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Comparison of Remission Criteria in Patients with Rheumatoid Arthritis: Results from a Smart System of Disease Management Group

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Purpose: This study aimed to compare the rates of disease remission evaluated using various remission criteria, including Boolean2.0, Boolean1.0, clinical disease activity index (CDAI), simplified disease activity index (SDAI), and disease activity score using 28 joints based on C-reactive protein (DAS28-CRP) in patients with rheumatoid arthritis (RA).

Patients and Methods: A cross-sectional observational analysis was performed using data from patients with RA enrolled in a smart system of disease management group (SSDM). The clinical remission rates of RA patients estimated using the DAS28-CRP, CDAI, SDAI, Boolean1.0 and Boolean2.0 criteria were investigated. Variables were compared using the *t*-test, *Mann–Whitney U*-test, or *chi*-squared test. The agreement between Boolean remission and the DAS28-CRP, CDAI, or SDAI definitions of remission was assessed using McNemar's test with k coefficient of agreement.

Results: A total of 5619 patients were included in the analysis. The mean age of the patients was 56.33 (±13.01) years, with the majority being female (4491, 79.9%). The rates of remission, as assessed by Boolean2.0, Boolean1.0, DAS28-CRP, CDAI, and SDAI, were 16.6%, 9.7%, 35.2%, 9.1%, and 9.4%, respectively. Comparison with Boolean1.0 criteria revealed higher concordance between Boolean2.0 and DAS28-CRP remission and lower concordance with CDAI and SDAI, regardless of whether the analysis was conducted on the entire population or subgroups based on gender, age or disease duration. Additionally, the administration of different medications may have influenced the rate of Boolean2.0 remission.

Conclusion: This study demonstrated a higher concordance between Boolean2.0 criteria and DAS28-CRP remission and a lower concordance with CDAI and SDAI when compared with Boolean1.0 remission criteria.

Keywords: Boolean, clinical disease activity index, concordance, disease activity score using 28 joints, remission, simplified disease activity index

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease, which leads to articular cartilage and juxta-articular bone destruction.[1] Remission, or low disease activity (LDA), has been a major treatment outcome for patients with RA in recent decades.[2] Achieving a state of low disease activity, especially remission, is associated with favorable outcomes.[3] The majority of clinical trials and practices have reported the benefits of achieving clinical remission on radiographic damage and daily activity maintenance.[4–6]

In 2022, ACR and EULAR proposed a new version of Boolean remission criteria,[7] allowing patients to achieve remission with a higher level of patients' global assessment (PtGA). In the updated version, the threshold for PtGA (on a 0–10 scale) is 2 (Boolean2.0), compared with the original threshold of 1 (Boolean1.0).[8] PtGA sometimes not only reflects symptoms based on inflammatory disease activity but also other factors such as depressive symptoms or functional limitations due to pre-existing joint damage or even comorbidities.[9,10] Previous studies have demonstrated that compared with the cut-off of disease activity score using 28 joints based on C-reactive protein (DAS28-CRP),

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patients fulfilling the new cut-offs of the clinical disease activity index (CDAI), simplified disease activity index (SDAI), and Boolean 1.0, were found to have less residual disease activity as well as less functional disability and joint damage.[11–13] However, research on the long-term effects of meeting various remission criteria, particularly those defined by Boolean 2.0, is still lacking. In the KOBIO-RA registry, after initiating treatment with biological/targeted synthetic disease-modifying anti-rheumatic drugs (b/tsDMARDs), the yearly remission rates were similar among the CDAI, SDAI and Boolean1.0 remission criteria.[14] However, concordance between Boolean2.0 criteria and CDAI, SDAI, and DAS28 in patients with RA undergoing treatment with DMARDs remains to be established.

A recent study showed that the use of a digital health application (a smart system of disease management group, SSDM) with patient-reported outcomes was associated with an increase in disease control rate.[15] However, disease activity and remission rates monitored in the SSDM have not been fully evaluated, especially compared with the Boolean2.0 definition. Therefore, in this study, we collected data on RA patients from six centers in the SSDM cohort enrolled from January 2014 to December 2023. We explored the concordance between Boolean remission and the DAS28-CRP, CDAI, and SDAI remission criteria. Furthermore, we examined the differences in treatment approaches between patients who attained Boolean2.0 remission and those who did not.

Materials and Methods

Study Design and Participants

A cross-sectional observational analysis was performed on the data from RA patients enrolled in the SSDM. The SSDM is a smart disease management system used to prospectively assess the clinical manifestations, disease activities, and outcomes of enrolled patients with rheumatic diseases in China.[15] When patients were enrolled in the SSDM, they were taught and trained to undertake self-assessment included in the system. All patients with RA were adults (≥18 years old) who met the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for RA.[16] A total of 10030 patients with RA were recruited from January 2014 to December 2023 in six tertiary hospitals, including the Sixth Affiliated Hospital of Sun Yat-sen University, Chongqing Hospital of Traditional Chinese Medicine, First Hospital Affiliated to Baotou Medical College, Northern Jiangsu People's Hospital, Dongguan City Traditional Chinese Medicine Hospital and Jiangmen Central Hospital. Patients without physician's global assessment (PhGA) score were excluded from this study. Patients with any other combined autoimmune inflammatory diseases, such as systemic lupus erythematosus, dermatomyositis, or spondyloarthritis, were also excluded (Supplementary Figure S1). The main variables documented in the SSDM included age, gender, disease duration, clinical features and medication use. Clinical data on tender joint count (TJC), swollen joint count (SJC), PtGA, PhGA, Health Assessment Questionnaire Disability Index (HAQ-DI) were collected. Methotrexate, leflunomide, hydroxychloroquine, sulfasalazine, b/tsDMARDs, glucocorticoids, and non-steroidal anti-inflammatory drugs (NSAIDs) administration were also compared between the groups classified by Boolean2.0 remission. The clinical remission rates of patients with RA estimated using the DAS28-CRP,[17] CDAI,[18] SDAI,[19] Boolean1.0[8] and Boolean2.0[7] criteria were investigated. This study complied with the Declaration of Helsinki, and was approved and monitored by the Committee on Scientific Research and Ethics of the Sixth Affiliated Hospital of Sun Yat-sen University (**NO. 2024ZSLYEC-121**).

Definition of Terms

Boolean1.0 remission is defined as meeting all the following criteria: TJC ≤ 1, SJC ≤ 1, C-reactive protein (CRP) ≤ 1 mg/dL, and PtGA ≤ 1 (on a 0–10 scale).[8] Boolean2.0 remission requires that TJC, SJC, and CRP scores are 1 or less, as well as PtGA ≤ 2.[7]

Additionally, the disease activity as measured by DAS28-CRP[17](with remission defined as ≤ 2.6, low disease activity [LDA] as 2.6–3.2, moderate disease activity [MDA] as 3.2–5.1, and high disease activity [HDA] as > 5.1), CDAI[18] (remission as ≤ 2.8, LDA as 2.8 < CDAI ≤ 10, MDA as 10 < CDAI ≤ 22, and HDA as > 22), and SDAI[19](remission as ≤ 3.3, LDA as 3.3 < SDAI ≤ 11, MDA as 11 < SDAI ≤ 26, and HDA as > 26) scores, as assessed by rheumatologists, was plotted for patients who achieved Boolean2.0 or Boolean1.0 remission versus those who did not.

Statistical Analysis

Demographic and disease characteristics are described as mean ± standard deviation (SD), median with interquartile range (IQR), or proportion (%). Continuous or discrete variables were defined as mean (±SD) or median (IQR) and were compared between the two groups using *t*-test for normally distributed data and *Mann–Whitney U*-test for data that were not normally distributed. Categorical variables were analyzed using *chi*-squared test and were presented as percentages. The agreement of Boolean remission criteria with the index-based remission definitions, including DAS28-CRP, CDAI, and SDAI definitions of remission, was assessed using McNemar's test with k coefficient of agreement (kappa) statistics. Statistical analyses were performed using the IBM SPSS Statistics software (version 26.0; IBM Corp., Armonk, NY, USA) and GraphPad Prism (version 8.0.1; GraphPad Software Inc., San Diego, CA, USA). Statistical significance was set at a two-tailed $P < 0.05$.

Results

Demographic and Clinical Characteristics of Enrolled RA Patients

The demographic and clinical characteristics of the enrolled RA patients are presented in Table 1. In this study, 5619 patients were included in the analysis. The mean age of the patients was 56.33 (±13.01) years, with the majority being female (4491, 79.9%). The median (IQR) disease duration was 48 (29–71) months, and the median (IQR) follow-up duration after enrollment in the SSDM group was 8 (0–30) months.

The patients who achieved Boolean2.0 remission (53.68 ± 12.67 years) were younger than those who did not (56.86 ± 13.02 years). The median (IQR) disease duration was shorter in the remission group (48 [25–62] months) compared to the non-remission group (48 [30–73] months), whereas the median follow-up duration after enrollment in the SSDM was longer in the remission group (19 [5–43] months vs 6 [0–27] months). The duration of morning stiffness was significantly

Table 1 Demographic and Clinical Characteristics of Enrolled RA Patients

	All Patients (n= 5619)	**Attained Boolean2.0 Remission (n= 930)**	**Not attained Boolean2.0 Remission (n= 4689)**	***P* - Value**
Age (y)	56.33 ± 13.01	53.68 ± 12.67	56.86 ± 13.02	**<0.001**
Gender, n (%)				0.700
Female	4491 (79.9)	739 (79.5)	3752 (80.0)	
Male	1128 (20.1)	191 (20.5)	937 (20.0)	
Disease duration (months)	48.00 (29.00, 71.00)	48.00 (25.00, 62.00)	48.00 (30.00, 73.00)	**0.021**
Follow-up (months)	8.00 (0, 30.00)	19.00 (5.00, 43.00)	6.00 (0, 27.00)	**<0.001**
RF positive, n (%)	409 (90.3)	61 (85.9)	348 (91.1)	0.176
Anti-CCP positive, n (%)	41 (70.7)	2 (50.0)	39 (72.2)	0.573
Stiffness duration (minutes)	0 (0, 15.00)	0 (0, 0)	2.00 (0, 22.00)	**<0.001**
No. of tender joints (0–28)	4.00 (2.00, 9.00)	1.00 (1.00, 1.00)	4.00 (2.00, 9.00)	**<0.001**
No. of swollen joints (0–28)	2.00 (1.00, 5.00)	1.00 (1.00, 1.00)	2.00 (2.00, 6.00)	**<0.001**
CDAI	10.00 (6.00, 17.10)	2.40 (2.00, 4.00)	12.00 (8.00, 19.50)	**<0.001**
SDAI	11.43 (6.76, 20.00)	2.85 (2.05, 4.20)	13.59 (9.05, 22.57)	**<0.001**
DAS28-CRP	3.15 (2.17, 4.27)	1.61 (1.38, 1.84)	3.48 (2.68, 4.52)	**<0.001**
CRP (mg/L)	5.16 (2.58, 19.00)	1.89 (0.69, 3.79)	7.20 (3.11, 23.85)	**<0.001**
ESR (mm/h)	23.00 (11.00, 42.00)	15.00 (7.00, 24.00)	25.00 (12.00, 46.00)	**<0.001**
PtGA score	34.00 (25.00, 50.00)	10.00 (10.00, 20.00)	38.00 (30.00, 50.00)	**<0.001**
PhGA score	33.00 (22.00, 50.00)	10.00 (8.00, 20.00)	37.00 (30.00, 50.00)	**<0.001**
HAQ-DI score	1.00 (0, 4.00)	0 (0, 0)	2.00 (0, 5.00)	**<0.001**
RAPID3 score	0 (0, 0)	0 (0, 0)	0 (0, 2.30)	**<0.001**

Notes: Values highlighted in bold represent statistically significant *P* values ($P < 0.05$). The validity of RF testing was established in 453 patients and Anti-CCP testing was established in 58 patients.

Abbreviations: Anti-CCP, anti-cyclic citrullinated peptide; CRP, C-reactive protein; CDAI, Clinical Disease Activity Index; DAS28-CRP, Disease Activity Score using 28 joints based on C-reactive protein; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire Disability Index; PhGA, physician's global assessment; PtGA, patient's global assessment; RAPID3, routine assessment of patient index data 3; RF, rheumatoid factor; SDAI, simplified disease activity index.

shorter in the patients achieving Boolean2.0 remission. The patients who did not achieve remission had a higher median number of tender (4 [2–9]) and swollen joints (2 [2–6]) than those in the remission group (1 [1–1] for both). The wrist and knee were the most common tender joints, whereas the wrist, knee, and third metacarpophalangeal points were the most common swollen joints among the patients not in remission (see Supplementary Figure S2 for details).

Patients who achieved Boolean2.0 remission exhibited significantly lower levels of inflammatory markers, including CRP and erythrocyte sedimentation rate (ESR). Furthermore, their disease activity scores, such as the CDAI, SDAI, and DAS28-CRP, as well as scores reflecting patient and physician assessments, including PtGA, PhGA, HAQ-DI, and routine assessment of patient index data 3 (RAPID3), were significantly reduced ($P < 0.001$).

Treatment Strategies of Enrolled RA Patients Categorized by Boolean2.0 Remission

We further explored the treatment strategies in different groups of patients with RA to determine whether achieving Boolean2.0 remission (Table 2). Leflunomide (1933, 34.4%) and methotrexate (1671, 29.7%) were the most commonly prescribed DMARDs, followed by hydroxychloroquine (448, 8.0%). Janus kinase inhibitors (JAKi) (251, 4.5%) and tumor necrosis factor inhibitors (TNFi) (193, 3.4%) were prescribed to enrolled patients. Glucocorticoids (633, 11.3%) and NSAIDs (788, 14.0%) were also administered to patients as adjunctive therapy.

Among patients who achieved Boolean2.0 remission, a lower percentage were prescribed leflunomide (279 [30.0%] vs 1654 [35.3%]), glucocorticoids (51 [5.5%] vs 582 [12.4%]), or NSAIDs (82 [8.8%] vs 706 [15.1%]). Conversely, a higher percentage of these patients was treated with hydroxychloroquine (102 [11.0%] vs 346 [7.4%]) or sulfasalazine (15 [1.6%] vs 41 [0.9%]).

Concordance of Boolean Remission with Remission Defined by DAS28-CRP, CDAI and SDAI

The rates of achieving remission, as assessed by Boolean1.0, Boolean2.0, DAS28-CRP, CDAI, and SDAI, in all included patients were 9.7%, 16.6%, 35.2%, 9.1%, and 9.4%, respectively (Figure 1A).

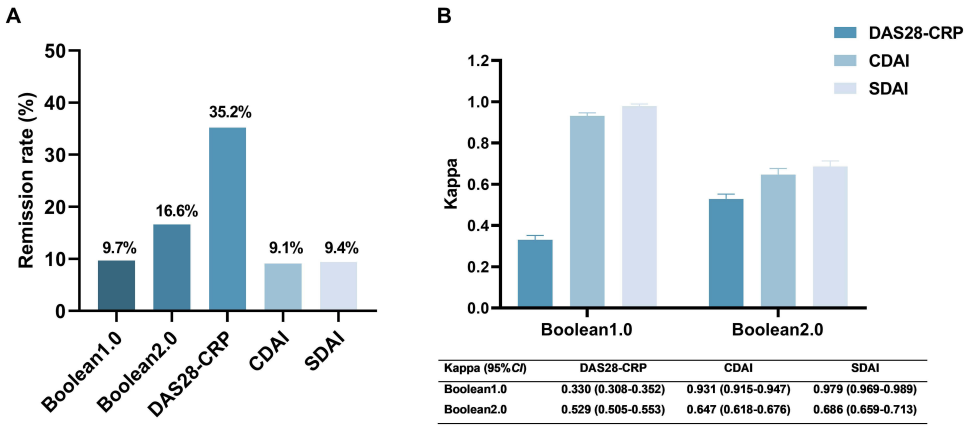
Compared with Boolean1.0 definition, lower concordance rates with CDAI (Boolean2.0: kappa = 0.647; Boolean1.0: kappa = 0.931) and SDAI (Boolean2.0: kappa = 0.686; Boolean1.0: kappa = 0.979) remission were observed in Boolean2.0 definition, whereas kappa values were higher for DAS28-CRP (Boolean2.0: kappa = 0.529; Boolean1.0: kappa = 0.330) remission in Boolean2.0 remission (Figure 1B). Additionally, the concordance between the Boolean2.0 and Boolean1.0 definitions, as measured by kappa with 95% confidence interval (*CI*), was 0.704 (0.677–0.731) ($P < 0.001$).

When examining disease activity categorized by CDAI, SDAI, and DAS28-CRP separately for patients who had attained Boolean2.0 remission or had not, we found that among patients with Boolean2.0 remission, 53.2%, 56.7%, and 99.4% achieved the remission criteria of CDAI, SDAI, and DAS28-CRP, respectively. Among patients who did not

Table 2 Treatment Strategies of Enrolled Patients Classified by Boolean2.0 Remission

	All Patients (n= 5619)	**Attained Boolean2.0 Remission (n= 930)**	**Not Attained Boolean2.0 Remission (n= 4689)**	***P* Value**
Methotrexate	1671 (29.7)	294 (31.6)	1377 (29.4)	0.171
Leflunomide	1933 (34.4)	279 (30.0)	1654 (35.3)	**0.002**
Hydroxychloroquine	448 (8.0)	102 (11.0)	346 (7.4)	**<0.001**
Sulfasalazine	56 (1.0)	15 (1.6)	41 (0.9)	**0.038**
JAKi	251 (4.5)	37 (4.0)	214 (4.6)	0.430
TNFi	193 (3.4)	19 (2.0)	174 (3.7)	0.011
Glucocorticoids	633 (11.3)	51 (5.5)	582 (12.4)	**<0.001**
NSAIDs	788 (14.0)	82 (8.8)	706 (15.1)	**<0.001**

Notes: Values highlighted in bold represent statistically significant *P* values ($P < 0.05$).
Abbreviations: JAKi, Janus kinase inhibitor; NSAIDs, nonsteroidal anti-inflammatory drugs; TNFi, tumor necrosis factor inhibitor.



Kappa (95%*CI*)	DAS28-CRP	CDAI	SDAI
Boolean1.0	0.330 (0.308-0.352)	0.931 (0.915-0.947)	0.979 (0.969-0.989)
Boolean2.0	0.529 (0.505-0.553)	0.647 (0.618-0.676)	0.686 (0.659-0.713)

Figure 1 Remission rates of enrolled RA patients evaluated by Boolean1.0, Boolean2.0, DAS28-CRP, CDAI, and SDAI and concordance of remission rate defined by different criteria. (**A**) The rates of achieving remission assessed by Boolean1.0, Boolean2.0, DAS28-CRP, CDAI, and SDAI among enrolled RA patients; (**B**) Kappa values and 95% *CI*s represent agreement between Boolean remission definitions and other criteria defined remissions. Kappa estimates and 95% *CI*s are provided in the accompanying table. **Abbreviations**: CDAI, Clinical Disease Activity Index; CIs, confidence intervals; DAS28-CRP, Disease Activity Score using 28 joints based on C-reactive protein; RA, rheumatoid arthritis; SDAI, Simplified Disease Activity Index.

achieve Boolean2.0 remission, all failed to meet the criteria for SDAI remission. Only 0.3% of these patients were classified as in remission based on the CDAI criteria, and 22.5% were considered in remission according to the DAS28-CRP criteria (Figure 2A, B and C).

When exploring disease activity categorized by CDAI, SDAI, and DAS28-CRP separately for patients achieving Boolean1.0 remission or not, we found that among patients attaining Boolean1.0 remission, 90.5%, 96.3%, and 99.8% of patients met the remission criteria of CDAI, SDAI, and DAS28-CRP, respectively. Among patients who did not achieve Boolean1.0 remission, none met the criteria for SDAI remission. However, 0.3% of these patients were classified as in remission according to the CDAI criteria, and 28.3% were considered in remission based on the DAS28-CRP criteria (Figure 2D, E and F).

Subgroup Analysis Between Different Groups Based on Gender

Considering the distinct clinical characteristics of RA and therapeutic strategies between genders, we further analyzed treatments among different genders based on Boolean2.0 remission. In total, 739 (16.5%) female patients achieved Boolean2.0 remission in this study (Supplementary Table S1). Among the female patients, leflunomide (1500, 33.4%) and methotrexate (1313, 29.2%) were the most common DMARDs, followed by hydroxychloroquine (386, 8.6%). A lower proportion of patients received leflunomide (212 [28.7%] vs 1288 [34.3%]) while a higher number of patients were prescribed hydroxychloroquine (89 [12.0%] vs 297 [7.9%]) among patients attained Boolean2.0 remission. JAK inhibitors (JAKi) and tumor necrosis factor inhibitors (TNFi) were prescribed to 206 (4.6%) and 157 (3.5%) patients, respectively. Fewer patients achieved Boolean2.0 remission during TNFi treatment (13 [1.8%] vs 144 [3.8%]). Additionally, glucocorticoids (488, 10.9%) and NSAIDs (609, 13.6%) were prescribed as adjuvant therapy, with lower proportions observed in the group of patients achieving Boolean2.0 remission. Among the 1128 male patients, 191 (16.9%) attained Boolean2.0 remission. Treatment strategies were also explored in male patients (Supplementary Table S2). However, only the proportion of glucocorticoids was significantly different between the two groups of male patients attained Boolean2.0 remission or did not (12 [6.3%] attained remission vs 133 [14.2%] did not attain remission).

The rates of disease remission were similar between male and female assessed using Boolean2.0, Boolean1.0, the CDAI, and the SDAI, except for DAS28-CRP (Figure 3A). Female patients had a relatively higher remission rate according to the DAS28-CRP criteria than male patients (36.1% vs 31.6%, $P < 0.001$). Similar to the overall population, the concordance rates were higher when assessing Boolean1.0 criteria using the CDAI and SDAI, whereas the concordance rate between DAS28-CRP and the Boolean1.0 definition was lower than that of Boolean2.0 remission, regardless of whether the patients were male or female (Figure 3B). In addition, the concordance between Boolean2.0

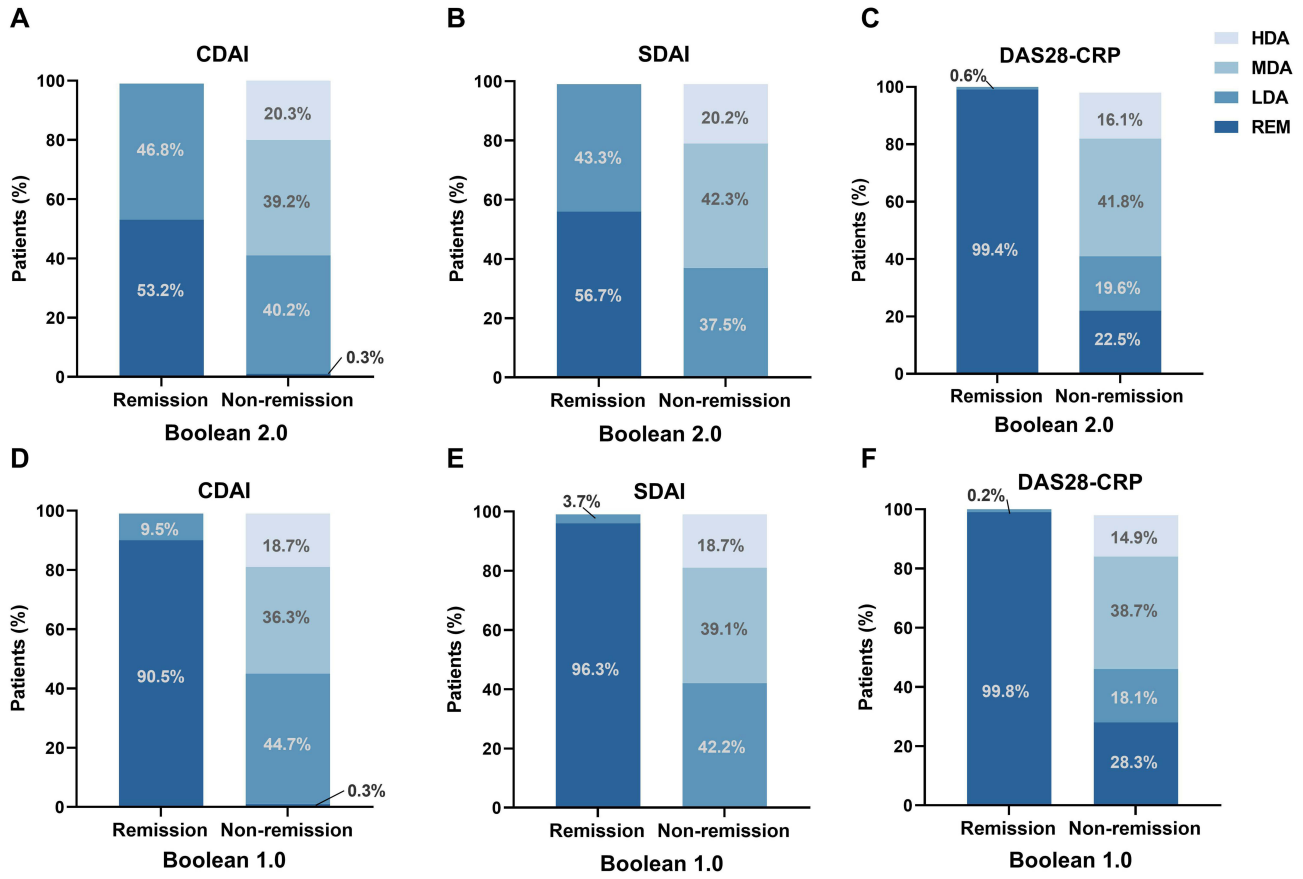


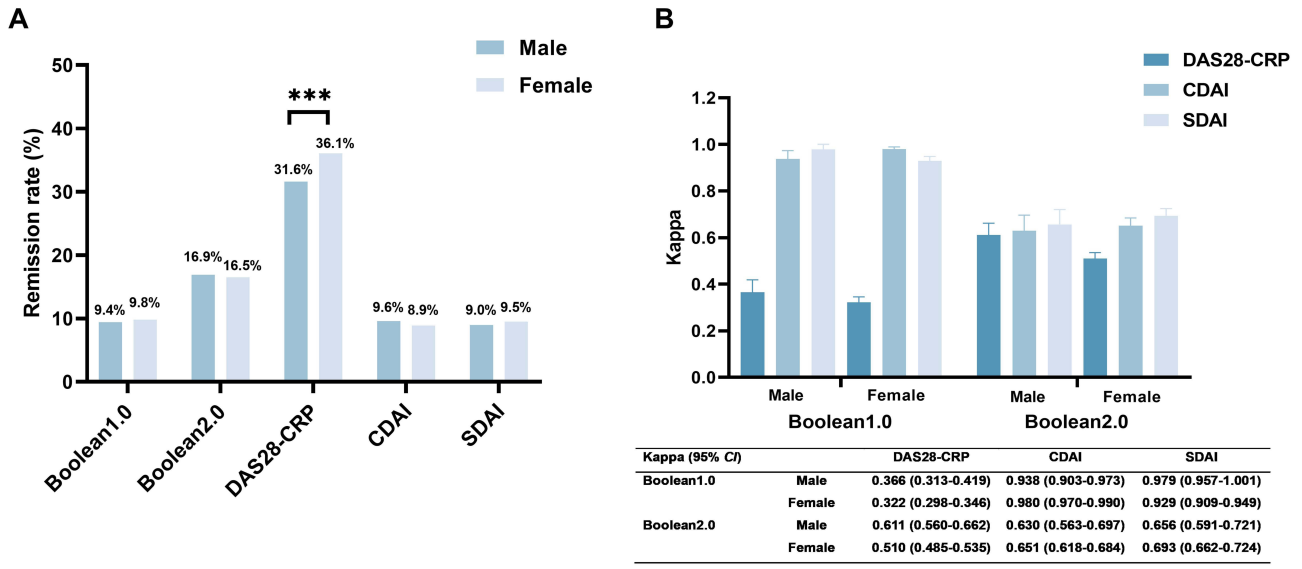
Figure 2 Disease activity categorized by (**A**) CDAI, (**B**) SDAI and (**C**) DAS28-CRP separately for patients who had attained Boolean2.0 remission or had not, and disease activity categorized by (**D**) CDAI, (**E**) SDAI and (**F**) DAS28-CRP separately for patients who had attained Boolean1.0 remission or had not.
Abbreviations: CDAI, Clinical Disease Activity Index; DAS28-CRP, Disease Activity Score using 28 joints based on C-reactive protein; RA, rheumatoid arthritis; SDAI, Simplified Disease Activity Index.

and Boolean1.0 definitions (by means of kappa [95% CIs]) among male and female patients was 0.674 (0.611–0.737) and 0.712 (0.683–0.741), respectively (both $P < 0.001$).

Subgroup Analysis Between Different Groups Based on Age

The cut-off point of age (54.5 years) were determined with ROC curves (high Youden index). In this study, 2364 patients aged ≤ 54.5 years and 3255 patients > 54.5 years were included. Among patients aged ≤ 54.5 years, three hundred and seventy-four (15.8%) attained Boolean2.0 remission (Supplementary Table S3). No significant difference of DMARDs prescription was observed between the two groups. Additionally, glucocorticoids (260, 11.1%) and NSAIDs (357, 15.1%) were prescribed as adjuvant therapy, with lower proportions observed in the group of patients achieving Boolean2.0 remission. Treatment strategies were also explored for patients aged > 54.5 years (Supplementary Table S4). Patients who achieved Boolean2.0 remission were more commonly administered with hydroxychloroquine (70, 12.6%) compared to those did not (207, 7.7%). However, these patients less frequently received leflunomide (151 [27.2%] vs 944 [35.0%] in the non-remission group), TNFi (6 [1.1%] vs 99 [3.7%] in the non-remission group), glucocorticoids (29 [5.2%] vs 344 [12.7%] in the non-remission group) and NSAIDs (47 [8.5%] vs 384 [14.2%] in the non-remission group).

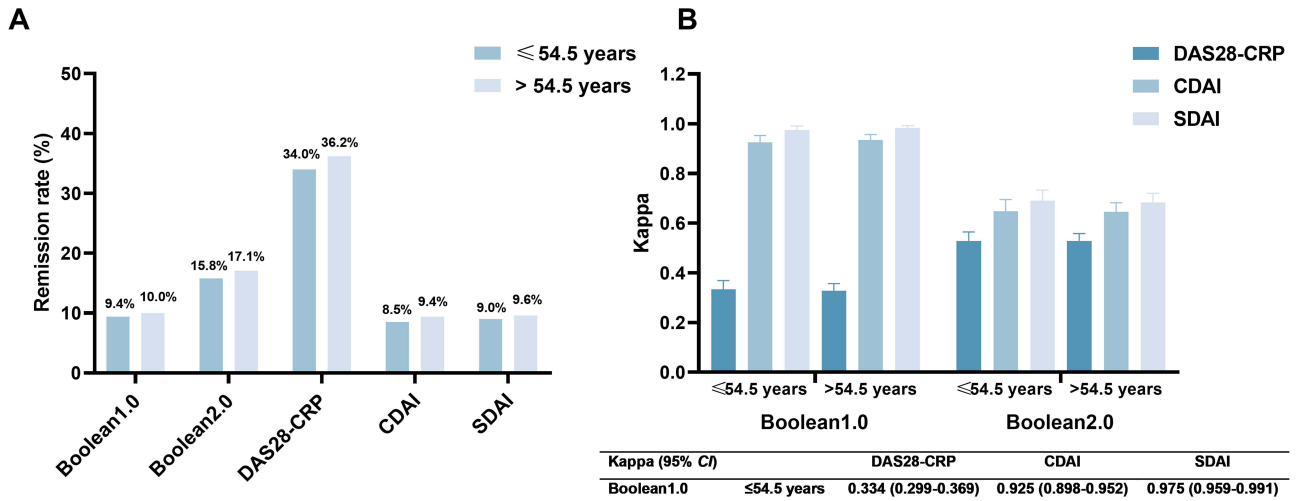
The remission rates evaluated using different definitions were further explored based on age (Figure 4A). There was no significant difference assessed by different remission criteria between the two groups based on age. Compared to Boolean1.0, the concordance between Boolean2.0 and DAS28-CRP definitions was higher in both age groups, whereas the accordance rates were lower with Boolean2.0 criteria when assessed by the CDAI and SDAI (Figure 4B). In addition, the concordance between Boolean2.0 and Boolean1.0 definitions among patients aged ≤ 54.5 years and >54.5 years, was 0.713 (0.670–0.756) and 0.698 (0.663–0.733), respectively (both $P < 0.001$).



Kappa (95% *CI*)		DAS28-CRP	CDAI	SDAI
Boolean1.0	Male	0.366 (0.313-0.419)	0.938 (0.903-0.973)	0.979 (0.957-1.001)
	Female	0.322 (0.298-0.346)	0.980 (0.970-0.990)	0.929 (0.909-0.949)
Boolean2.0	Male	0.611 (0.560-0.662)	0.630 (0.563-0.697)	0.656 (0.591-0.721)
	Female	0.510 (0.485-0.535)	0.651 (0.618-0.684)	0.693 (0.662-0.724)

Figure 3 Remission rates of male and female patients evaluated by Boolean1.0, Boolean2.0, DAS28-CRP, CDAI, and SDAI and concordance of remission rate among male and female patients defined by different criteria. (**A**) Discrepancies of remission rates between genders. ***$P < 0.01$; (**B**) Kappa values and 95% *CI*s represent concordance between Boolean remission definitions and other criteria defined remissions among male and female patients. Kappa estimates and 95% *CI*s are provided in the accompanying table.

Abbreviations: CDAI, Clinical Disease Activity Index; CIs, confidence intervals; DAS28-CRP, Disease Activity Score using 28 joints based on C-reactive protein; RA, rheumatoid arthritis; SDAI, Simplified Disease Activity Index.



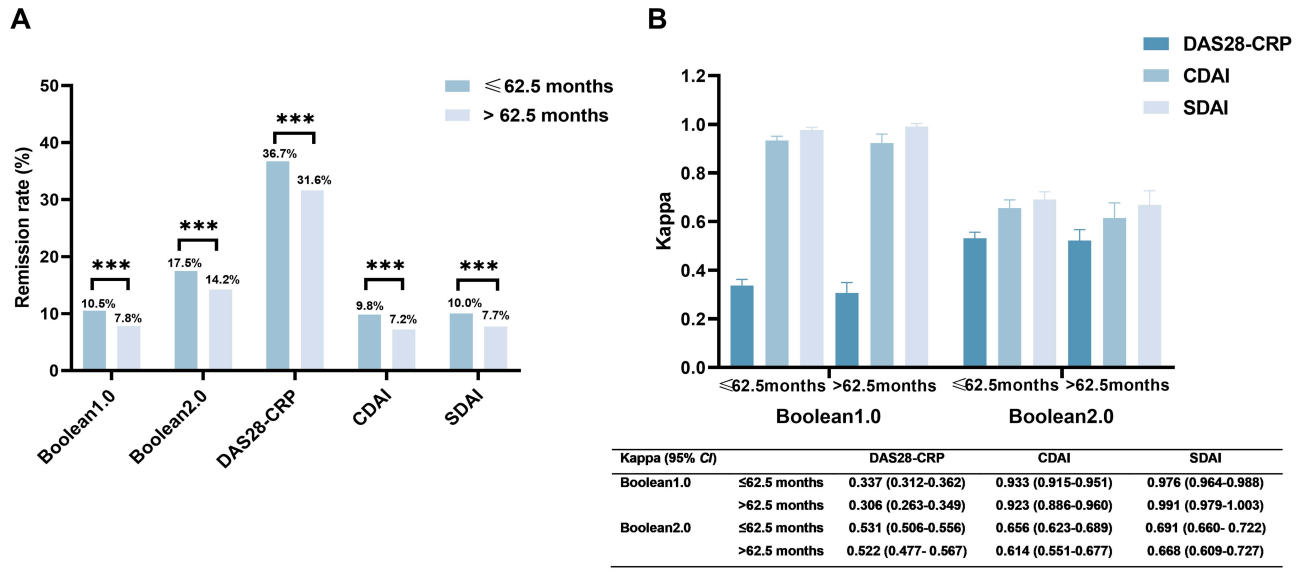
Kappa (95% *CI*)		DAS28-CRP	CDAI	SDAI
Boolean1.0	≤54.5 years	0.334 (0.299-0.369)	0.925 (0.898-0.952)	0.975 (0.959-0.991)
	>54.5 years	0.327 (0.298-0.356)	0.935 (0.913-0.957)	0.983 (0.973- 0.993)
Boolean2.0	≤54.5 years	0.529 (0.494-0.564)	0.648 (0.601-0.695)	0.690 (0.647-0.733)
	>54.5 years	0.529 (0.500-0.558)	0.645 (0.608-0.682)	0.683 (0.646-0.720)

Figure 4 Remission rates of patients at different ages evaluated by Boolean1.0, Boolean2.0, DAS28-CRP, CDAI, and SDAI and concordance of remission rate among patients≤ 54.4 years and> 54.5 years defined by different criteria. (**A**) Discrepancies of remission rates between patients at different ages. (**B**) Kappa values and 95% *CI*s represent concordance between Boolean remission definitions and other criteria defined remissions among male and female patients. Kappa estimates and 95% *CI*s are provided in the accompanying table.

Abbreviations: CDAI, Clinical Disease Activity Index; CIs, confidence intervals; DAS28-CRP, Disease Activity Score using 28 joints based on C-reactive protein; RA, rheumatoid arthritis; SDAI, Simplified Disease Activity Index.

Subgroup Analysis Between Different Groups Based on Disease Duration

The cut-off point of disease duration (62.5 months) were determined with ROC curves (high Youden index). In this study, 4030 patients with disease duration ≤ 62.5 months and 1589 patients with disease duration longer than 62.5 months were included. Among patients with disease duration ≤ 62.5 months, seven hundred and four (17.5%) attained Boolean2.0



Kappa (95% *CI*)		DAS28-CRP	CDAI	SDAI
Boolean1.0	≤62.5 months	0.337 (0.312-0.362)	0.933 (0.915-0.951)	0.976 (0.964-0.988)
	>62.5 months	0.306 (0.263-0.349)	0.923 (0.886-0.960)	0.991 (0.979-1.003)
Boolean2.0	≤62.5 months	0.531 (0.506-0.556)	0.656 (0.623-0.689)	0.691 (0.660- 0.722)
	>62.5 months	0.522 (0.477- 0.567)	0.614 (0.551-0.677)	0.668 (0.609-0.727)

Figure 5 Remission rates of patients with different disease durations evaluated by Boolean1.0, Boolean2.0, DAS28-CRP, CDAI, and SDAI and concordance of remission rate among patients with different disease duration ≤ 62.5 months and> 62.5 months defined by different criteria. (**A**) Discrepancies of remission rates between patients at different ages. ***$P < 0.01$; (**B**) Kappa values and 95% *CIs* represent concordance between Boolean remission definitions and other criteria defined remissions among male and female patients. Kappa estimates and 95% *CIs* are provided in the accompanying table.

Abbreviations: CDAI, Clinical Disease Activity Index; CIs, confidence intervals; DAS28-CRP, Disease Activity Score using 28 joints based on C-reactive protein; RA, rheumatoid arthritis; SDAI, Simplified Disease Activity Index.

remission (Supplementary Table S5). A lower proportion of patients received leflunomide (210 [29.8%] vs 1178 [35.4%]) while a higher number of patients were prescribed hydroxychloroquine (73 [10.4%] vs 250 [7.5%]) among patients attained Boolean2.0 remission. Fewer patients achieved Boolean2.0 remission during TNFi (13 [1.8%] vs 129 [3.9%]), glucocorticoids (38 [5.4%] vs 419 [12.6%]) and NSAIDs (59 [8.4%] vs 506 [15.2%]) treatment. Two hundred and twenty-six patients (14.2%) achieved Boolean2.0 remission among patients with disease duration exceeding 62.5 months (Supplementary Table S6). Hydroxychloroquine was more commonly administered among patients achieving remission (29 [12.8%] vs 96 [7.0%]) whereas glucocorticoids was less frequently utilized (23 [10.2%] vs 200 [14.7%]). Figure 5A illustrates that remission rates were significantly higher in patients with a disease duration of ≤62.5 months compared to those with a duration exceeding 62.5 months, according to the Boolean2.0, Boolean1.0, DAS28-CRP, CDAI, and SDAI criteria ($P < 0.001$). The concordance between Boolean2.0 and DAS28-CRP remission criteria was higher than Boolean1.0 in both groups with different disease durations, whereas the accordance rates were lower with Boolean2.0 criteria when assessed by the CDAI and SDAI (Figure 5B). Moreover, the level of agreement between the Boolean2.0 and Boolean1.0 criteria for remission in patients with a disease duration of ≤62.5 months and those exceeding 62.5 months was 0.713 (0.682–0.744) and 0.676 (0.619–0.733), respectively, with both comparisons demonstrating statistical significance ($P < 0.001$).

Discussion

To our knowledge, this is the first large-sample study conducted among Asian patients with RA to investigate the concordance between Boolean2.0 remission and index-based remission criteria. This cross-sectional observational study collecting data from the SSDM demonstrated a relatively higher concordance between Boolean2.0 criteria and DAS28-CRP remission and lower concordance with the CDAI and SDAI when compared with Boolean1.0 remission criteria. In addition, administration of different DMARDs might have an effect on Boolean2.0 remission rate.

The disease activity of RA was initially defined by a number of core set variables, including TJC, SJC, PtGA, PhGA, HAQ, and an acute-phase reactant such as CRP.[20] The Boolean1.0 definition required each of the four core set variables (TJC, SJC, PtGA, and CRP) to have a value of ≤1 to attain remission.[8] However, some arguments claimed that the Boolean1.0 definition might be too stringent, with the risk of overtreatment if it was used as a treatment target. The Boolean2.0 criteria were endorsed and classified more patients as achieving remission and increased the agreement with

index-based remission criteria without jeopardizing the predictive value for radiographic or functional outcomes.[7] However, in our study, the Boolean2.0 definition had a relatively lower concordance with the CDAI and SDAI, which may be due to population and ethnic divergence. In addition, the patients enrolled in this study had relatively longer disease and follow-up durations, which might influence their self-assessments. Related factors, including economy and education, could also influence remission status, which could be further analyzed. A previous study used data from six randomized controlled trials in early and established RA, illustrated that the concordance between Boolean2.0 remission and SDAI remission among established RA was relatively low, with kappa values approximately 0.68,[21] which was similar to the results of this study. However, the reason for the relatively low concordance still needs further exploration.

PtGA integrates components of disease activity that are not captured by other core variables, and predicts physical function, well-being, and work productivity in patients with RA.[8,21,22] Although pain and fatigue predominantly influence PtGA, irrespective of disease activity,[23] they may also reflect active inflammation and disease activity in many patients.[24] In the early stages of RA, when structural joint damage and non-nociceptive pain processing mechanisms have not yet accumulated, PtGA might, in theory, more strictly reflect patients' perception of inflammation.[25] Consequently, PtGA may play a crucial role in assessing disease activity, which could assist rheumatologists in adjusting treatment strategies appropriately. However, the cutoff score for PtGA still needs to be further validated across various RA patient populations, including those from different countries with diverse disease durations and receiving various types of DMARDs.

This study demonstrated a positive correlation between attaining Boolean2.0 remission criteria, and therapy with hydroxychloroquine and sulfasalazine but a negative correlation with leflunomide, glucocorticoids, and NSAIDs. A large-scale multicenter study carried out in the Asia-Pacific region showed that, compared to patients not in remission, those in remission had significantly higher rates of b/tsDMARDs and lower rates of glucocorticoids usage.[26] However, the b/tsDMARDs prescription rate was low in our study, which requires more data to explore this issue further.

Digital applications may have the potential to assist physicians in collecting patient data and monitoring disease activity, especially among patients with chronic diseases such as RA. A randomized, non-inferiority clinical trial conducted in RA patients with low disease activity showed that patient-initiated care supported by smartphone self-monitoring was non-inferior to usual care in terms of change in the DAS28-ESR score and led to a 38% reduction in rheumatologist consultations.[27] When comparing RA patients from the SSDM group with the control group in a multicenter, open-label randomized clinical trial, the rate of patients with DAS28-CRP $\leq$ 3.2 was higher (71.0%) in the SSDM group than in the control group (64.5%) at 6 months, whereas the rates of patients with DAS28-CRP $\leq$ 3.2 were comparable between the two groups (78.2% vs 77.7%) at 12 months.[15] Smartphone applications, such as SSDM, could be used in daily clinical practice to reduce the management burden of rheumatologists. However, it is still unclear how often patients must be monitored to be able to target consultations according to need, which requires more data and further investigation.

This study has several limitations. First, imaging-based assessments of the joint damage were not performed. However, the focus of this study was on the concordance of disease remission as evaluated using various criteria, and radiographic assessment was not part of this analysis. Second, our results demonstrated differences in the concordance of Boolean2.0 and Boolean1.0 with index-based remission criteria in Chinese patients with RA, which may not be applicable to RA populations in other countries. Third, the study did not explore the adjustment of treatment strategies in response to changes in disease activity assessed using different criteria nor did it examine the subsequent impact of these adjustments on disease remission. Further investigation is required to address these issues.

Conclusion

In conclusion, this study demonstrated a relatively higher concordance between Boolean2.0 criteria and DAS28-CRP remission and a lower concordance with CDAI and SDAI when compared with Boolean1.0 remission criteria. In addition, administration of different DMARDs may have an effect on Boolean2.0 remission rate. However, more data and further investigations are required to evaluate the concordance of the various remission criteria in patients with RA.

Abbreviations

Anti-CCP, anti-cyclic citrullinated peptides; CDAI, clinical disease activity index; CRP, C-reactive protein; DAS28-CRP, disease activity score using 28 joints based on C-reactive protein; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire Disability Index; JAKi, Janus kinase inhibitors; NSAIDs, non-steroidal anti-inflammatory drugs; PhGA, physician's global assessment; PtGA, patient's global assessment; RA, rheumatoid arthritis; RAPID3, routine assessment of patient index data 3; RF, rheumatoid factor; SDAI, simplified disease activity index; SSDM, a smart system of disease management group; TNFi, tumor necrosis factor inhibitors.

Ethics Approval and Informed Consent

This study complied with the Declaration of Helsinki, and was approved and monitored by the Committee on Scientific Research and Ethics of the Sixth Affiliated Hospital of Sun Yat-sen University (**NO. 2024ZSLYEC-121**). The Committee on Scientific Research and Ethics of the Sixth Affiliated Hospital of Sun Yat-sen University does not mandate obtaining patient consent for the review of medical records when the study employs records derived from previous clinical diagnoses and treatments, provided that all the following conditions are met simultaneously:

1) The research objective is important.
2) The risk to the subjects is not greater than minimal risk.
3) Waiving informed consent will not adversely affect the rights and health of the subjects.
4) The privacy and personal identity information of the subjects is protected.
5) If the patient/subject has previously explicitly refused the use of their medical records and specimens in future research, then their medical records and specimens might only be used in the event of a public health emergency.
6) Patient data obtained were only used for the analyses in this study.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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