rituximab and Belimumab) may be associated with transiently low B-cell counts in the neonate, which usually recover within 6 months of birth and do not appear to be associated with fetal malformation [17, 18]. Due to limited data, non-TNF biologics may be considered when necessary to control maternal disease in the preconceptional period.

The use of Janus Kinase (JAK) inhibitors in the preconceptional period is not advisable due to limited safety data, and they should be discontinued at least 2 weeks before planning conception [3, 19]. In view of the current limited data and conflicting evidence, including some reports suggesting no increase in APOs, the panel took the view that with the emergence of new data, recommendations regarding the preconceptional and prenatal use of JAK inhibitors may be modified [20].

3.3.3 | Paternal Medication

Cyclophosphamide is a potent gonadotoxic agent in men and can negatively impact sperm quality and count. Although teratogenicity data are not available in human studies, in males, it is advisable to discontinue CYC 3 months before attempting conception [21]. Thalidomide is a potent human teratogen and should be discontinued a month before attempting conception in males [3].

Sulfasalazine causes reversible abnormalities in sperm parameters and may contribute to subfertility. In men receiving sulfasalazine who experience difficulty conceiving, substitution with an alternative therapy, along with a formal evaluation for male infertility, should be undertaken [21].

3.3.4 | Pregnancy in Women With SLE Without Renal Involvement

Active SLE at conception or during pregnancy elevates the risk of peripartum flares and APOs. Key risk factors for APOs include hypertension, nephritis, high disease activity, APS/aPL positivity, thrombocytopenia, and hypocomplementemia [22].

Women with SLE should be followed up at least once every trimester for a detailed clinical examination. Pregnancies in SLE carry an increased risk of placenta-related complications, specifically small for gestational age (SGA) and fetal growth restriction (FGR); early detection of these outcomes is possible through Doppler ultrasonography and biometric monitoring [23].

Women with SLE who have anti-Ro/SSA and/or anti-La/SSB antibodies are advised to undergo fetal cardiac monitoring between 16 and 26 weeks of pregnancy once every 1–2 weeks [1]. Weekly monitoring is recommended in those with a prior history of congenital heart block [1]. Some panelists felt that, given the limited availability and cost of fetal echocardiography, Doppler-based fetal heart rate monitoring could be used. However, fetal echocardiography may be recommended on an individualized basis, guided by risk factors such as the maternal autoantibody profile, a prior history of congenital complete atrioventricular block (CHB), and other relevant obstetric history.

In women with SLE, continuation of hydroxychloroquine (HCQ) lowers the risk of disease flares compared with treatment discontinuation [24, 25]. It is the standard of care throughout pregnancy unless contraindicated by medication hypersensitivity, pre-existing retinal toxicity, or severe adverse reactions [26].

Low-dose aspirin (81 mg daily) as prophylaxis for all patients at high risk of pre-eclampsia has been recommended [27]. In SLE pregnancies, low-dose aspirin (75–81 mg) has been shown to reduce the risk of pre-eclampsia and fetal growth restriction, particularly when initiated before 16 weeks of gestation [1]. Absolute contraindications to aspirin therapy include aspirin allergy and hypersensitivity to salicylates, while severe hepatic dysfunction and active gastrointestinal or genitourinary bleeding constitute relative contraindications.

Glucocorticoids remain essential for managing SLE flares during pregnancy, with dosing titrated based on disease severity and organ involvement. Non-fluorinated GCs (e.g., prednisone) are preferred over fluorinated alternatives (e.g., dexamethasone) due to their minimal transplacental transfer [1, 5]. Given that adverse effects are both dose- and duration-dependent, clinical practice should prioritize the use of the minimum effective dose, early tapering, and the inclusion of pregnancy-compatible GC-sparing agents to optimize maternal and neonatal outcomes [15].

Intravenous immunoglobulin (IVIg) can be given for severe lupus flares or when other pregnancy-compatible medications are unable to control the disease activity [5]. Azathioprine, tacrolimus, and cyclosporine are safe and effective for controlling disease activity in pregnant women with lupus and can be continued throughout pregnancy [3, 28–30].

Due to its teratogenicity, the use of CYC is restricted to the second or third trimesters as a salvage therapy for life-threatening maternal manifestations when all other pregnancy-compatible immunosuppressants have failed [30, 31].

The data supporting the use of Rituximab in pregnant women with SLE is limited to case reports. For belimumab, data from the pregnancy registry and a retrospective study revealed no fetal safety issues [32, 33]. However, when B-cell depleting drugs are given to pregnant women, it might lead to neonatal B-cell depletion; therefore, live vaccinations should be avoided for the first 6 months of life.

3.3.5 | Pregnancy in Women With SLE With Nephritis

Renal involvement and hypertension in SLE pregnancies significantly increase the risk of APOs such as FGR, preterm birth, and pre-eclampsia [22, 34]. To mitigate these risks, women with SLE should plan conception only after achieving 6 months of renal remission, with rigorous blood pressure monitoring and use of low-dose aspirin to reduce the risk of pre-eclampsia.

To manage lupus nephritis throughout pregnancy, HCQ, azathioprine, tacrolimus, cyclosporine, or non-fluorinated GC in mild-to-moderate doses are advisable. Severe renal flares may be treated with high-dose oral GC or intravenous methylprednisolone pulses [3].

3.3.6 | Pregnancy in Women With Positive Antiphospholipid Antibodies and Obstetric or Thrombotic APS

The presence of aPL antibodies confers a higher risk of adverse maternal and fetal outcomes in pregnancy, including thrombotic events. As women with asymptomatic aPL antibody positivity are at a higher risk of preeclampsia, low-dose aspirin may be considered [27, 35]. There may be clinical situations in which women do not meet the classification criteria for APS, but may be considered at risk for thrombotic or obstetric morbidity [36]. Examples include women with one or two pregnancy losses and aPL antibody positivity, those with recurrent pregnancy loss who do not fulfill the serological criteria for APS, and individuals with triple aPL antibody positivity in the absence of thrombotic or obstetric manifestations. In such scenarios, the potential risks associated with withholding treatment may exceed those of therapy [37]. Decisions regarding the use of low-dose aspirin and/or anticoagulation should be made based on careful consideration of individual risk factors.

Women with obstetric APS should receive prophylactic-dose anticoagulation, and those with thrombotic APS should receive therapeutic-dose anticoagulation, in combination with aspirin. Treatment should be initiated once pregnancy is confirmed and continued for 6–12 weeks postpartum to improve pregnancy outcomes [38]. Hydroxychloroquine is a useful adjunct in the management of APS, where it may reduce thrombotic risk and improve pregnancy outcomes [39].

In women with refractory obstetric APS who experience pregnancy failure despite the standard therapy of aspirin and Low-molecular-weight-heparin (LMWH), evidence for the efficacy of IVIg or prednisolone remains limited [40, 41]. While some data suggest prednisolone may marginally improve live birth rates, IVIg has failed to demonstrate consistent clinical benefits. Consequently, the high costs and logistical challenges of IVIg, alongside the potential adverse effects of prednisolone, often outweigh their marginal utility in these cases.

3.3.7 | Pregnancy in Women With Anti-Ro/SSA and/or Anti-La/SSB Positivity

In pregnancies of women positive for anti-Ro/SSA and/or anti-La/SSB autoantibodies, the incidence of CHB is estimated at approximately 2% in those without a prior history of cardiac involvement, with the risk increasing to 13%–18% in subsequent pregnancies following a previously affected infant. As it may develop between 16 and 24 weeks of gestation, fetal cardiac monitoring is recommended during this period for early detection and potential intervention [42]. Due to the rarity of the condition, a paucity of robust clinical data, and disparities in healthcare infrastructure, an international consensus on cardiac monitoring protocols has yet to be established. All the panelists agreed that fetal cardiac monitoring may be considered from the 16th to the 26th week of gestation at fortnightly intervals. Weekly monitoring may be performed when there is a history of prior fetal cardiac involvement.

The use of HCQ is advocated in pregnant women who have Anti-SSA/Ro or Anti-SSB/La antibodies as a prophylactic strategy to mitigate the risk of congenital heart block [43].

When first- or second-degree heart blocks are detected, dexamethasone, fluorinated GC at 4 mg daily, may be initiated to improve outcomes. The efficacy of treatment in CHB is unproven, so initiating dexamethasone in these cases is not warranted [44].

Based on small studies, IVIg or plasmapheresis may be considered when dexamethasone is ineffective [45, 46]. The global mortality rate for autoimmune CHB is approximately 20%, and 64% of live births may require pacemakers [47].

3.3.8 | Management of Other Conditions During Pregnancy

Active disease at the time of conception has also been shown to be associated with a higher incidence of APOs. For women with AIRDs, maintaining the maternal disease in remission for a period of at least 6 months before conception is advisable for better pregnancy outcomes. In AIRDs, including rheumatoid arthritis (RA), systemic sclerosis, spondyloarthritis, psoriatic arthritis, Takayasu's arteritis, and ANCA-associated vasculitis, almost all APOs have been noted more frequently, necessitating careful monitoring of relevant disease activity parameters [48–53]. Inflammatory myositis may also flare in the postpartum period and requires careful clinical monitoring, including the creatinine kinase levels.

For the management of Scleroderma Renal Crisis in pregnancy, Angiotensin-converting-enzyme (ACE) inhibitors are the treatment of choice, even in the second and third trimesters. For this scenario, the panel agreed that maternal survival takes precedence over potential fetal fetopathy, even though data remain limited to observational case reports.

3.3.9 | Post-Partum Period

Many AIRDs may flare in the postpartum period, particularly RA, SLE, and spondyloarthritis. Postpartum flare rates of 47% have been reported in RA, while in SLE, 27.7% experience mild flares and 1.7% severe flares [54, 55]. Women with AIRDs, therefore, require close postpartum monitoring with appropriate clinical and laboratory assessment [56].

3.3.10 | Medications During Pregnancy

Due to the dose-related maternal and fetal risks, the dose of GC to maintain the disease in remission should be as low as possible (preferably < 5 mg/day Prednisolone) and withdrawn if possible. Non-fluorinated GCs are preferred as they do not cross the placenta at low doses and do not affect the fetus [15].

Prolonged use of GC may lead to adrenal suppression [57]. Therefore, during surgical procedures such as cesarean section, a stress dose of GC may be needed, but it may not be needed for women having a vaginal delivery. Due to a lack of robust evidence, treatment should be individualized via collaborative decision-making between obstetricians and anesthesiologists based on the patient's specific clinical presentation.

Some studies indicate a slightly higher risk of miscarriage in those exposed to NSAIDs in early pregnancy [58]. In contrast, shorter durations of exposure to NSAIDs do not appear to increase the risk of maternal adverse events. If needed, the use of shorter–acting and non-selective NSAIDs as compared to COX-2 inhibitors for a limited duration (7–10 days) may be considered in pregnancy [59].

Methotrexate is a proven embryotoxic and teratogenic agent and should not be used during pregnancy [60]. Both mycophenolate and CYC are potent teratogens and are strictly contraindicated in early pregnancy due to high rates of spontaneous abortion and a distinct spectrum of severe structural malformations [61, 62]. In exceptional cases of life-threatening, refractory maternal disease, their use may be considered in the second or third trimesters, when the risk of structural anomalies declines after organogenesis [63, 64].

The safety of TNF inhibitors during pregnancy has the strongest global evidence [65]. As Certolizumab has no significant transplacental transfer, the BCG vaccine can be given as per the standard schedule to the infant. To prevent disseminated BCG infection, infants exposed to infliximab, adalimumab, or golimumab after the second trimester (20 weeks of gestation), or etanercept after 32 weeks of gestation, should not receive the BCG vaccine until 6 months of age, by which time the TNF-inhibitor concentrations typically return to baseline [3]. The evidence for non-TNF-inhibitor biologics is weaker than that for TNF-inhibitors; these agents may be used to control maternal disease if no alternative is available. Live vaccines should be postponed for 6 months in infants exposed to non-TNF-inhibitor biologics, during the second and third trimesters [3].

Although there is no evidence of teratogenicity of Sildenafil, due to lack of safety data, it may be reserved for use in selected cases of maternal pulmonary artery hypertension [66]. For JAK inhibitors, apremilast, avacopan and voclosporin, current data is insufficient evidence to establish safety during pregnancy, rather than evidence demonstrating harm [67]. Given the teratogenic potential of leflunomide and bosentan, these agents should be avoided in pregnancy due to insufficient safety data in humans [16].

3.3.11 | Medications During Lactation

Breastfeeding has important benefits for the mother and baby; the World Health Organization recommends exclusive breastfeeding for at least 6 months. Women with AIRDs should be encouraged to breastfeed their babies, and compatible medication should be used during this period.

In women receiving intravenous methylprednisolone pulses (1000 mg), the peak levels of the drug are achieved at 2 h in breast milk and then fall exponentially. Studies on nursing mothers receiving 1000 mg intravenous doses show that the relative infant dose is approximately 0.5% to 0.71%, which is significantly lower than the 10% threshold typically used to denote a level of concern [68]. Thus, infant exposure to methylprednisolone through breast milk is minimal, and delaying breastfeeding for 2 to 4 h after an infusion further significantly reduces drug transfer.

The TNF inhibitors are the most extensively evaluated group for compatibility and have minimal levels in breast milk. The evidence for other biologics is not as robust, but available data suggest that breastfeeding can be continued, even during maternal administration.

3.3.12 | Contraception

As patients with AIRDs have a greater chance of unplanned pregnancies, contraception counseling is an essential component of caring for women with AIRDs [69]. It helps prevent unintended pregnancies, avoids fetal exposure to teratogenic medications, and enables conception during disease remission, while facilitating the selection of safe and effective methods. Emergency contraception is considered safe and effective in women with AIRDs.

Intrauterine devices (IUDs) and progestin-only pills are safe and effective for women with AIRDs [70]. Some panelists considered IUDs as the first option, as IUDs have a relatively lower failure rate than progestin-only pills (< 1% vs. < 7% per 100-woman years).

Depot medroxyprogesterone acetate (DMPA) may increase the risk of venous thromboembolism and is therefore not recommended in individuals with a high baseline thrombotic risk, including those with APS or positive aPL antibodies [71]. In addition, prolonged DMPA use may lead to a measurable reduction in bone mineral density by suppressing ovarian estrogen production [72].

In women with stable SLE and without high-risk aPL antibody profiles, hormonal contraceptives, including combined oral contraceptives, do not increase disease activity or flare risk, supporting their use within a selected patient population [73, 74].

Estrogen-free methods, IUDs, and progestin-only pills are safe in patients with moderate to severe active lupus [1.70]. In patients with APS or women with positive aPL antibodies, estrogen-containing contraceptives should be avoided, and they may be offered IUDs or progestin-only pills instead [75].

TABLE 3 | Unmet needs in managing reproductive health in patients with AIRDs from the Asia Pacific region.

- *Data and registries*: Establish national and regional registries to address gaps in epidemiological data and pregnancy outcomes in AIRDs, while fostering multidisciplinary collaboration among rheumatologists, obstetricians, and other specialists.
- *Expanded disease scope*: Broaden research beyond systemic lupus erythematosus, antiphospholipid syndrome, and rheumatoid arthritis to include other rheumatic diseases and diverse patterns of organ involvement (such as cardiac and lung involvement) that are currently underrepresented in clinical guidelines.
- *Monitoring of long-term development*: Conduct longitudinal studies of children born to mothers with AIRDs to evaluate disease heritability, effects of in utero medication exposure, and long-term neurodevelopmental and health outcomes.
- *Pediatric and reproductive health*: Investigate the impact of AIRDs and their treatments on growth, pubertal development, and future fertility in juvenile and adolescent patients.
- *Fertility and assisted reproductive techniques*: Develop clear, standardized protocols for fertility preservation and assisted reproductive techniques, including optimal timing of procedures and uniform drug regimens tailored to women with AIRDs.
- *Diagnostic tools and biomarkers*: Develop pregnancy-specific disease activity indices and identify biomarkers to better predict maternal and fetal risks.
- *Medication safety*: Prioritize research on the safety of biologics and small-molecule therapies during pregnancy and the postpartum period, including effects on infant vaccination schedules and paternal medication exposure.
- *Advanced antiphospholipid syndrome management*: Standardize testing for non-criteria antiphospholipid antibodies and refine management strategies for seronegative, refractory, and secondary APS.
- *Preventive screening and vaccination*: Implement routine cervical cancer screening and assess the safety, immunogenicity, and efficacy of human papillomavirus vaccination in women with AIRDs.
- *Mental health and psychosocial care*: Address mental health aspects, including anxiety, depression, and psychosocial stressors, through integrated screening, counseling, and support services across the reproductive life course.
- *Genetic counseling*: Strengthen access to genetic counseling to support informed reproductive decision-making, particularly regarding disease heritability, fetal risk, and medication exposure.
- *Address socioeconomic heterogeneity*: Recognize and address heterogeneity in socioeconomic status, health-care infrastructure, and accessibility to specialized care across regions, including rural and underserved populations.
- *Impact of cultural context*: Examine cultural factors influencing reproductive choices, including during pregnancy and lactation.
- *Education, awareness, and patient empowerment*: Enhance patient education and awareness through culturally sensitive resources, shared decision-making, and strategies for empowerment tailored to varying levels of health literacy.
- *Inclusion in clinical trials*: Promote the inclusion of women with AIRDs, including during pregnancy and postpartum, in clinical trials to strengthen the evidence base.
- *Education and access to care*: Address socioeconomic and geographic barriers through teleconsultation services, patient support groups, and enhanced physician training in contraception, hormone replacement therapy, and assisted reproduction.
- *Rare and complex clinical scenarios*: Develop guidance for challenging situations, including consideration of pregnancy termination in severe maternal disease or teratogenic drug exposure, and strategies for the prevention and management of neonatal lupus, particularly in cases with cardiac involvement.

Abbreviation: AIRDs, auto-immune rheumatic diseases.

3.3.13 | Assisted Reproductive Techniques

Current evidence suggests that the ART success rates in women with AIRDs, including SLE, are comparable to the general population, with no significant increase in disease flares when the disease is well controlled at the time of the procedure [76–78]. To minimize the risk of flares, patients should maintain their pregnancy-compatible medication regimens throughout the ART process [1].

The risk of thrombosis in women with APS increases further during ART procedures due to high estrogen caused by ovarian stimulation. The decision to treat asymptomatic aPL-positive women with aspirin or heparin must be made according to individual risk factors such as previous miscarriages, concurrent lupus, and antibody status [79, 80]. A prophylactic dose of LMWH is advisable in women with obstetric APS, and a therapeutic dose of LMWH is advisable during ART in women with thrombotic APS [76, 81]. Milder stimulation protocols, such as GnRH antagonist protocols, are preferable in women with AIRDs because they reduce estradiol peaks and have less risk of OHSS [2].

3.3.14 | Fertility Preservation

Fertility preservation techniques should be discussed with all patients who may need to be treated with gonadotoxic agents or may

need to delay pregnancy due to various reasons [7]. The use of Gonadotropin-releasing hormone (GnRH) agonist therapy during monthly CYC therapy has been shown to preserve ovarian reserve [81, 82]. Ovarian tissue or oocyte/embryo cryopreservation may also be considered depending on the clinical situation [7].

Male patients with AIRDs requiring gonadotoxic agents should be offered the option of sperm cryopreservation, preferably before administering CYC or 3 months after the last dose [7, 83].

3.3.15 | Hormone Replacement Therapy

The use of HRT in SLE has shown that estrogen-progestin HRT did not increase severe lupus flares in stable, aPL-negative SLE, but was associated with increased mild flares and possible thrombotic risk in aPL-positive patients [84]. The beneficial effect of HRT on bone health is an added advantage for eligible postmenopausal women receiving glucocorticoids for their disease [85]. It may be offered to women with AIRDs with quiescent disease, negative aPL antibodies, and severe vasomotor symptoms.

3.3.16 | Human Papillomavirus (HPV) Vaccination

Women with AIRDs and particularly SLE are at a higher risk of cervical dysplasia and cancers due to HPV infection, making HPV vaccination an important preventive strategy [86]. Vaccine efficacy has been studied mainly in SLE and has shown good seroconversion, though the response was lower in those on higher doses of Prednisolone or other immunosuppressants [87].

4 | Discussion

Limited region-specific evidence in reproductive rheumatology, particularly from the Asia-Pacific regions, affects the generalizability of current international recommendations. As most data are derived from Western cohorts, they may not reflect variations in disease patterns, access to care, and sociocultural factors of the Asia-Pacific regions. Our SLR highlights key gaps, including limited prospective data on fertility outcomes and preservation strategies. Evidence on the safety of newer biologics and targeted therapies during pregnancy and lactation remains inadequate. Male fertility and paternal drug exposure are also underexplored. There is a lack of standardized reporting of pregnancy, neonatal, and long-term child outcomes. Patients with overlapping AIRDs and comorbidities are underrepresented in existing studies. Implementation of available guidelines is further challenged by limited access to multidisciplinary care and fertility preservation services. High costs, restricted drug availability, and inadequate monitoring infrastructure add to these barriers. Context-specific adaptations of guidelines and strengthening of clinician and patient awareness are essential to improve equitable care delivery. The present consensus statements are a step in this direction.

5 | Conclusions

In areas lacking high-quality randomized data, these consensus statements from the APLAR provide a structured, evidence-informed framework to support comprehensive, patient-centered reproductive health care in AIRDs, while highlighting context-specific considerations. In doing so, the expert panel appraised the evidence available from the Asia-Pacific region and considered the limitations and challenges of this wide geographical area with diverse populations. The SLR revealed a paucity of high-quality, relevant research from the Asia-Pacific regions. In addition, the expert panel identified several other priority areas for future research and action to improve maternal and offspring outcomes (Table 3). We envisage that these consensus statements will help foster multidisciplinary collaboration and address regional knowledge deficits. Further, we hope that they will not only strengthen reproductive health care but also support educational and training efforts and help shape future research priorities.

Author Contributions

Conceptualization: Vinod Ravindran, Samar Al Emadi; Methodology: All authors; Validation: Madhuri H. Radhakrishna, Sunitha Kayidhi, Vinod Ravindran; Formal analysis: Madhuri H. Radhakrishna, Sunitha Kayidhi, Vinod Ravindran; Investigation: All authors; Data curation: Madhuri H. Radhakrishna, Sunitha Kayidhi; Writing – Original Draft: Madhuri H. Radhakrishna, Sunitha Kayidhi; Writing – Review and Editing: Vinod Ravindran; Writing – Final Approval: All authors; Visualization: Madhuri H. Radhakrishna, Sunitha Kayidhi, Vinod Ravindran; Supervision: Vinod Ravindran; Project administration: Vinod Ravindran.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The authors have nothing to report.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** Questions framed using the Population, Intervention, Comparison, and Outcome (PICO) approach. **Data S2:** Keywords used to carry out a systematic review of literature. **Data S3:** Summary of relevant international guidelines and evidence from the APLAR regions, including summary tables.

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LETTER TO THE EDITOR

Case Report: Antisynthetase Syndrome With Severe Interstitial Lung Disease During Pregnancy

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Dear Editor,

Antisynthetase Syndrome (ASS) is a rare chronic autoimmune disorder characterized by positive anti-aminoacyl tRNA synthetase antibodies with various clinical manifestations, mainly including interstitial lung disease (ILD), arthritis, myositis, etc. ASS is rare in pregnancy and may lead to adverse maternal and fetal outcomes, lacking treatment guidelines. We report a 40-year-old pregnant woman with ASS-ILD who developed respiratory failure at 28 weeks but delivered a healthy baby via caesarean at 29 weeks after treatment. This is the first detailed case from China; we rapidly clarified the diagnosis and created a favorable outcome for the mother and baby, highlighting the importance of rapid diagnosis and multidisciplinary care in severe cases.

A 40-year-old gravida 4 para 1 woman had pharyngeal discomfort, recurrent cough and sputum, accompanied by shortness of breath after activity at 24 weeks of pregnancy. Treatment with cefoperazone sulbactam failed. By 28 weeks, symptoms persisted, with increased heart rate, leading to her transfer to our hospital, where she had low oxygen saturation (SPO2 of 95% in nasal cannula oxygen 4 L/min), coarse breath sounds in both lungs, elevated leukocytes (10.4 × 109/L) and neutrophils (82.0%), and a repeated CT showing ILD (Figure 1). This was a high-resolution CT (slice thickness = 1 mm), reconstruction kernel, planes (axial/coronal) were obtained, and the follow-up scan used the same technique. But inspiratory and expiratory series were not obtained.

The patient received meropenem and symptomatic treatments upon admission; the fetal monitor showed irregular contractions, leading to dexamethasone for fetal lung maturation. Immunoassay revealed strong positivity (3+) for anti-JO-1 and Ro52 antibodies, with elevated ANA and KL-6 levels, indicating ASS diagnosis, treated with intravenous methylprednisolone infusion 40 mg QD. Over three days, the patient had recurrent fever, worsening respiratory symptoms, and type I respiratory failure, prompting multidisciplinary consultations, including departments of respiratory medicine, infectious diseases, pharmacy, and rheumatology, to transfer her to the ICU for continued treatment, including meropenem and clindamycin, noninvasive ventilation, and enoxaparin sodium for anticoagulation.

After a discussion at the hospital-wide consultation, a caesarean section (CS) was performed at 29 weeks gestation +2 to relieve her lungs, and a live baby boy weighing 1.5 kg was delivered. The newborn's Apgar score was 8 points (1 for muscle tone and 1 for skin color) at 1 min and 9 (1 for skin color) at 5 min. The Apgar score was 10 at 10 min after endotracheal intubation and infusion of Curosurf. After CS, voriconazole and ganciclovir were added for fungal and viral infections, and enoxaparin sodium was given for thrombosis prevention. After treatment with methylprednisolone, fluid management, and nutritional support, tracheal intubation was removed, and sequential invasive mechanical ventilation combined with high flow oxygen therapy was performed on postoperative day 12. She was stable with CT revealing absorbed chest lesions (Figure 2), and discharged 21 days after surgery.

ASS is an autoimmune disease caused by immune tolerance breakdown, leading to antibody production and organ damage [1]. The serological hallmark of ASS is the presence of positive antibodies against aminoacyl tRNA synthase. ASS has symptoms such as ILD, polyarthritis, myositis, Raynaud's phenomenon, etc. [2], with ILD, myositis, and arthritis being typical.

ILD is the hallmark pulmonary manifestation of ASS. 15%–30% of ASS patients present with ILD as the initial manifestation [1]. Johnson C et al. [3] discovered that patients with ASS-ILD tend

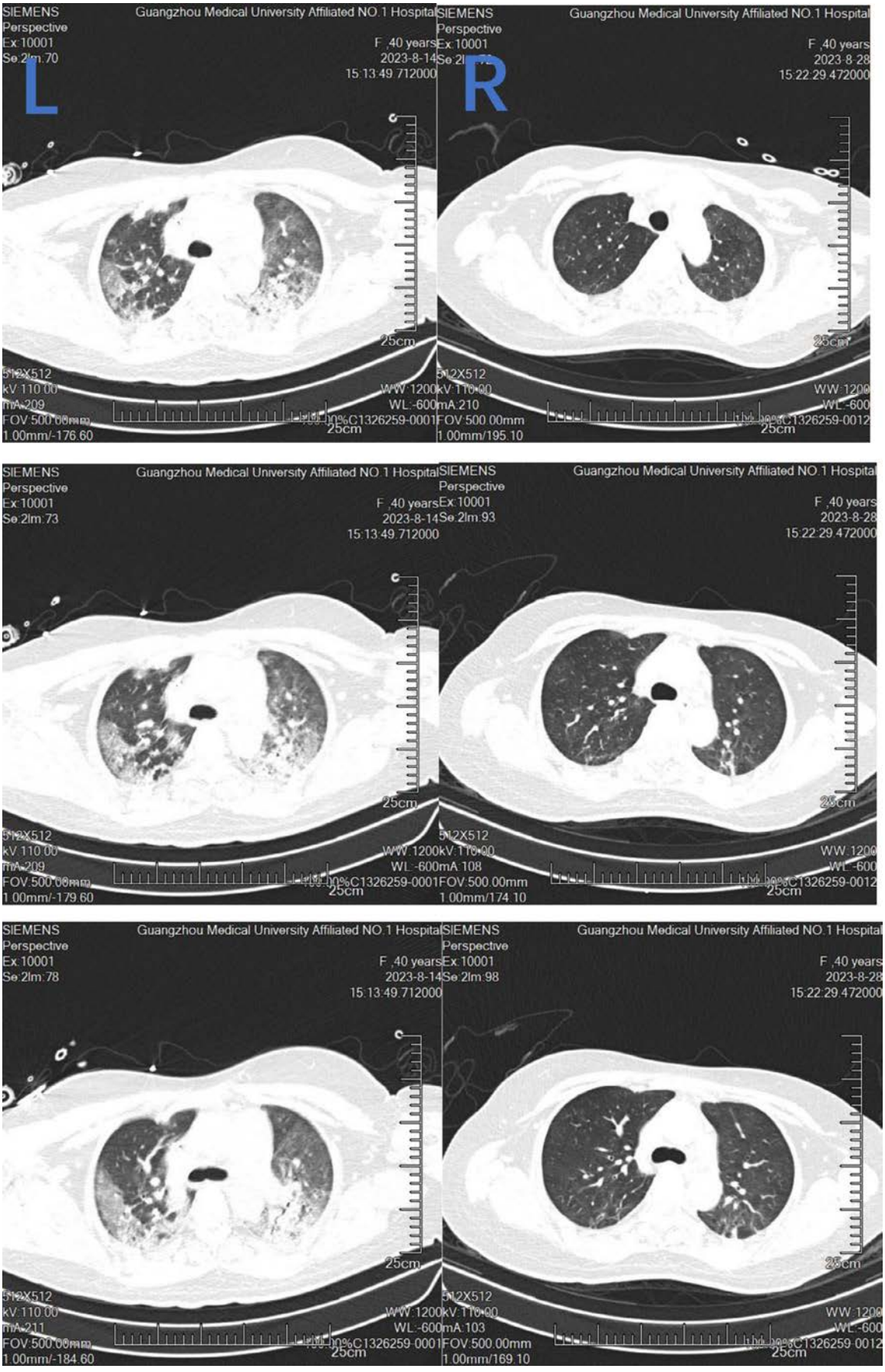

FIGURE 1 | Legend on next page.

FIGURE 1 | A lung CT on admission at 28 weeks of pregnancy (At 28–29 weeks' gestation, we used fetal/maternal shielding, DLP was 362 mGy*cm.). On lung window images, increased lung markings in both lungs, with multiple patchy consolidations and ground-glass opacities, as well as extensive reticular opacities, are observed, consistent with combined nonspecific interstitial pneumonia (NSIP)-organizing pneumonia (OP). After a 14-day course of treatment, there are multiple bilateral patchy ground-glass opacities and consolidations, which have decreased in extent and density compared to the prior study, appearing more indistinct, with predominant involvement of the lower lung zones. (Left: Before therapy, Right: After therapy).

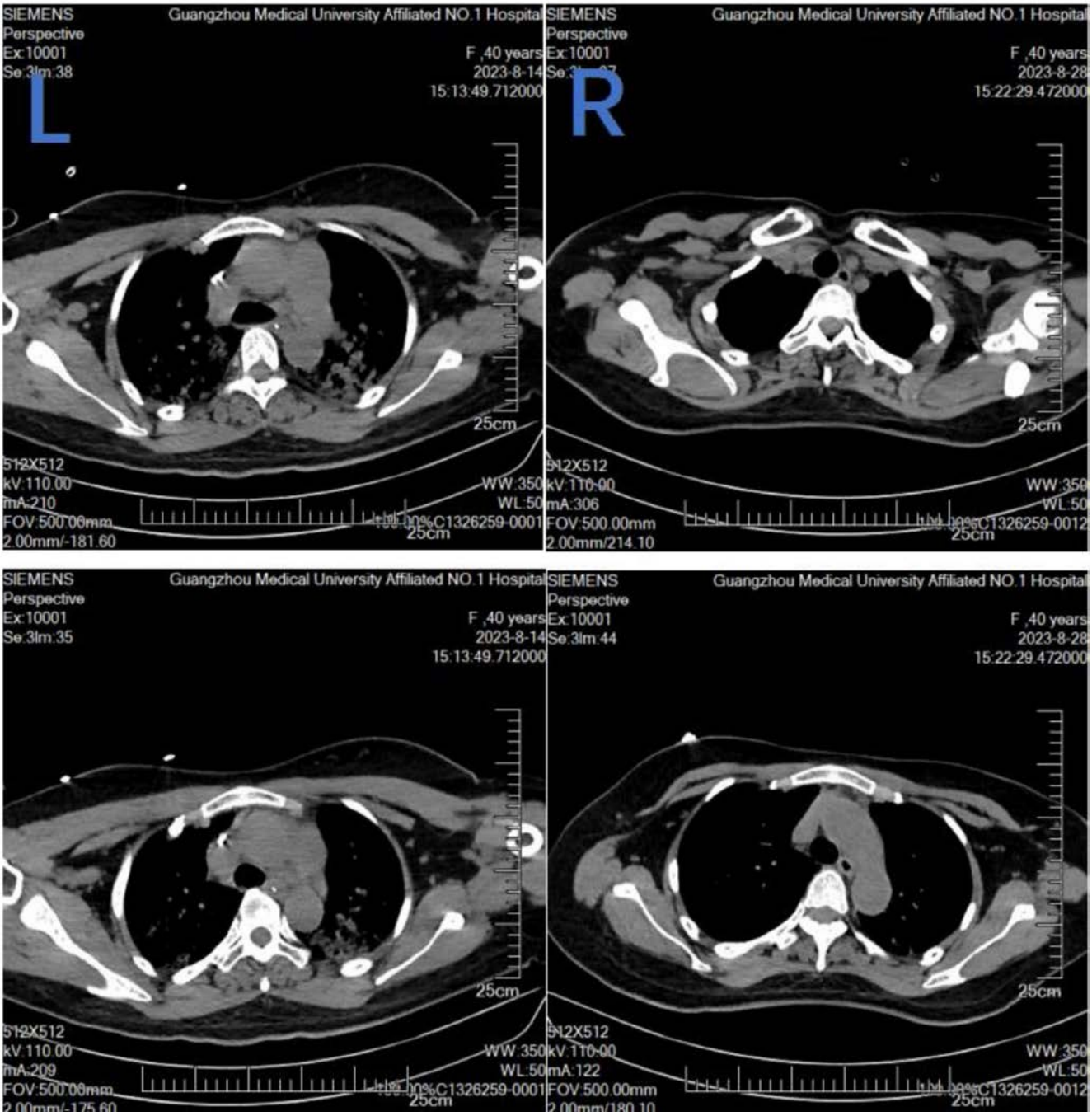

FIGURE 2 | This is demonstrated on mediastinal window settings.

to have worse lung function and imaging of ILD than those with other myopathies. Most ILD patients had progressive dyspnea and even acute respiratory distress syndrome. In this case, the pregnant woman exhibited respiratory symptoms, with CT indicating ILD and strong positivity for anti-Jo-1 and Ro52, meeting the diagnostic criteria for ASS [1, 4]. To date, eight ASS-related antibodies have been identified, including anti-Jo-1, anti-PL7, anti-PL12, anti-OJ, anti-EJ, anti-KS, anti-YRS/Ha, and anti-Zo [2]. Their

detection is a strong indication of ASS and may predict different prognosis and outcome. In ASS associated with positive anti-Jo1 and anti-SSA/Ro, ILD presents more seriously [5]. Additionally, KL-6, a biomarker of alveolar epithelial cell injury [2], was elevated in this woman; thus, KL-6 elevation may also indicate ASS-ILD. ASS often coexists with non-specific antibody-positive manifestations, leading to heterogeneous clinical features.

As is well known, autoimmune diseases during pregnancy can negatively affect both mother and fetus. The reported morbidities in ASS include preeclampsia, preterm delivery, miscarriage, nephritis, fetal growth restriction, congenital heart block, and neonatal lupus [4], which may be related to the presence of autoantibodies. For example, a woman with ASS and positive anti-PL7 had severe dermatomyositis in mid-pregnancy, became resistant to corticosteroids and azathioprine, and miscarried [6].

Some have suggested a connection between anti-Jo-1 and adverse pregnancy outcomes related to massive perivillous fibrin deposition, involving miscarriage, intrauterine growth restriction, and preterm birth [7]. Furthermore, anti-SSA/Ro and anti-SSB/La can cross the placenta and cause fetal congenital heart block [8], which often occurs at 16–24 weeks of gestation but may persist until 34 weeks. So, fetal echocardiography is recommended at 18–20 weeks and repeating it later in around 28 weeks [8].

Current studies on ASS treatment in pregnancy are limited; corticosteroids are the main treatment. ASS-ILD treatment emphasizes support and infection prevention, starting with oral prednisolone 0.5–1 mg/(kg·d), reducing to 40 mg/d after improvement, and maintaining at 5–10 mg/d for one year before discontinuation [1]. Patients with progressive ILD and respiratory failure may receive intravenous methylprednisolone 250–1 000 mg/d or prednisolone 1 mg/(kg·d) for pulse therapy [9]. Prevention and treatment of pulmonary infections are crucial. In this case, the pregnant woman had severe ILD complicated by multiple infections, complicating treatment. ILD causes hypoxemia and pulmonary hypertension, while pregnancy raises oxygen demand and lowers lung volume. High-dose glucocorticoids increase pregnancy and infection risks, so combining immunosuppressants is advised. First-line agents are azathioprine, mycophenolate mofetil, and cyclophosphamide, with azathioprine preferred during pregnancy and lactation [7]. Cyclophosphamide is used in pregnant women with severe ILD after 12 weeks [10], while mycophenolate mofetil and methotrexate are contraindicated due to teratogenicity [4]; tacrolimus and IVIg are safe [10].

In summary, ASS-ILD during pregnancy is rare at home and abroad. Therefore, rapid and accurate diagnosis is essential. Once diagnosed, multidisciplinary cooperation should be sought to improve the maternal and neonatal outcomes. More samples and a longer time are needed to explore the treatment of ASS-ILD during pregnancy.

Author Contributions

W.D. collated the clinical case data and wrote the manuscript. X.G. provided the charts and imaging examination results. M.H. and H.X. participated in the discussion and edited the paper. All authors have read and approved the final manuscript.

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Ethics Statement

Ethics approval and consent to participate in this case report were obtained from The First Affiliated Hospital of Guangzhou Medical University.

Consent

Written informed consent was obtained from the patient for publication of this case 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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ORIGINAL ARTICLE

Association of the Intensity, Frequency, Duration, and Volume of Physical Activity With Sarcopenia and Its Related Indicators

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ABSTRACT

Background: Sarcopenia is a crucial factor leading to a decline in physical function and quality of life among middle-aged and older adults. However, the associations between physical activity (PA) and sarcopenia-related diagnostic indicators in this population remain unclear within the Chinese context.

Methods: Using data from the China Health and Retirement Longitudinal Study (CHARLS), we conducted a longitudinal analysis spanning from 2011 to 2015. Cox regression analysis was performed to explore the associations of PA intensity, frequency, duration, and volume with sarcopenia incidence and its diagnostic indicators, which are made up of muscle strength, muscle mass, and physical performance, including gait speed (GS), the five-time chair stand test, and the short physical performance battery (SPPB).

Results: Among 3069 participants, no significant associations were observed between PA and sarcopenia incidence or muscle mass (both $p > 0.05$), whereas all dimensions of PA were associated with muscle strength (all $p < 0.05$). Except for low- or vigorous-intensity PA, moderate- and low-intensity PA frequency of 3–5 days/week, moderate PA volume ≥ 300 min/week, and moderate-to-vigorous PA volume 600–2249 metabolic equivalents, all other PA dimensions were associated with physical performance (all $p < 0.05$). Further sensitivity analyses confirmed the robustness of these findings.

Conclusions: These findings indicate that PA enhances muscle strength and improves muscular function, thereby reducing the severity and improving the prognosis of sarcopenia.

1 | Background

According to the Seventh National Population Census in 2020, the population aged 65 and older in China accounted for 13.50% of the total population [1]. In some Western societies, up to 42% of individuals over 60 experience impairment in activities of daily living [2, 3]. Among various risk factors, a decline in skeletal muscle performance is a key cause. This age-related loss of skeletal muscle mass and function, often termed sarcopenia, is closely associated with this decline.

Sha-Sha Tao, Xiao-Yu Chen, and Yi-Fan Cai have contributed equally to this work and should be considered co-first authors.

Sarcopenia is a condition marked by reductions in muscle mass, muscle strength, and physical performance, primarily affecting middle-aged and older adults [4]. It can cause joint injuries, slowed movement, and fatigue, thereby increasing the risks of falls, fractures, and depression, ultimately elevating the risk of all-cause mortality [5–7]. As an age-related disease, sarcopenia not only impairs quality of life but also exacerbates the disease burden among older Chinese individuals [8]. Previous studies have shown that physical activity (PA) is beneficial for muscle growth and has a preventive effect on muscle atrophy [9].

PA has been reported to be associated with the risk of sarcopenia. A pooled analysis of 42 randomized controlled trials (RCTs) demonstrates that exercise in general is beneficial for muscle growth and function in individuals aged ≥60 years [10]. A systematic review and meta-analysis including 25 studies also reported the preventive effect of PA against sarcopenia [9]. However, existing evidence has several limitations: the study subjects are often limited to patients with sarcopenia or individuals aged ≥60 years, the study periods are typically short, and the intensity and frequency of PA are frequently not considered [9–11]. Consequently, it remains largely unclear whether the risk of sarcopenia is associated with PA intensity, frequency, duration, or volume.

Using the China Health and Retirement Longitudinal Study (CHARLS) dataset, we examined the relationship between multidimensional PA parameters (including intensity, frequency, duration, and volume) and sarcopenia, as well as its associated diagnostic indicators in middle-aged and older Chinese adults.

2 | Methods

2.1 | Study Population

The CHARLS surveyed over 17 000 individuals aged 45 years and older from approximately 10 000 households across 28 provinces in China. Baseline demographic data, physical assessments, and blood samples were collected in 2011 (Wave 1). As of 2025, five waves (2011, 2013, 2015, 2018, and 2020) have been carried out [12]. Due to insufficient sarcopenia data during Waves 4 and 5, only data from Waves 1 to 3 were incorporated. The CHARLS data are publicly accessible at http://charls.pku.edu.cn/en. All data acquisition procedures received ethical clearance from the Ethics Review Board of Peking University, and informed consent was obtained from all participants.

A total of 14 638 participants were excluded for the following reasons: 4965 had missing baseline sarcopenia data; 7345 had missing PA data; 111 had missing age data or age <45 years; 1 had missing sex data; 849 had pre-existing sarcopenia; and 1367 had missing follow-up sarcopenia data. Finally, the longitudinal study included 3069 participants. Figure 1 depicts the participants' selection procedure.

2.2 | Measurement of PA

In the CHARLS, data on the intensity, frequency, and duration of PA were collected through a questionnaire survey. PA intensity was categorized into three levels [13]: (1) low-intensity physical activity (LPA): walking or light activities at work or home; (2) moderate physical activity (MPA): tasks that may cause faster breathing than normal; (3) vigorous-intensity physical activity (VPA): exercises that may result in breathlessness. The volume for each activity level was determined by multiplying the weekly frequency (days per week) by the average daily duration (minutes per day) spent on each activity. When calculating the moderate-to-vigorous PA (MVPA) score, the volumes of the VPA and MPA were multiplied by their respective metabolic equivalent (MET) values: 4 MET for MPA and 7.5 MET for VPA [14, 15].

2.3 | Measurement of the Three Indicators of Sarcopenia: Muscle Strength, Appendicular Skeletal Muscle Mass, and Physical Performance

2.3.1 | Muscle Strength Measurement

In CHARLS, participants' handgrip strength (kg) was measured in both hands using a dynamometer, with the test performed at least twice. The available maximum grip-strength value was recorded for analysis.

2.3.2 | Muscle Mass Assessment

Muscle mass was estimated using Appendicular Skeletal Muscle Mass (ASM), calculated with a validated anthropometric equation for Chinese populations, showing strong agreement with dual-energy X-ray absorptiometry [16]. The following formula was utilized to calculate the ASM: $\mathrm{ASM} = 0.193 \times \text{weight (kg)} + 0.107 \times \text{height (cm)} - 4.157 \times \text{sex} - 0.037 \times \text{age (years)} - 2.631$, where sex was coded as 1 for males and 2 for females.

2.3.3 | Physical Performance Assessment

Standardized measures were implemented to assess physical performance, including gait speed (GS), short physical performance battery (SPPB), and the five-time chair stand test. Each participant completed two 2.5-m walks (there and back) at a regular pace, and their GS (m/s) was calculated by dividing the distance (2.5 m) by the recorded completion time (s). The five-time chair stand test measured how long it took for a participant to rise five times from a 47-cm high chair with arms crossed in front of the chest. The SPPB evaluation is a composite measure that incorporates the aforementioned gait speed and chair stand tests, along with three 10-s balance tests: (1) side-by-side, (2) semi-tandem (heel next to the other's big toe), and (3) tandem (heel in front of and touching the other's toes). The overall score ranges from 0 to 12 points, with a maximum of 4 points assigned to each of the three functional components.

2.4 | Diagnosis of Sarcopenia

Based on the Asian Working Group for Sarcopenia (AWGS) 2019 diagnostic criteria, sarcopenia was diagnosed in participants with low ASM accompanied by reduced muscle strength and/or

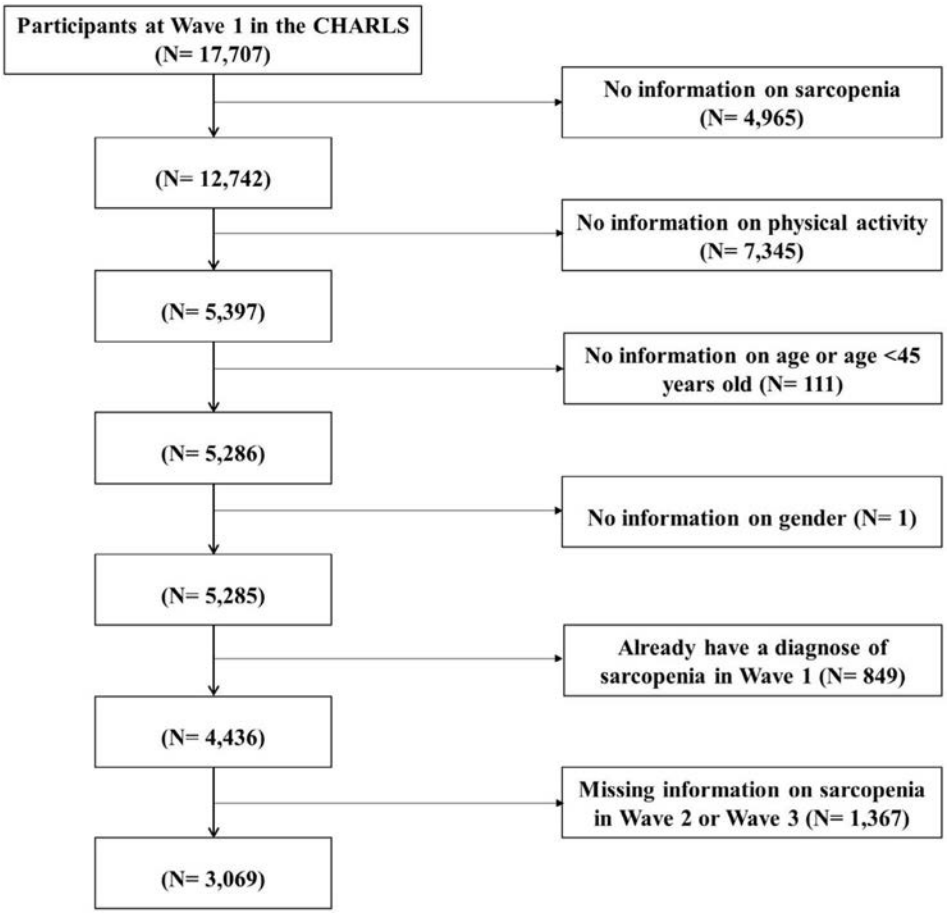

FIGURE 1 | Flowchart of the sample selection process.

impaired physical performance [17]. Those not meeting these criteria were classified into the "no sarcopenia" group. In line with established methodology, low muscle mass was defined as an ASM index (ASM/height^2) below the sex-specific 20-th percentile (7.00 kg/m^2 for men and 5.27 kg/m^2 for women) [18–20]. Reduced muscle strength was indicated by grip strength < 18 kg for females and 28 kg for males. Poor physical performance was defined by a GS < 1 m/s, a five-time chair stand test time exceeding 12 s, or an SPPB score of 9 or lower.

2.5 | Covariates

Sociodemographic factors, health behaviors, and health status variables were included as covariates in the regression models. Sociodemographic factors included sex, age, education level, and marital status. Health behavior indicators included alcohol consumption and smoking status. Health status variables comprised hypertension, body mass index (BMI), and health biomarkers such as total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), C-reactive protein (CRP), and uric acid (UA).

2.6 | Statistical Analysis

Continuous variables were described using the mean ± standard deviation (SD) or median (interquartile range [IQR]), while categorical data were presented as frequencies and proportions. Group comparisons for categorical outcomes were performed using the chi-square test. The associations of PA with sarcopenia and its diagnostic indicators were examined using Cox proportional hazards modeling, with results reported as hazard ratios (HRs) and 95% confidence intervals (CIs). In the Cox regression analysis, age, sex, and BMI were adjusted for Model 1; Model 2 further adjusted for smoking, alcohol consumption, and hypertension; education and marital status were additionally adjusted in Model 3; and biomarkers were further adjusted in Model 4, including total cholesterol, triglycerides, LDL-C, HDL-C, CRP, and UA. The level of statistical significance was set at a $p < 0.05$ (two-tailed).

3 | Results

3.1 | Prevalence of Sarcopenia and PA Status

Based on the 2015 data, 6779 participants were excluded due to missing sarcopenia assessment data, missing age data, or age < 45 years, resulting in 14 332 eligible participants for the analysis of sarcopenia prevalence and PA status. Among the included participants, the median age was 60.0 years (IQR: 52.0–67.0). The overall prevalence of sarcopenia in 2015 was 15.92% (2281/14332). Participants with sarcopenia had a median age of 70.0 years (IQR: 64.0–77.0), while those without sarcopenia had a median age of 59.0 years (IQR: 51.0–65.0)

(Table S1). According to the World Health Organization (WHO) guidelines [21], 17.51% of participants achieved the recommended PA levels, while 23.72% exceeded the recommended thresholds.

3.2 | Characteristics of the 3069 Participants

Following the inclusion and exclusion criteria, 3069 participants were recruited in this study; the median age was 57.0 years (IQR: 51.0–63.0), and 55.3% were female (Table 1). After 4 years of follow-up, 205 individuals were diagnosed with sarcopenia. The incidence of sarcopenia was approximately 6.68% (205/3069). The results showed that age, sex, education level, smoking status, BMI, triglyceride level, and LDL-C levels (all $p < 0.05$, Table 1), as well as MPA frequency ($p = 0.045$, Table S2) were different across the groups.

3.3 | Relationship Between PA and Sarcopenia

No significant associations were observed between the four dimensions of PA (intensity, frequency, duration, and volume) and sarcopenia in crude and adjusted models (all $p > 0.05$) (Table S3 and Figure 2).

3.4 | Relationship Between PA and Muscle Strength

In this study, significant associations between all PA dimensions (intensity, frequency, duration, and volume) and muscle strength were observed in Model 4 (all $p < 0.05$) (Table S4 and Figure 2).

3.5 | Relationship Between PA and Muscle Mass

No significant associations were observed between the different PA dimensions and muscle mass in all models (all $p > 0.05$) (Table S5 and Figure 2).

3.6 | Relationship Between PA and Physical Performance

In Model 4, no significant associations with physical performance were observed for: (1) PA intensity (LPA or VPA), (2) MPA frequency (3–5 or 6–7 days/week), (3) LPA frequency (3–5 days/week), (4) MPA volume (≥ 300 min/week), and (5) MVPA volume (600–2249 MET) (all $p > 0.05$). Associations between the remaining PA groups and physical performance were all significant in Model 4 (all $p < 0.05$) (Table S6 and Figure 2).

In Model 4, no significant associations with GS were observed for: (1) LPA, (2) MPA frequency (3–5 or 6–7 days/week), (3) LPA frequency (3–5 days/week), (4) LPA duration (≥ 240 min), (5) MPA volume (≥ 300 min/week), (6) LPA volume (> 1260 min/week), and (7) MVPA volume (600–2249 MET) (all $p > 0.05$). Associations between the remaining PA groups and GS were observed in Model 4 (all $p < 0.05$) (Table S7 and Figure 3).

In Model 4, no significant associations with the five-time chair stand test time were observed for: (1) LPA, (2) VPA frequency (3–5 days/week), (3) LPA frequency (3–5 days/week), (4) MPA volume (150–299 min/week), and (5) MVPA volume (600–2249 MET) (all $p > 0.05$). Associations between the remaining PA groups and the five-time chair stand test time were observed in Model 4 (all $p < 0.05$) (Table S8 and Figure 3).

Except for MPA volume ≥ 300 min/week (HR = 1.65, 95% CI: 0.95–2.85, $p = 0.073$), all other PA groups were significantly associated with a higher SPPB score in Model 4 (all $p < 0.05$) (Table S9 and Figure 3).

3.7 | Sensitivity Analysis

The subclinical phase of sarcopenia preceding clinical diagnosis may reduce an individual's PA levels, potentially introducing reverse causality that confounds the true causal association between PA and sarcopenia. To minimize this bias, we conducted a sensitivity analysis by excluding participants who were free of sarcopenia at baseline (2011) but received a diagnosis in 2013, yielding a final sample of 2909 eligible participants. Upon repeating all analyses, the associations between PA and sarcopenia, as well as its related components, remained highly consistent with the primary findings, indicating that the present results are robust (Tables S10–S16).

4 | Discussion

To our knowledge, this study constitutes the first exploration of the relationships of PA intensity, frequency, duration, and volume with sarcopenia in a Chinese cohort study of middle-aged and older adults. In this study, although no significant associations were observed between PA and the risk of sarcopenia or ASM, we found that PA frequency, duration, intensity, and volume were related to handgrip strength and physical performance. This indicates that PA may not change the incidence of sarcopenia but can improve the physical function of patients.

According to AWGS 2019, the prevalence of sarcopenia was 13.6% in 2015, which is much higher than the 6.7% previously reported according to AWGS 2014 [22, 23]. This increase in prevalence may reflect a true rise or be due to more lenient diagnostic criteria, leading to an increased number of diagnosed cases. Analysis of the 2015 CHARLS data revealed that only about one-fifth of participants achieved the WHO-recommended PA levels, with another one-fifth exceeding these targets. Barriers to PA in the elderly include reduced motivation, mobility issues, poor cardiopulmonary function, withdrawn personality, and so forth [24–26].

The relationship between PA and sarcopenia was not observed in the adjusted models. This may be attributed to the fact that sarcopenia is associated with aging, hormone and cytokine imbalances, protein synthesis and regeneration, heredity, and

TABLE 1 | Characteristics of the participants in this study.

Characteristics	Total ($n = 3069$)	No sarcopenia ($n = 2864$)	Sarcopenia ($n = 205$)	p
Age (median [IQR])	57.0 [51.0, 63.0]	57.0 [50.0, 62.0]	65.0 [60.0, 70.0]	< 0.001
Age				
45–54	1144 (37.3)	1130 (39.5)	14 (6.8)	< 0.001
55–64	1303 (42.5)	1215 (42.4)	88 (42.9)	
65–74	507 (16.5)	434 (15.2)	73 (35.6)	
≥ 75	115 (3.7)	85 (3.0)	30 (14.6)	
Sex				
Male	1373 (44.7)	1262 (44.1)	111 (54.1)	0.006
Female	1696 (55.3)	1602 (55.9)	94 (45.9)	
Education				
Illiterate	816 (26.6)	752 (26.3)	64 (31.2)	< 0.001
≤ Primary school	1283 (41.8)	1172 (40.9)	111 (54.1)	
Middle school	667 (21.7)	644 (22.5)	23 (11.2)	
≥ High school	303 (9.9)	296 (10.3)	7 (3.4)	
Marital status				
Divorced/widowed/single	2777 (90.5)	2597 (90.7)	180 (87.8)	0.116
Separated	11 (0.4)	9 (0.3)	2 (1.0)	
Married/partnered	281 (9.2)	258 (9.0)	23 (11.2)	
Smoke				
Current	857 (27.9)	775 (27.1)	82 (40.0)	< 0.001
Former	242 (7.9)	229 (8.0)	13 (6.3)	
Never	1970 (64.2)	1860 (64.9)	110 (53.7)	
Drink				
Current	929 (30.3)	868 (30.3)	61 (29.8)	0.280
Former	228 (7.4)	207 (7.2)	21 (10.2)	
Never	1912 (62.3)	1789 (62.5)	123 (60.0)	
BMI, kg/m^2 (median [IQR])	24.0 [22.2, 26.5]	24.2 [22.4, 26.6]	21.5 [20.7, 22.5]	< 0.001
BMI category				
Underweight	6 (0.2)	4 (0.1)	2 (1.0)	< 0.001
Normal weight	1502 (49.2)	1323 (46.4)	179 (88.2)	
Overweight	1113 (36.5)	1095 (38.4)	18 (8.9)	
Obesity	431 (14.1)	427 (15.0)	4 (2.0)	
Hypertension				
No	2157 (70.7)	2017 (70.8)	140 (68.6)	0.553
Yes	894 (29.3)	830 (29.2)	64 (31.4)	
Biomarkers				
Total cholesterol, mg/dL	191.0 [167.4, 215.7]	191.8 [167.8, 216.1]	183.8 [162.5, 211.1]	0.100
Triglycerides, mg/dL	112.0 [77.2, 163.7]	112.4 [78.8, 164.6]	97.3 [67.0, 141.6]	0.002

(Continues)

TABLE 1 | (Continued)

Characteristics	Total ($n = 3069$)	No sarcopenia ($n = 2864$)	Sarcopenia ($n = 205$)	p
LDL cholesterol, mg/dL	115.2 [94.7, 137.6]	116.0 [95.1, 137.6]	112.9 [91.1, 133.2]	0.001
HDL cholesterol, mg/Dl	47.9 [39.4, 57.6]	47.6 [39.0, 57.2]	51.4 [40.9, 63.7]	0.289
CRP	1.1 [0.6, 2.1]	1.1 [0.6, 2.0]	1.0 [0.5, 2.5]	0.945
UA	4.3 [3.6, 5.2]	4.3 [3.5, 5.2]	4.4 [3.7, 5.2]	0.309

Abbreviations: BMI, body mass index; CRP, C-reactive protein; HDL, high density lipoprotein; LDL, low density lipoprotein; UA, uric acid.

FIGURE 2 | The relationship between PA and sarcopenia, handgrip strength, ASM, physical performance. Note that Model 1 incorporated adjustments for age, sex, and BMI; Model 2 further adjusted for smoking, drinking, and hypertension; Model 3 further adjusted for education and marital status; Model 4 further adjusted for biomarkers, including total cholesterol, triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, C-reactive protein, and uric acid.

evolution, alongside physical activity levels [27]. In the early stages of sarcopenia, the main characteristic is a reduction in muscle size, which progresses to muscle mass loss, muscle fibrosis, and the degeneration of neuromuscular connections, ultimately leading to muscle atrophy and mobility loss [28].

This study examined the associations linking PA to three diagnostic indicators of sarcopenia and found that PA positively affected muscle strength and physical performance, including GS, five-time chair stand test time, and SPPB score, but it had no relationship with ASM. Muscle mass is determined by the dynamic balance between protein synthesis and protein breakdown, which is more heavily influenced by genetics, metabolism, and age. Since ASM is directly calculated using height, weight, sex, and age in this study, it was less affected by PA. While PA cannot directly alter muscle mass, it can enhance muscle function and exercise strength, which

FIGURE 3 | The relationship between PA and GS, the five-time chair stand time, SPPB. Note that Model 1 incorporated adjustments for age, sex, and BMI; in Model 2, smoking, drinking, and hypertension were further adjusted; in Model 3, education and marital status were further adjusted; Model 4 further adjusted for biomarkers, including total cholesterol, triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, C-reactive protein, and uric acid.

significantly influence the severity, progression, and prognosis of sarcopenia.

Therefore, PA may have a relatively limited direct impact on the risk of sarcopenia, given its modest effect on muscle mass. Although PA does not increase muscle mass, it enhances muscle function and strength. Consequently, PA can exert a substantial indirect influence on the severity and prognosis of sarcopenia by modulating muscular motor function. This provides a novel perspective on the complex interplay between PA and sarcopenia.

A notable finding in our study was the differential relationships between various PA patterns and physical performance.

Specifically, a significant correlation was observed only with MPA, while VPA and LPA exhibited no such associations. VPA is often performed by individuals with a heavier economic burden and lower family income levels, which may lead to chronic overexertion and insufficient recovery, increasing their risk of sarcopenia. On the other hand, LPA typically represents the basal level of activities necessary for daily living and may not provide sufficient exercise stimuli to enhance muscle mass, strength, or function. These findings offer a novel understanding of the specificity of PA patterns in influencing physical performance and protecting against sarcopenia.

Model 4 showed that PA contributes to enhanced muscle strength among older adults, which has also been confirmed in previous studies. Throughout the life cycle, muscle strength declines eight times faster than muscle mass and is closely associated with the risk of impaired function, disease, and death. Thus, we highlight the need for a paradigm shift in the approach to sarcopenia management from solely focusing on muscle mass augmentation to a more holistic strategy that prioritizes preserving and enhancing muscle strength to maintain overall health and improve the quality of life [29, 30]. Moreover, numerous studies have shown that resistance training aids in recovery and prognosis in older adults with sarcopenia, and a regular training regimen can enhance muscle strength and physical performance in individuals meeting AWGS diagnostic criteria [11, 31, 32].

Our study had several strengths. First, we investigated the relationship between multiple dimensions of PA (intensity, frequency, duration, and volume) and multiple diagnostic measures of sarcopenia, comprising muscle strength, muscle mass, and physical performance (including GS, the five-time chair stand test, and SPPB). Second, while previous studies have primarily focused on the older adults aged 60 years and above, our study utilized a nationally representative dataset encompassing a broader age range of middle-aged and older adults (45–80 years). This enhances population-level generalizability and clinical relevance across heterogeneous health statuses. Finally, multiple covariates were considered, and four models were used. Our study rigorously accounted for health-related factors (such as hypertension and BMI) and health behaviors (including alcohol consumption and smoking). This approach helps to minimize potential biases and offers a more accurate evaluation of relationships.

However, several limitations of this study should be acknowledged. First, reliance on self-reported PA may introduce recall bias and underestimate actual activity levels. Second, the exclusion of a large number of participants due to missing PA data may have introduced selection bias, potentially limiting generalizability. Third, PA duration was assessed using only four broad categories (<30 min, <2 h, <4 h, and ≥ 4 h), potentially compromising the precise calculation of overall PA volume. Fourth, although the study adjusted for several important confounders, it lacked data on confounders such as nutritional status, endocrine profiles, and prior history of falls or fractures. The omission of favorable factors (e.g., better nutritional status, stable endocrine function, and no history of falls or fractures) may slightly overestimate the protective effect of PA, whereas omitting unfavorable factors (e.g., poor nutrition, endocrine disorders, or prior falls/fractures) could underestimate it. Finally, considering the chronic progression of sarcopenia, a four-year follow-up may be insufficient to capture the long-term structural changes, partly explaining the non-significant association between PA and ASM. Consequently, the functional benefits observed likely reflect short-term adaptations, and longer follow-up is required to validate the long-term protective effect.

5 | Conclusions

Our study reveals that although PA does not directly affect the risk of sarcopenia or ASM, it can enhance muscle strength and improve muscular motor function. These findings indicate that PA may mitigate the severity and improve the prognosis of sarcopenia by optimizing muscle function. This highlights the need for a paradigm shift in sarcopenia management, moving from a sole focus on muscle mass to a more comprehensive strategy that prioritizes preserving and enhancing muscle strength. Such an approach can help reduce severity, slow progression, and improve outcomes by boosting muscle strength and function, ultimately contributing to better overall health and quality of life.

Author Contributions

Sha-Sha Tao contributed to manuscript editing and statistical analysis. Xiao-Yu Chen contributed to manuscript review. Yi-Fan Cai contributed to manuscript review. Wen-Jie Lie contributed to statistical analysis. Xiao-Xiao Li contributed to literature search. Meng-Han Wang contributed to literature search. Qian Huang contributed to literature search. Shu-Zhen Xu contributed to literature search. Peng Wang contributed to data analysis. Zhiwei Xu contributed to data analysis. Hai-Feng Pan contributed to design of intellectual content. All authors reviewed and approved the final version and no other person made a substantial contribution to the paper.

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Ethics Statement

The CHARLS surveys were approved by the Ethics Review Committee of Peking University in accordance with the Declaration of Helsinki. The ethical approval number is IRB 00001052-11015.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

All data generated or analyzed during this study are included in this published article and its Supporting Information files.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Characteristics and PA states of participants in 2015. **Table S2:** PA states of the participants in longitudinal analysis. **Table S3:** The association between PA and sarcopenia in longitudinal analysis. **Table S4:** The association between PA and muscle strength in longitudinal analysis. **Table S5:** The association between PA and ASM in longitudinal analysis. **Table S6:** The association between PA and physical performance in longitudinal analysis. **Table S7:** The association between PA and gait speed in longitudinal analysis. **Table S8:** The association between PA and the five-time chair stand test time in longitudinal analysis. **Table S9:** The association between PA and the SPPB in longitudinal analysis. **Table S10:** The association between PA and sarcopenia in sensitive analysis. **Table S11:** The association between PA and muscle strength in sensitive analysis. **Table S12:** The association between PA and ASM in sensitive analysis. **Table S13:** The association between PA and physical performance in sensitive analysis. **Table S14:** The association between PA and gait speed in sensitive analysis. **Table S15:** The association between PA and the five-time chair stand test time in sensitive analysis. **Table S16:** The association between PA and the SPPB in sensitive analysis.

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EDITORIAL

Osteoporosis in Rheumatoid Arthritis: Current Paradigms and Targeted Treatment Strategies

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1 | Introduction

The therapeutic management of rheumatoid arthritis (RA) has undergone a fundamental transformation with the widespread adoption of the "Treat-to-Target" strategy. While this approach has secured substantial improvements in the control of synovial inflammation and the preservation of articular structure, the management of systemic osteoporosis (OP) persists as a complex clinical challenge.

Current evidence indicates that skeletal fragility in RA is not merely a secondary consequence of glucocorticoid therapy or immobility, but an intrinsic extra-articular manifestation driven by shared pathogenic mechanisms [1]. The relationship between RA and osteoporosis represents "dangerous liaisons" driven by overlapping immune and metabolic pathways. RA-associated osteoporosis must be conceptualized differently from primary postmenopausal osteoporosis; it is an active, inflammation-driven resorptive state [2]. As precision medicine advances, integrating the management of skeletal health into the core therapeutic algorithm for RA has become an essential mandate, shifting the paradigm from reactive fracture management to proactive structural preservation.

2 | Genetic and Immunologic Uncoupling

The susceptibility to bone loss in RA is encoded at a fundamental genomic level, serving as a critical but often overlooked risk factor. Recent genomic analysis confirms a shared genetic architecture between RA and osteoporotic fracture phenotypes, demonstrating that RA polygenic risk confers fracture susceptibility independent of bone mineral density (BMD) [3]. The clinical implication of this finding is profound: the intrinsic immunologic and inflammatory milieu of RA predominantly degrades bone quality—specifically by disrupting trabecular microarchitecture and increasing cortical porosity—rather than simply reducing overall bone quantity. Recent micro-finite element analysis studies provide robust evidence for this phenomenon. These advanced imaging techniques confirm that autoantibody positivity and chronic inflammation directly impair the biomechanical properties of bone, significantly reducing structural stiffness and failure load even in patients with preserved bone mineral density [4]. This structural degradation supports the view that rheumatoid arthritis may confer clinically important fragility risk even when DXA findings are not frankly osteoporotic, warranting more careful risk assessment.

This genetic predisposition is inextricably amplified by the inflammatory milieu. The upregulation of pro-inflammatory cytokines (TNF-alpha, IL-6, IL-17) acts in concert with autoimmunity to disrupt the RANKL/osteoprotegerin axis. Anti–citrullinated protein antibodies (ACPA) and anti-carbamylated protein (anti-CarP) antibodies have been implicated in promoting osteoclast activation even prior to clinical disease onset [5]. In addition, chronic TNF-mediated inflammation upregulates sclerostin, a potent inhibitor of the Wnt/beta-catenin pathway. This blockade suppresses osteoblast differentiation and bone formation, effectively "uncoupling" the remodeling unit: resorption is accelerated by RANKL, while formation is arrested by sclerostin. This dual defect explains why standard antiresorptives often fail to fully restore bone integrity in severe RA.

3 | Risk Stratification

Current clinical practice often fails to capture the true fracture risk in RA because it relies on tools calibrated for the general postmenopausal population. Recent meta-analytic data clarifies the hierarchy of risk, demonstrating that while traditional factors like age and female sex remain dominant, strictly disease-dependent variables: specifically high DAS28 (OR 1.60), elevated CRP, extended disease duration, and positivity for ACPA/anti-CarP are potent, independent predictors of osteoporosis [5, 6]. Therefore, reliance on standard *T*-scores is insufficient. Incorporating Trabecular Bone Score (TBS) to evaluate bone texture may be critical in RA, where artifactual elevation of lumbar BMD by severe degenerative sclerosis or vascular calcifications can mask profound trabecular decay [7]. Routine lateral imaging via Vertebral Fracture Assessment (VFA) is also strongly recommended to detect morphometric deformities, which are highly prevalent yet frequently asymptomatic [8]. However, recognizing that TBS and VFA are not universally available, clinicians in routine practice may utilize RA-adjusted FRAX scores combined with standard lateral thoracolumbar radiographs to identify subclinical fractures. Additionally, emerging technologies such as 3D-Shaper, derived from standard DXA, offer non-invasive assessments of cortical and trabecular compartments, complementing traditional diagnostics [9]. Finally, inflammatory burden quantification is essential, recognizing that patients with persistent high disease activity or high titers of RF/ACPA/anti-CarP possess a fracture risk that transcends their densitometric parameters.

4 | The Therapeutic Strategy: Targeted and Sequential Therapy

A uniform approach to bone protection may be suboptimal in rheumatoid arthritis, where fracture risk reflects varying combinations of inflammation, glucocorticoid exposure, erosive burden, and baseline skeletal fragility. A stratified, phenotype-informed treatment framework may be useful in clinical practice and should be considered alongside long-term DMARD optimization (Table 1), deeply integrated with long-term DMARD therapy. For patients with stable joint disease (low DAS28) who require glucocorticoids or possess general risk factors, bisphosphonates remain the foundational standard of care, establishing an antiresorptive floor. Meta-analytic evidence confirms that bisphosphonates are highly effective in this specific population, significantly reducing the relative risk of vertebral fractures and preserving BMD [10].

For patients with active erosive disease and high systemic markers, the therapeutic goal is to uncouple focal destruction from systemic loss. Phase III trial data demonstrates that denosumab significantly inhibits the progression of joint destruction (modified Total Sharp Score) while increasing BMD in patients on methotrexate [14]. This finding is corroborated by recent meta-analyses showing that denosumab improves BMD and reduces erosion scores compared to controls [11]. Consequently, denosumab may offer distinct advantages over bisphosphonates in this subset of patients to leverage its unique capacity to arrest structural joint damage.

Finally, for patients with established osteoporosis, multiple fractures, or "adynamic" bones, anabolic therapy may be considered to restore microarchitecture. Observational studies identify a phenomenon of "anabolic sensitization," where RA patients treated with daily teriparatide achieve significantly greater gains in femoral neck BMD compared to postmenopausal controls [12]. This suggests the inflamed skeleton is primed for PTH-mediated repair. Romosozumab (anti-sclerostin) also represents a logical, mechanism-based option, offering dual anabolic and antiresorptive action to potentially reverse the inflammation-induced Wnt inhibition. Currently, evidence on sequential

TABLE 1 | Management strategy for osteoporosis in rheumatoid arthritis.

Clinical phenotype	Clinical characteristics	Preferred therapeutic strategy	Clinical rationale
The Glucocorticoid/At-risk	• Stable DAS28 • Chronic GC use (> 3 months) • Low-risk *T*-score • No prevailing fractures	Bisphosphonates (e.g., Alendronate, zoledronic acid) [10]	Establishes an "antiresorptive floor" to mitigate iatrogenic GC effects and baseline inflammatory resorption.
The erosive-inflammatory	• High DAS28 • Progressive joint erosions • ACPA/anti-CarP positive • High CRP/ESR	Denosumab (RANKL Inhibitor) [11]	Simultaneously increases systemic BMD and attenuates local joint erosion progression
The severely compromised	• Existing fragility fractures • VFA deformity • Degraded TBS/Bone Quality	1. Anabolic (Teriparatide or Romosozumab) 2. Followed by sequential antiresorptive	Utilizes "Anabolic Sensitization" to reverse Wnt inhibition. Sequential transition maintains BMD gains [12]. Concomitant DMARD therapy is crucial [13].

Abbreviations: ACPA, Anti-Citrullinated Protein Antibodies; BMD, Bone Mineral Density; CarP, carbamylated protein; CRP, C-Reactive Protein; DAS, Disease Activity Score; ESR, Erythrocyte Sedimentation Rate; GC, Glucocorticoids; PTH, Parathyroid Hormone; RA, Rheumatoid Arthritis; RANKL, Receptor Activator of nuclear factor Kappa-B Ligand; TBS, Trabecular Bone Score; VFA, Vertebral Fracture Assessment; Wnt, Wingless-related int-1.

therapy approach on Osteoporosis in RA is limited. However, the gains achieved by bone-forming agents are mostly transient; therefore, it is generally recommended that anabolic therapy be followed by a potent antiresorptive agent to consolidate and maintain microarchitectural improvements. Additionally, because anabolic agents do not repair focal erosions, rigorous concomitant DMARD optimization remains crucial to suppress the underlying inflammatory driver [13].

5 | Conclusion

The skeletal health of the RA patient is integral to long-term prognosis. Adopting a granular risk stratification that includes TBS and VFA, and matching therapies to the patient's inflammatory and erosive phenotype, allows for the prevention of the first fragility fracture as effectively as the prevention of the first erosion.

Author Contributions

All authors contributed to the design and implementation of the study and original draft preparation. Ming-Yuan Victor Chao contributed in writing and revising the manuscript with critical support from Ming-Chi Wu and Tien-Tsai Cheng, who provided critical feedback and helped revise the manuscript multiple times. All authors reviewed the results and approved the final version of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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

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EDITORIAL

Bridging the Gap in Hydroxychloroquine Monitoring for SLE: Evidence, Limitations, and Future Directions

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1 | Background and Current Standard of Care

Hydroxychloroquine (HCQ) remains a cornerstone therapy in systemic lupus erythematosus (SLE), universally recommended for its immunomodulatory, anti-inflammatory, and anti-thrombotic properties. To optimize safety and efficacy, the current standard of care mandates a strict weight-based dosing strategy. Recent 2025 guidelines from the American College of Rheumatology (ACR) and 2024 updates from the European Alliance of Associations for Rheumatology (EULAR) recommend HCQ dosing at ≤ 5 mg/kg/day of actual body weight, capping at 400 mg/day for certain individual conditions [1, 2]. Furthermore, rigorous ophthalmologic screening must be performed at baseline and annually after 5 years of use—or earlier if additional risk factors such as renal impairment or tamoxifen use are present—to mitigate the risk of cumulative retinal toxicity [3].

However, adherence to this weight-based dosing can still result in highly variable intracellular concentrations due to individual differences in pharmacokinetics, varying disease manifestations, and variable patient adherence [4]. This pharmacokinetic variability establishes a strong clinical rationale for Therapeutic Drug Monitoring (TDM).

2 | The Rationale for Therapeutic Drug Monitoring (TDM)

When assessing HCQ concentrations, it is essential to distinguish between whole blood and serum or plasma levels. Because HCQ extensively accumulates intracellularly, particularly within erythrocytes, whole blood measurement is the gold standard. Serum or plasma levels are typically much lower and highly variable; applying whole blood therapeutic thresholds to serum measurements will inevitably lead to misinterpretation and clinical mismanagement.

In whole blood analyses, subtherapeutic HCQ concentrations (typically < 500 ng/mL) have been associated with an increased risk of disease flares and greater organ damage accrual over time [5, 6]. Conversely, large multinational cohort analyses have refined the effective therapeutic reference range to 750–1150 ng/mL, linking these sustained levels to optimal SLE outcomes [7, 8]. It is important to contextualize this evidence: much of the current data is based on observational associations rather than robust, outcome-based prospective trials. Therefore, achieving these thresholds should not supersede clinical judgment, and HCQ TDM should be viewed as a valuable adjunctive tool rather than a strict standard-of-care mandate.

3 | Guidelines and the Reality of Clinical Practice

While routine, universal monitoring of HCQ levels is not currently advocated across all guidelines due to the lack of definitive outcome-based evidence and variability in measurement platforms, leading consensus groups acknowledge its utility in targeted scenarios. The 2024 EULAR recommendations and the 2025 ACR guidelines support utilizing HCQ blood levels to optimize dosing in specific clinical contexts, such as suspected non-adherence or unexplained disease flares [1, 2]. Additionally, the

KDIGO 2024 Lupus Nephritis Guideline explicitly suggests that whole blood HCQ levels may serve an important prognostic role in managing severe organ manifestations [9].

4 | Reevaluating Barriers: Cost, Access, and Implementation

Historically, high costs and limited laboratory access have been cited as primary barriers to TDM implementation. However, the economic burden of testing is frequently overestimated. In the United States, for example, the CPT code 80230 (hydroxychloroquine blood level measurement) commands a national average reimbursement of approximately $15 to $57 USD. This cost is modest and highly favorable when contrasted against the immense downstream financial burden of SLE flares, prolonged hospitalizations, or irreversible retinal toxicity.

Rather than viewing cost as a permanent barrier, the rheumatology community should advocate for active adoption, leveraging the well-established principle of economies of scale. Wider adoption of HCQ testing will inherently drive down per-test costs. Furthermore, modern implementation strategies can overcome geographical and logistical barriers. The integration of volumetric absorptive microsampling (VAMS) and dried blood spot (DBS) methods enables home-based sampling using minimal blood volumes (e.g., 10 μL). These mail-in logistic solutions prioritize clinical precision without necessitating frequent clinic visits.

5 | Future Directions and Agenda

To successfully integrate HCQ TDM into routine clinical pathways, future efforts must be stratified into near-term evidence generation and longer-term policy goals.

- Near-term priorities: Conduct robust, prospective outcome-based trials to validate whether maintaining whole blood HCQ levels within the 750–1150 ng/mL range actively prevents flares and reduces cumulative damage compared to standard weight-based dosing.
- Near-term implementation: Validate and expand the clinical use of VAMS and DBS methods in diverse patient populations to improve testing accessibility and precision.
- Long-term policy goals: Integrate HCQ TDM codes into national reimbursement frameworks universally, promoting economies of scale and reducing health disparities in rheumatology care.

6 | Conclusion

Hydroxychloroquine remains indispensable in SLE management, and standard weight-based dosing remains the foundation of therapy. While HCQ whole blood monitoring offers a clinically precise strategy to evaluate non-adherence and individual pharmacokinetic variations, it remains an adjunctive tool pending further outcome-based evidence. By adopting novel sampling technologies and advocating for standardized reimbursement, HCQ TDM can transition from an investigational concept to a practical, accessible element of personalized lupus care.

Author Contributions

Tang-Kai Cheng and James Cheng-Chung Wei contributed to the conception and design of the study, drafting the manuscript, and critically revising it for important intellectual content. Both authors have read and approved the final version of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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

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LETTER TO THE EDITOR

Methodological Considerations in Lifestyles, Metabolomics, and Diabetic Kidney Disease

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Dear Editor,

Deng et al. [1] examined the associations among lifestyle factors, metabolomic profiles, and diabetic kidney disease (DKD). The study provides valuable data, but several issues may affect interpretation of the findings.

The mediation analyses should be interpreted cautiously. Lifestyle behaviors and the 251 NMR-derived metabolites were both measured at baseline [2], so the temporal order between exposure and mediator cannot be firmly established. Therefore, the proposed pathway from lifestyle factors to DKD through metabolic biomarkers is better viewed as an association rather than definitive evidence of a causal mechanism.

Lifestyle assessment may also be limited by baseline-only measurement. Diet, sleep duration, physical activity, smoking status, and alcohol intake can change during long-term follow-up, particularly with progression of diabetes, comorbidities, or early kidney dysfunction. This may introduce exposure misclassification and regression dilution bias. Repeated lifestyle assessments or time-updated models would help clarify these long-term associations.

Finally, DKD was identified using ICD-10 codes from hospitalization records and death registries, which may mainly capture clinically recognized or advanced disease rather than earlier DKD detectable by albuminuria [3]. This distinction is important when interpreting the suggested role of metabolomic markers in early detection and risk stratification. Further discussion of this limitation would be helpful.

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Chung-Chu Tung: writing – original draft. **Chen Hui-Yuan:** writing – original draft. **Renin Chang:** conceptualization. **Sun-Lin Huang:** conceptualization, writing – review and editing.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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