How to Define Boolean Low Disease Activity in Rheumatoid Arthritis: Experience from a Large Real-World Cohort

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Research article

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Abstract

Objectives: To propose Boolean-defined low disease activity (LDA) and to test its utility in rheumatoid arthritis (RA).

Methods: We used data from a longitudinal academic clinical database of RA in Peking University First Hospital over a decade. The initial proposal of Boolean-defined LDA with ascending thresholds from 2 to 5 in steps of 1. Agreement and residual swollen joint count (SJC) pattern with the index-based (Simplified Disease Activity Index [SDAI] and Clinical Disease Activity Index [CDAI]) LDA was analyzed. To confirm discovery, we randomly classified RA patients in a 3:2 ratio into either analysis cohort or validation cohort.

Results: In total 4,881 visits of 672 patients were included in the analysis cohort. Of these visits, the frequencies of achieving LDA were 71.9% (SDAI), 73.6% (CDAI), 52.8% (Boolean-LDA2), 65.2% (Boolean-LDA3), 73.5% (Boolean-LDA4), and 80.7% (Boolean-LDA5). High consistency and similar SJC pattern with SDAI-LDA or CDAI-LDA were observed in Boolean-LDA3 (kappa=0.796, 0.771). Further analysis found meeting SDAI-LDA but not Boolean-LDA3 were largely attributable to higher patient's global assessment (PGA) scores (62.9%). In further modification of Boolean-LDA3, best agreement with SDAI-LDA or CDAI-LDA was reached when evaluator's global assessment (EGA) replaced PGA with cutoff of 3.0 (kappa=0.851, 0.825), rather than exclusively increasing the PGA cut-offs. These findings were further replicated in randomly-generated validation cohort of 449 patients with 3,306 clinic visits.

Conclusions: Using cut-off of 3 to Boolean-LDA with a substitute EGA for PGA provides highest consistency and similar residual SJC pattern with index-based LDA. This may deserve considering in clinical practice.

Introduction

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease, characterized by progressive, symmetric arthritis, leading to irreversible joint destruction [1, 2]. Over the past decades, treat-to-target strategy and novel therapeutic agents have tremendously transformed the clinical trajectory of RA patients [3–5]. In the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) management recommendations for RA, a state of clinical remission is placed as the primary target for RA treatment [6]. Alternatively, low-disease activity (LDA) may also be an acceptable therapeutic goal, particularly in long-standing disease, in the context of complicated clinical scenario [7].

In general, the states of LDA and remission can be defined according to different composite measures with corresponding cut-offs, including the Disease Activity Score in 28 joints (DAS28) [8], Simplified Disease Activity Index (SDAI) [9], Clinical Disease Activity Index (CDAI) [10]. As for each target, each of these different composite measures or cut-offs are intended to measure the same construct. Ideally, they would all strongly agree with each other and result in the same treatment consequences. Although CDAI

and SDAI-defined LDA and remission are reported to strongly agree with each other, other measures had higher discordance [11, 12]. For example, the DAS28 remission allows for a significant number of residual swollen joints, which cannot be overcome by modifying the cut-off [13, 14]. Apart from these criteria, ACR/EULAR Boolean definition provided remission criteria for RA patients almost one decade ago, which includes swollen joint count (SJC), tender joint count (TJC), patient's global assessment (PGA, 0–10 scale), and C-reactive protein (CRP) levels (mg/dL). A patient must have scores of 1 or less in each component to attain Boolean remission [15]. The LDA is an alternative therapeutic goal, however, Boolean-defined LDA is not unequivocally established, which indeed restricts the application of the definition in daily practice.

To fill the gap, we aim to propose Boolean definition for LDA, and test its clinical utility with a comparator of either SDAI-LDA or CDAI-LDA, on basis of a large real-world database of RA patients.

Methods

Study population

All patients were identified from the outpatient clinic of our department in real-world longitudinal database, which has been previously described and approved by the local ethics committee [5, 12, 16, 17]. In brief, a longitudinal database of a large cohort of RA patients had been established over the course of more than 10 years. RA was diagnosed according to the 1987 ACR classification criteria [18] and/or 2010 ACR/EULAR classification criteria for RA [19]. At the first visit in the database, demographics, symptom duration, RA core set variables (TJC28, SJC28, PGA, evaluator's global assessment (EGA, 0–10 scale)), laboratory testing (CRP, mg/dl)) and treatment details (e.g. methotrexate (MTX); leflunomide (LEF); hydroxychloroquine (HCQ); sulfasalazine (SSZ)) were documented. After the initial visit, each patient contact was prospectively documented at least three-monthly for the patients in moderate/high diseases activity and every 3–12 months (usually 3–6 months) for the patients in remission/LDA. Extra follow-up was additionally scheduled besides those at regular intervals if clinical necessary. The treatment decisions at each visit were made at discretion of rheumatologists based on disease activity scores for the explicit goal of clinical remission.

A retrospective analysis of prospectively collected data was performed for all participants in the real-world longitudinal database with RA. To confirm discovery, we randomly classified RA patients in the database at a ratio of 3:2 into either analysis cohort or validation cohort. Early and established RA was defined as the duration from onset of first arthritic symptom to the first visiting in our center with definite diagnosis of RA $\leq$ 1 year or > 1 year, respectively. A patient who never received disease-modifying antirheumatic drugs (DMARDs) treatment or was on DMARD treatment for less than 3 months at first visit was defined as a DMARD-naive patient.

Definitions of LDA

At present, various composite instruments were available to measure disease activity for RA patients, however no universal consensus on the assessment of LDA. In this study, the SDAI and CDAI index-based definitions of LDA were applied as comparators. The SDAI is obtained from a linear sum of SJC28, TJC28, PGA, EGA, and CRP (mg/dL), and SDAI ≤ 11 is defined as LDA [9]. Similarly, the CDAI comprises the linear sum of SJC28, TJC28, PGA, and EGA, with an LDA definition of CDAI ≤ 10 [10].

The Boolean remission includes SJC28, TJC28, PGA and CRP. For a patient to meet remission criteria, all of these components must have scores of ≤ 1. Since no definition of LDA exists for Boolean, we initially put forward the candidates for Boolean-LDA by increasing the cut-off of the four core set variables in steps of 1 from 2 to 3, 4, 5. We respectively referred them as Boolean-LDA2, Boolean-LDA3, Boolean-LDA4 and Boolean-LDA5 thereafter. Furthermore, we investigated the reasons for discordance between the initial Boolean-LDA proposals and SDAI index-based LDA, and further modifications on the impeditive variables were made to increase the agreement.

Statistical analysis

The data were presented as means (standard deviation (SD)) or median (interquartile range (IQR)) depending on the level of resemblance to the normal distribution. Absolute and relative frequencies were reported for categorical variables. The frequencies of LDA were measured by each definition, reported as percentages with 95% confidence intervals (95% CIs). We assessed the agreement of proposed Boolean-LDA with the SDAI definition of LDA by k-coefficient for agreement at all documented visits and initial visits of included patients, respectively. The kappa values were interpreted according to Landis and Koch (agreement: poor < 0.00; slight 0.00-0.20; fair 0.21–0.40; moderate 0.41–0.60; substantial 0.61–0.80; almost perfect 0.81-1.00) [20]. Besides, reference to previous reports, the number of SJC was significantly associated with radiographic progression among all components in RA patients [13, 14, 21, 22]. Therefore, to reflect the impact of different Boolean LDA on radiographic progression, in part, we compared the distribution of SJC across the different LDA definitions. All the analyses were conducted using SPSS version 22.0.

Results

Characteristics of patients at baseline

In total, 1,121 patients with 8,187 clinic visits in the longitudinal database were included and randomly grouped into analysis cohort or validation cohort, respectively (Table 1). In the analysis cohort, there were 672 participants comprising 4,881 visits, with a mean onset age of 49 (SD 15) years, 77.2% females (Table 1). Most of the patients were rheumatoid factor (76.1%), anti-cyclic citrullinated peptides (85.6%) positive. 61.0% of all patients were DMARD-naïve at baseline. Of included patients with a mean disease duration of 24 (6–84) months, there were 314 (46.7%) early RA and 358 (53.3%) established RA patients. The median (IQR) SDAI and CDAI of patients at cohort entry was 16.1 (9.1–27.1) and 14.0 (8.0–24.0). DMARDs were initiated to all patients after enrollment to the cohort, with MTX (80.4%), LEF (45.2%) and HCQ (40.5%) as the top three. Glucocorticoids were applied as part of initial therapeutic strategies in 283

(42.1%) patients. The validation cohort comprising 449 participants with 3,306 clinic visits possessed similar demographics, clinical characteristics and treatment details to analysis cohort (Table 1)

Table 1
Demographics and clinical characteristics of RA patients

Characteristics of RA patients	All (n = 1121)	Analysis cohort (n = 672)	Validation cohort (n = 449)
Basic characteristics			
Age of onset (years)	48 ± 15	49 ± 15	48 ± 16
Female, n (%)	879 (78.4%)	519 (77.2%)	359 (80.0%)
Disease duration (months)	24 (6–84)	24 (6–84)	20 (6–84)
Early RA, n (%)	531 (47.4%)	314 (46.7%)	216 (48.1%)
DMARD-naïve, n (%)	671 (59.9%)	410 (61.0%)	261 (58.1%)
RF positive, n (%)	851/1112 (75.9%)	507/666 (76.1%)	343/445 (77.1%)
Anti-CCP positive, n (%)	900/1051 (85.6%)	537/627 (85.6%)	363/424 (85.6%)
Baseline disease activity measures			
TJC28	3 (1–7)	3 (1–7)	3 (1–7)
SJC28	2 (1–4)	2 (1–5)	2 (1–4)
PGA, 0-10cm	5 (3–6)	5 (3–6)	5 (3–6)
EGA, 0-10cm	4 (2–6)	4 (2–6)	4 (2–6)
ESR, mm/h	29 (14–47)	29 (15–48)	29 (14–47)
CRP, mg/dl	0.88 (0.33–2.30)	0.90 (0.35–2.39)	0.80 (0.31–2.15)
SDAI	15.5 (9.0-26.5)	16.1 (9.1–27.1)	15.2 (8.4–26.1)
CDAI	14.0 (8.0–24.0)	14.0 (8.0–24.0)	14.0 (7.0–23.0)
Initial therapy, n (%)			
MTX	897 (80.0%)	540 (80.4%)	357 (79.5%)
LEF	511 (45.6%)	304 (45.2%)	207 (46.1%)
HCQ	423 (37.7%)	272 (40.5%)	151 (33.6%)

Values are presented as mean (S.D.) or median (IQR), as applicable. SD: standard deviation, IQR: interquartile ranges

RF: rheumatoid factor; Anti-CCP: anti-cyclic citrullinated peptides; TJC: tender joint count; SJC: swollen joint count; PGA: patient's global assessment; EGA: evaluator's global assessment; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; SDAI: Simplified Disease Activity Index; CDAI: Clinical Disease Activity Index; MTX: methotrexate; LEF: leflunomide; HCQ: hydroxychloroquine; SSZ: sulfasalazine; DMARDs: disease modifying antirheumatic drugs.

Characteristics of RA patients	All (n = 1121)	Analysis cohort (n = 672)	Validation cohort (n = 449)
SSZ	64 (5.7%)	41 (6.1%)	23 (5.1%)
Glucocorticoids	440 (39.3%)	283 (42.1%)	157 (35.0%)
Values are presented as mean (S.D.) or median (IQR), as applicable. SD: standard deviation, IQR: interquartile ranges			
RF: rheumatoid factor; Anti-CCP: anti-cyclic citrullinated peptides; TJC: tender joint count; SJC: swollen joint count; PGA: patient's global assessment; EGA: evaluator's global assessment; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; SDAI: Simplified Disease Activity Index; CDAI: Clinical Disease Activity Index; MTX: methotrexate; LEF: leflunomide; HCQ: hydroxychloroquine; SSZ: sulfasalazine; DMARDs: disease modifying antirheumatic drugs.			

The concordance across LDA definitions

The rate of reaching LDA assessed by SDAI and CDAI in all included visits was 71.9% (3510) and 73.6% (3593), respectively. For initial proposals of Boolean-LDA definitions, the frequency of LDA was as follows: 52.8% (2577) for Boolean-LDA2, 65.2% (3182) for Boolean-LDA3, 73.5% (3588) for Boolean-LDA4, and 80.7% (3937) for Boolean-LDA5 (Fig. 1). When assessing the best cut-off for concordance of index-based LDA and Boolean-defined LDA, we found that high concordance rates with SDAI- or CDAI-based LDA were observed in Boolean-LDA3 (SDAI: kappa = 0.796; CDAI: kappa = 0.771) and Boolean-LDA4 (SDAI: kappa = 0.807; CDAI: kappa = 0.794) (Fig. 2). Similar findings were observed in separate analysis of either early or established RA patients (Fig. 2). Besides, we also compared the concordance across LDA criteria based on 500 initial visits among RA patients in analysis cohort, yielding similar results (**Supplementary Figure S1**).

Residual SJC has been found to be most closely associated with the radiographical progression in RA patients [13, 14, 21, 22]. We, therefore, compared the distribution of residual SJC between SDAI or CDAI-based LDA and proposed Boolean definition of LDA (Fig. 3). For the visits met SDAI (CDAI)-defined LDA, the proportion of SJC = 1, SJC = 2 and SJC ≥ 3 was 14.16% (14.22%), 6.67% (7.26%), and 2.59% (2.95%), respectively. As expected, the residual SJC of Boolean-LDA increased with the cut-off increment and most similar distribution of SJC was observed between index-based LDA and Boolean-LDA3 (13.55% of SJC = 1; 7.17% of SJC = 2; 2.36% of SJC = 3) (Fig. 3). Taken together, Boolean-LDA3 showed great performance in defining LDA.

The reasons for discordance between Boolean-LDA3 and SDAI-LDA

Of included 4,881 visits, a total of 431 discordances were observed, with meeting SDAI-LDA but not Boolean-LDA3 in 380 visits and meeting Boolean-LDA3 but not SDAI-LDA 51 visits. Subsequently, the reasons for meeting SDAI-LDA but not Boolean-LDA3 were analyzed. Of 380 discordances, the most common reason was higher PGA scores (239; 62.9%), followed by higher TJC (87; 23.0%), CRP (39;

10.3%) and SJC (36; 9.5%) (**Supplementary Figure S2**). For the higher PGA scores, there were 137 times of 3.1-4.0, 86 times of 4.1-5.0 and 16 times of over 5.0 (**Supplementary Figure S2**).

Further modification of Boolean-LDA3

Accordingly, the further modifications of PGA for Boolean-LDA3 were made by increasing the cut-off of the PGA criterion stepwise by 0.5 increments from 3.5 to 5.0 (Boolean-LDA3(PGA3.5/4.0/4.5/5.0)) or replacement of PGA with EGA using cut-off of 3.0 (Boolean-LDA3(EGA3.0)).

For modified proposals of Boolean-LDA3, the frequency of included visits was 65.4% for Boolean-LDA3(PGA3.5), 69.1% for Boolean-LDA3(PGA4.0), 69.2% for Boolean-LDA3(PGA4.5), 72.3% for Boolean-LDA3(PGA5.0) and 70.7% for Boolean-LDA3(EGA3.0) (Fig. 1). Highest consistency was reached with Boolean-LDA3(EGA3.0) (SDAI: kappa = 0.851; CDAI: kappa = 0.825) (Fig. 4). Similar findings were detected either in early RA (SDAI: kappa = 0.833; CDAI: kappa = 0.805) or established (SDAI: kappa = 0.863; CDAI: kappa = 0.837) (Fig. 4). The additional comparisons of the concordance across LDA criteria based on 672 initial visits among RA patients were made in analysis cohort, yielding similar results (**Supplementary Figure S3**). Meanwhile, exclusively increasing PGA cutoffs or replacement of PGA with EGA using cut-off of 3.0 on basis of Boolean-LDA3 did not substantially impact the pattern of residual SJC compared with Boolean-LDA3 (Fig. 5). Therefore, Boolean-LDA3(EGA3.0) exhibited the greatest clinical utility in defining LDA.

Validation analysis

Finally, we validated our results in a randomly-generated internal cohort, in which 449 RA patients with 3,306 visits were included and their baseline characteristics were shown in Table 1. In validation cohort, high concordance rates and most similar pattern of SJC with SDAI or CDAI definition of LDA were achieved with Boolean-LDA3 (SDAI: kappa = 0.802; CDAI: kappa = 0.791 for all patients; SDAI: kappa = 0.785; CDAI: kappa = 0.780 for early RA; SDAI: kappa = 0.810; CDAI: kappa = 0.797 for established RA) and further modification with a substitute EGA for PGA provided best agreement with either SDAI or CDAI definition of LDA (SDAI: kappa = 0.849; CDAI: kappa = 0.836 for all patients; SDAI: kappa = 0.830; CDAI: kappa = 0.819 for early RA; SDAI: kappa = 0.861; CDAI: kappa = 0.846 for established RA) (**Supplementary Figure S4-5**).

Discussion

To our knowledge this is the first study aimed at proposing Boolean-defined LDA and testing its utility in RA. Based on the large real-world cohort of early and established RA patients in our center, we proposed the initial and modified Boolean-LDA, and further tested their performance in comparison with SDAI- and CDAI-based LDA, which are frequently applied in nowadays daily practice. Moreover, we also compared the SJC patterns in the clinic visits meeting LDA based on the corresponding definitions.

Generally, Boolean-defined LDA with a cut-off of 3 showed high consistency and similar SJC distribution to the SDAI- or CDAI-defined LDA in our cohort. Further analysis of the reasons for the discordances between Boolean-LDA3 and SDAI-LDA suggested over half of the discordances were attributable to the higher PGA, mostly ranging from 3.1 to 5.0. Accordingly, the targeted modifications of PGA were designed by increasing the cut-off of the PGA criterion stepwise by 0.5 increments from 3.5 to 5.0, and replacement of PGA with EGA using cut-off of 3.0. The results showed highest concordance rates with similar pattern of residual SJC were achieved with replacement of PGA with EGA in Boolean-LDA3. In fact, although Boolean definition of remission seems to be most strict, it has been also criticized. Patients with no actively inflamed joints and a normal CRP often however with PGA exceeding the cut-off of 1 are rated as non-remission [23]. Previous clinical research found patients in SDAI or CDAI remission but not Boolean remission had higher PGA compared with patients in Boolean remission [24]. In a recent study pooling 6 different large clinical trials of 1680 early and established RA, Studenic et al. found increasing PGA cut-off to 1.5 or 2.0 would provide high consistency between Boolean remission and SDAI-based remission [25]. Similarly, in the present study, we found the most common reason for meeting SDAI-LDA but not Boolean-LDA3 was higher PGA, mostly ranging 3.1-5.0. Further modifications indicated best agreement with similar pattern of SJC was reached when PGA was replaced by EGA with cutoff of 3, instead of exclusively increasing PGA cut-off from 3.5 to 5.0.

LDA is an acceptable therapeutic goal, particularly in long-standing disease. The corresponding analyses were separately performed in both early and established RA population and yielded similar findings, supporting the potential clinical utility of the Boolean-defined LDA presented in the present study. In addition, subsequent validation in a randomly-generated internal cohort of 449 RA patients with similar findings supported the validity of the Boolean-LDA with a substitute EGA for PGA using cut-off of 3. In summary, the agreement was almost perfect and the distribution of residual SJC was similar among CDAI-LDA, SDAI-LDA, and Boolean-LDA with cut-off of 3 and a substitute EGA for PGA in our analyses. Our study, for the first time, proposed the definition of Boolean LDA, and could help promote the adoption of Boolean definition in daily practice.

There are several potential weaknesses of this study that should be acknowledged. No radiographic or functional assessment was analyzed in this study, which may weaken the strength of the proposed Boolean definition of LDA. In consideration of the association between residual SJC and radiographic progression according to previous studies [13, 14, 21, 22], we further compared the distribution of SJC in the clinic visits meeting LDA based on the corresponding LDA definitions, and yielded similar pattern of residual SJC. This finding may strengthen the clinical utilization of the proposed Boolean-defined LDA. Of course, the impact of proposed Boolean-LDA on radiographic and physical outcomes definitely needs to be further validated in future studies. In addition, although subgroup analysis according to diseases course and internal validation analysis were performed in the present study, the findings were sorely on basis of single-center longitudinal cohort of unselected RA population, which may limit the external generalization of the present results. Therefore, extended studies are warranted to prove these findings in other ethnicities or regions in the future.

Conclusion

In conclusion, our findings suggest that Boolean-LDA with a substitute EGA for PGA using cut-off of 3 leads to best agreement and most similar residual SJC pattern with the SDAI- and CDAI-based definition of LDA. This needs to be replicated in other settings and can be used in the management of RA patients in daily practice.

Abbreviations

RA: rheumatoid arthritis; ACR: American College of Rheumatology; EULAR: European League Against Rheumatism; LDA: low disease activity; SJC: swollen joint count; DAS28: the Disease Activity Score in 28 joints; SDAI: Simplified Disease Activity Index; CDAI: Clinical Disease Activity Index; SIC: swollen joint count; TJC: tender joint count; PGA: patient's global assessment; CRP: C-reactive protein; EGA: evaluator's global assessment; MTX: methotrexate; LEF: leflunomide; HCQ: hydroxychloroquine; SSZ: sulfasalazine; SD: standard deviation; IQR: interquartile range.

Declarations

Ethical Committee Approval:

This study was approved by the Ethics Committee of Peking University First Hospital.

Consent for publication:

Informed consent for publication was obtained from all the patients.

Author contribution:

ZZ conceived of the study, participated in its design and coordination, and critically revised the manuscript. WX had full access to all of the data collection, analysis, interpretation, and drafted the manuscript. GL and HH contributed to the process of data collection. All the authors listed have approved the enclosed manuscript.

Declarations of interest:

none

Data availability statement:

All data relevant to the study are included in the article or uploaded as supplementary information

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The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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Figures

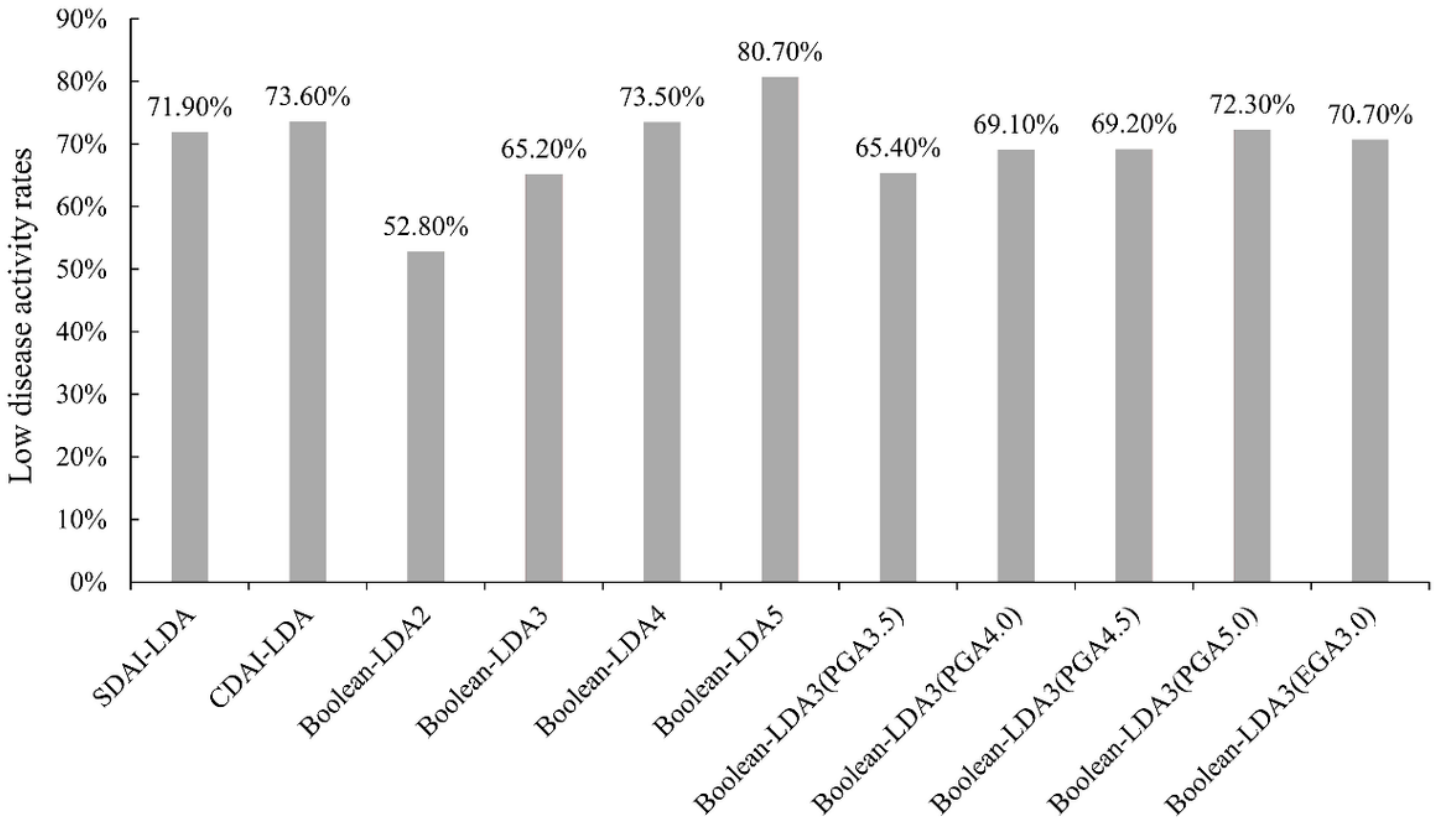

Figure 1

Rates of low disease activity assessed by SDAI, CDAI, initial proposed Boolean definition, using cut-off of in steps of 1 from 2 to 3, 4, 5 (Boolean-LDA2/3/4/5), and modified Boolean definition by increasing the cut-off of the PGA by 0.5 cm increments from 3.5 cm to 5.0 cm (Boolean-LDA3(PGA3.5/4.0/4.5/5.0)) or replacement of PGA with EGA using cut-off of 3.0 cm (Boolean-LDA3(EGA3.0)). SDAI: Simplified Disease Activity Index; CDAI: Clinical Disease Activity Index; PGA: patient's global assessment; EGA: evaluator's global assessment.

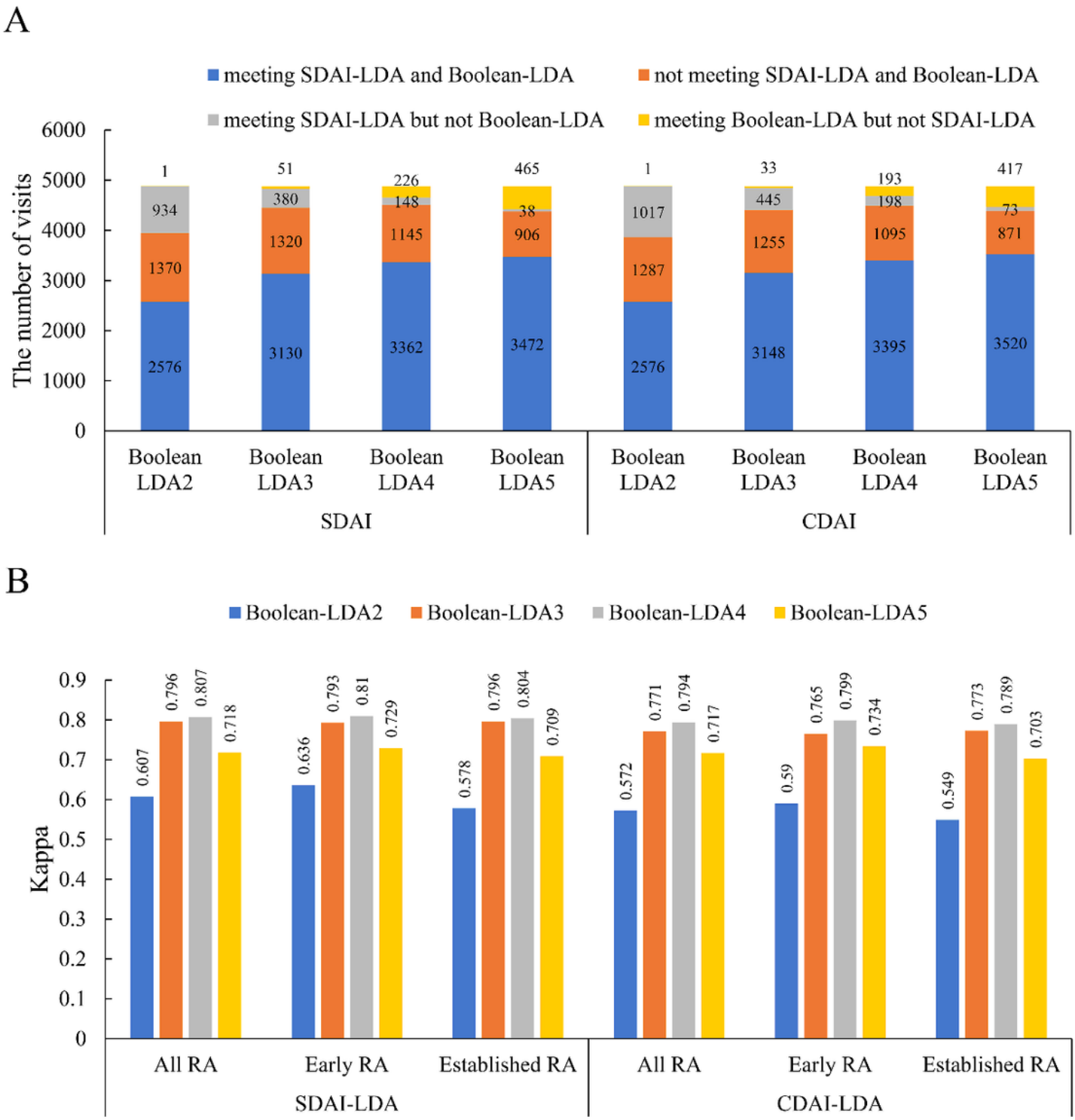

Figure 2

The agreement in included visits between initial proposed Boolean definition of LDA, using cut-off of in steps of 1 from 2 to 3, 4, 5 (Boolean-LDA2/3/4/5) and SDAI- or CDAI-based LDA, (A): The concordances and discordances; (B): Kappa value. LDA: low disease activity; SDAI: Simplified Disease Activity Index; CDAI: Clinical Disease Activity Index.

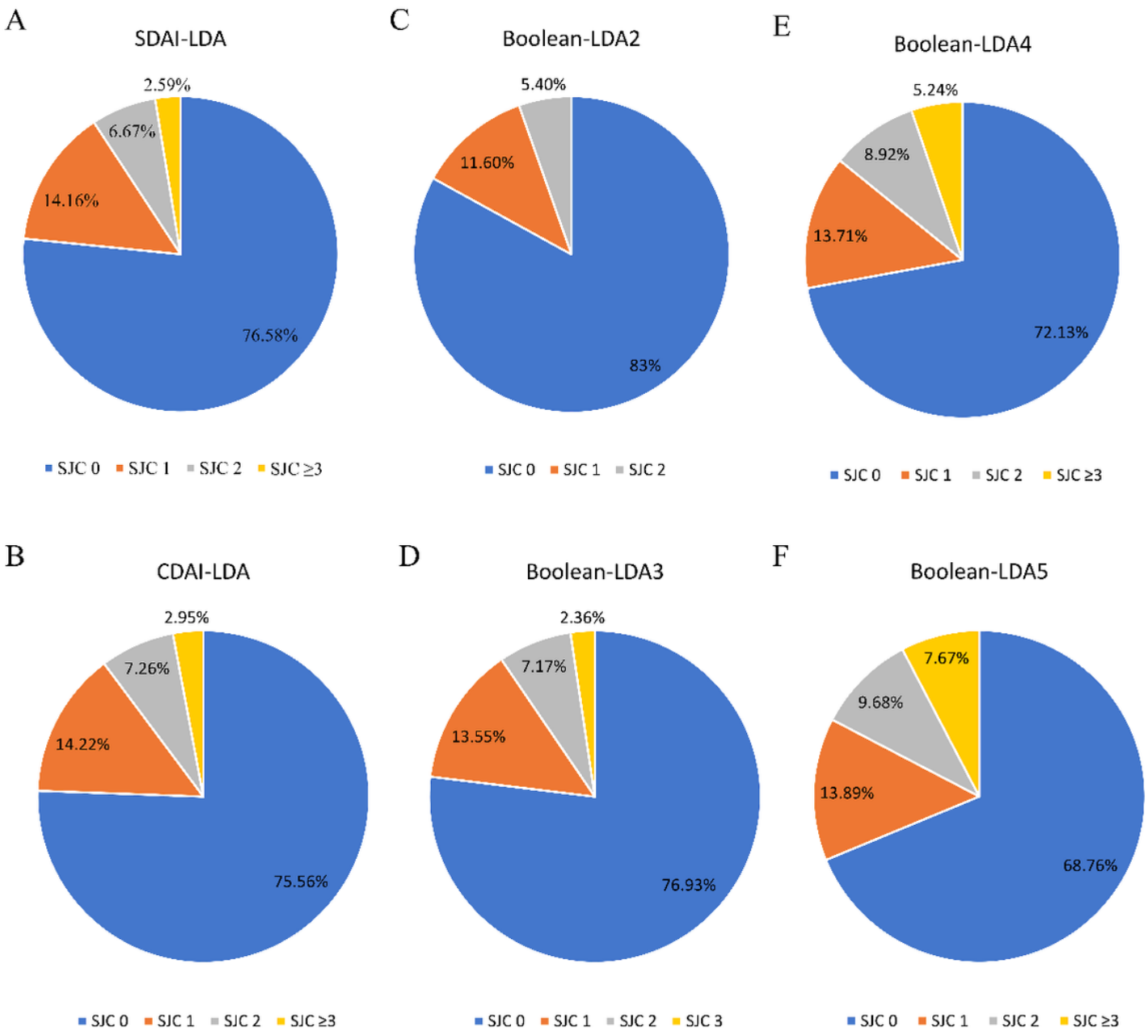

Figure 3

The distribution of swollen joint count in the included clinic visits meeting low disease activity based on SDAI, CDAI and initial proposed Boolean definition, using cut-off of in steps of 1 from 2 to 3, 4, 5 (Boolean-LDA2/3/4/5). LDA: low disease activity; SDAI: Simplified Disease Activity Index; CDAI: Clinical Disease Activity Index.

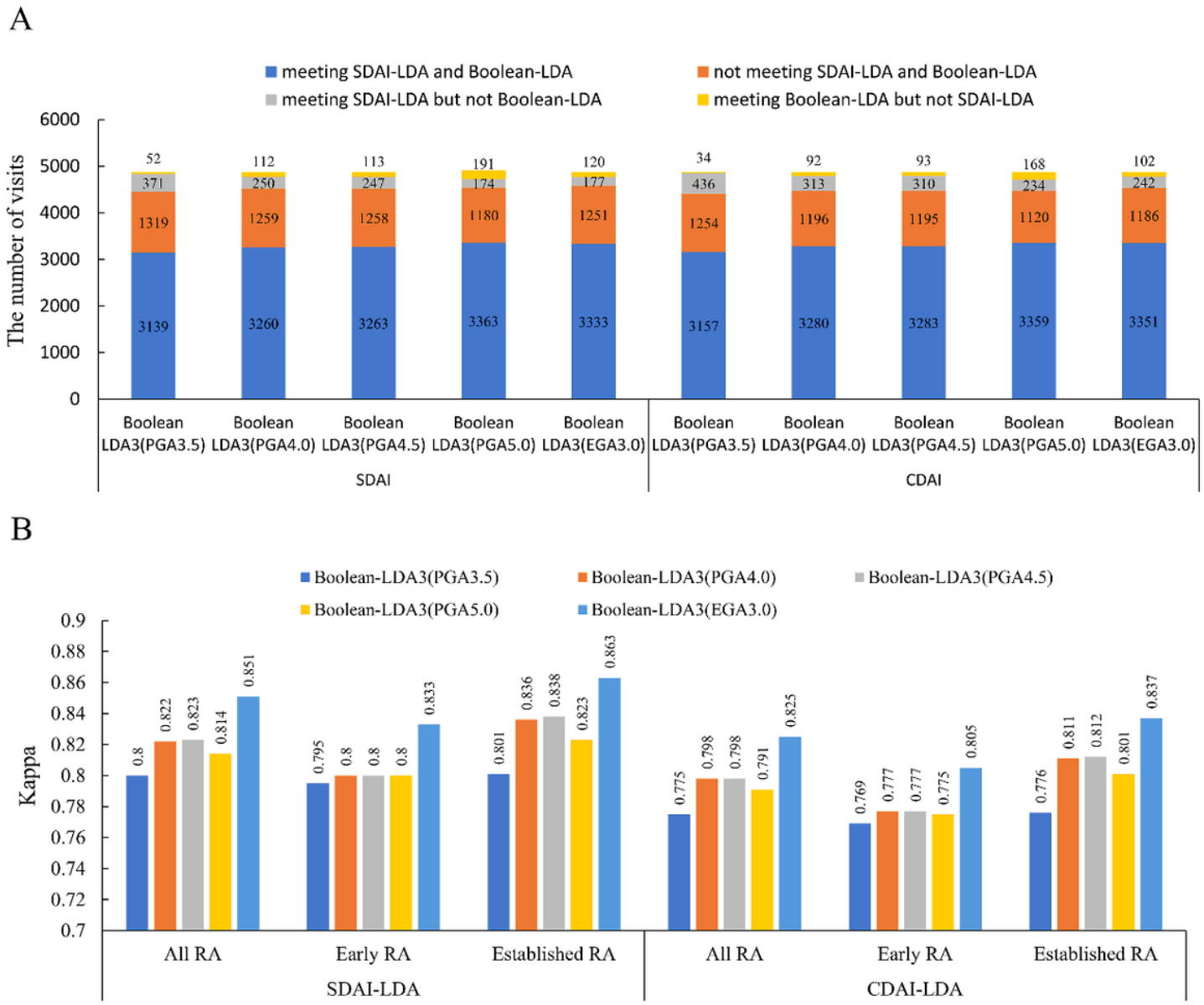

Figure 4

The agreement in included visits between SDAI- or CDAI-based LDA and modified Boolean definition by increasing the cut-off of the PGA by 0.5 cm increments from 3.5 cm to 5.0 cm (Boolean-LDA3(PGA3.5/4.0/4.5/5.0)) or replacement of PGA with EGA using cut-off of 3.0 cm (Boolean-LDA3(EGA3.0)), (A): The concordances and discordances; (B): Kappa value. LDA: low disease activity; SDAI: Simplified Disease Activity Index; CDAI: Clinical Disease Activity Index; PGA: patient's global assessment; EGA: evaluator's global assessment.

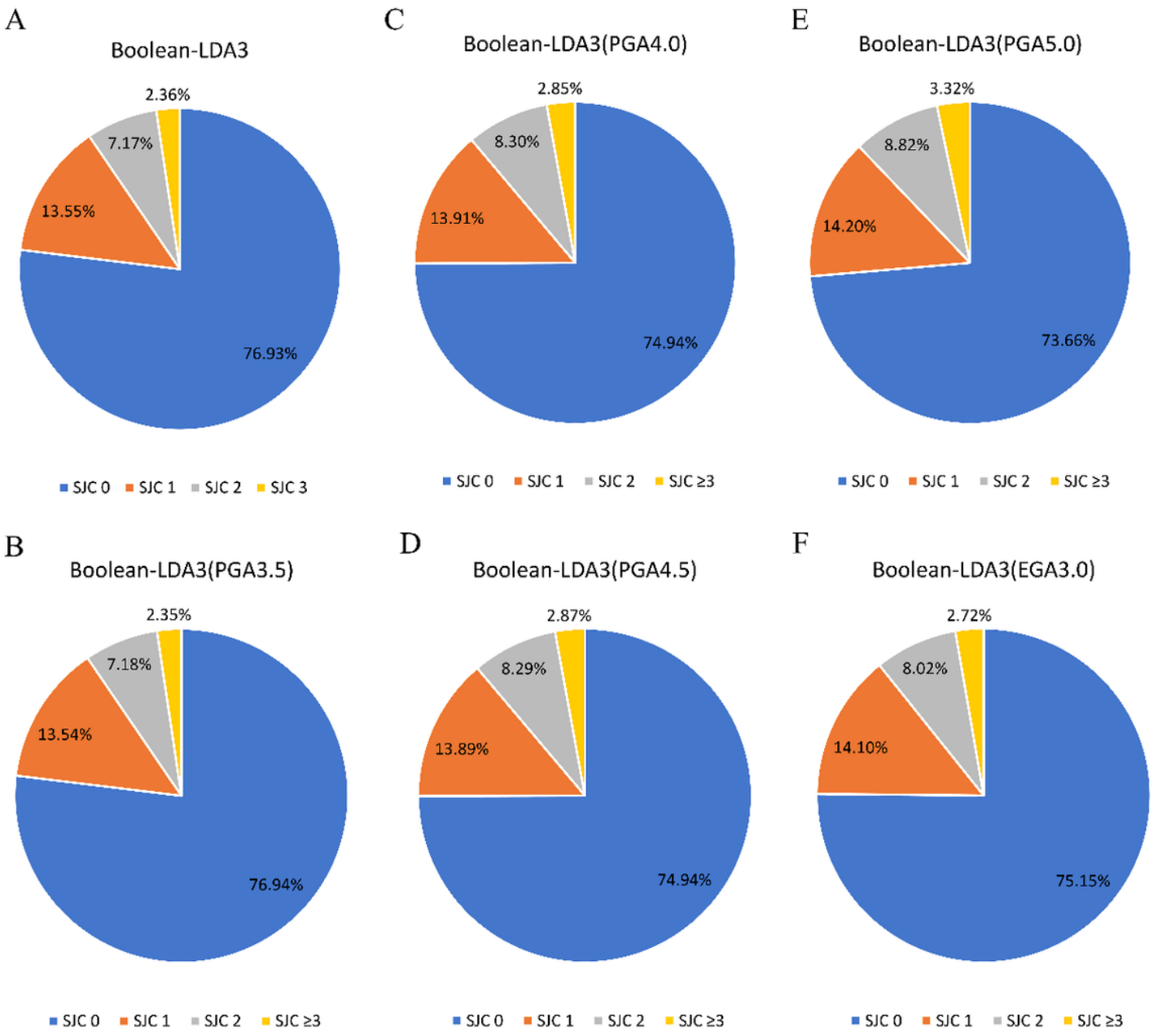

Figure 5

The distribution of swollen joint count in the included clinic visits meeting low disease activity based on SDAI, CDAI and modified Boolean definition by increasing the cut-off of the PGA by 0.5 cm increments from 3.5 cm to 5.0 cm (Boolean-LDA3(PGA3.5/4.0/4.5/5.0)) or replacement of PGA with EGA using cut-off of 3.0 cm (Boolean-LDA3(EGA3.0)). LDA: low disease activity; SDAI: Simplified Disease Activity Index; CDAI: Clinical Disease Activity Index; PGA: patient's global assessment; EGA: evaluator's global assessment.

Supplementary Files

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