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Validation of the Systemic Immune-Inflammation Index (SII) as a Biomarker for Disease Activity and Treatment Response in Rheumatoid Arthritis: A Real-World Study

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Background

The SII condenses innate immune activation (neutrophilia, thrombocytosis) and relative lymphopenia into one number from a routine CBC. First proposed in oncology [1], elevated SII in RA is linked to disease presence [5], disease activity [4,6,7], and mortality [2].

SII needs no extra assay, making it attractive where CDAI [8] is unrecorded. But proposed cut-offs vary widely (about 306 to 611) across small cohorts [3-6] and have not been tested against clinician-scored CDAI at scale.

SII = (Platelets × Neutrophils) ÷ Lymphocytes

reported in $\times 10^9$/L, from a single routine CBC

Objectives

- Correlate SII with CDAI in US real-world practice
- Find an optimal SII cut-off for active disease (CDAI >10) vs remission/LDA (CDAI ≤10)
- Characterize the SII-LDA dose-response across the full SII range

Data Source & Cohort

- OM1 Real-World Data Cloud RA registry (EHR), 2013-2024; 281,235 US RA patients
- Index event: recorded CDAI with complete CBC within ±7 days (closest lab per component)
- Adults with ≥365 d EMR baseline and calculable SII; extreme SII (0.25% tails) excluded
- Patient-level: first index event, complete covariates (N = 63,968); visit-level: all 454,955 index events (100,336 patients)

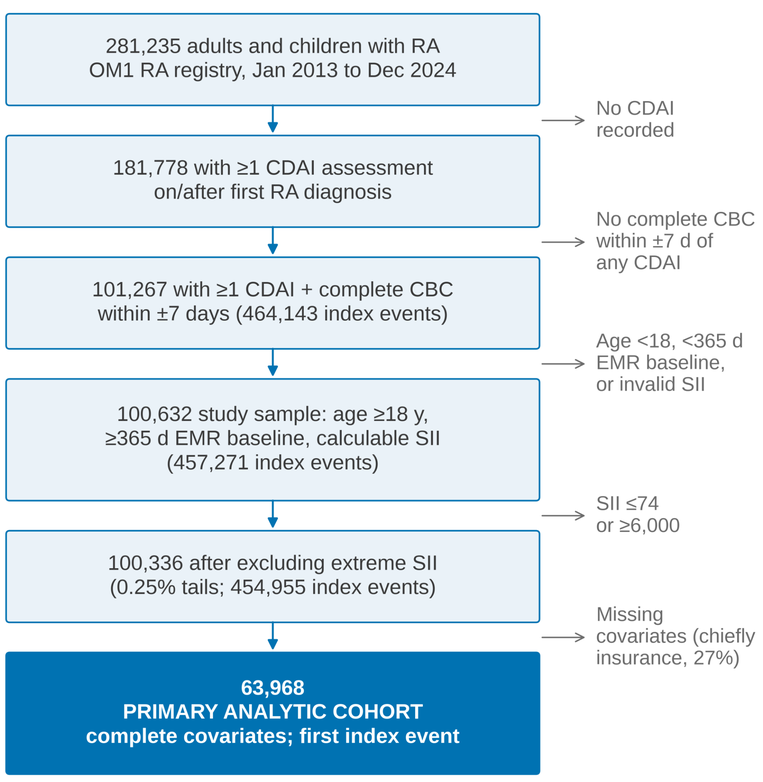


Figure 1. Cohort attrition.

Statistical Methods

- Outcomes: remission/LDA (CDAI ≤10) vs active disease (CDAI >10) [8]; Spearman correlation of SII with CDAI
- ROC analysis; adjusted model with age, sex, race, ethnicity, region, Charlson index, smoking, insurance; cut-off by Youden index
- Restricted cubic spline (3 knots); SII quintile logistic regression (Q1 reference) with ordinal p-trend; patient-clustered and GEE checks; sensitivity excluding infection, malignancy, autoimmune disease
- Analyses were performed with SAS 9.4 (SAS Institute, Cary, NC)

Cohort Characteristics (N = 63,968)

Characteristic	Value
Age, years, mean (SD)	63.6 (13.1)
Female	49,850 (77.9%)
White race	51,601 (80.7%)
Not Hispanic or Latino	59,322 (92.7%)
US South region	44,914 (70.2%)
Commercial / Medicare insurance	35.9% / 36.9%
Charlson index 0-1	32,354 (50.6%)
Ever smoker	17,111 (26.7%)
CDAI, median (IQR)	12.0 (4.0-21.0)
Remission (CDAI ≤2.8)	10,197 (15.9%)
Low (2.9-10)	19,340 (30.2%)
Moderate (10.1-22)	20,618 (32.2%)
High (>22)	13,813 (21.6%)
In remission/LDA at index	29,537 (46.2%)
SII $\times 10^9$/L, median (IQR)	602 (397-947)
Neutrophils /µL, median (IQR)	4,171 (3,100-5,591)
Platelets $\times 10^3$/µL, median (IQR)	259 (214-311)
Lymphocytes /µL, median (IQR)	1,730 (1,300-2,267)

First index event per patient, complete-case cohort.

SII Rises with Concurrent CDAI Category

CDAI category	N	SII, median (IQR)
Remission (CDAI ≤2.8)	10,197	560 (376-852)
Low (2.9-10)	19,340	576 (383-892)
Moderate (10.1-22)	20,618	619 (405-981)
High (>22)	13,813	659 (424-1,051)

SII $\times 10^9$/L; Kruskal-Wallis p < 0.001 (N = 63,968).

Results: Correlation & Discrimination

SII correlated weakly with CDAI (Spearman r = 0.09, p < 0.001), the same direction as small clinical cohorts [4,6,7].

SII alone discriminated poorly (AUC 0.546); with covariates the AUC was only 0.600. The Youden point mapped to SII = 542.7 (sens 53%, spec 62%).

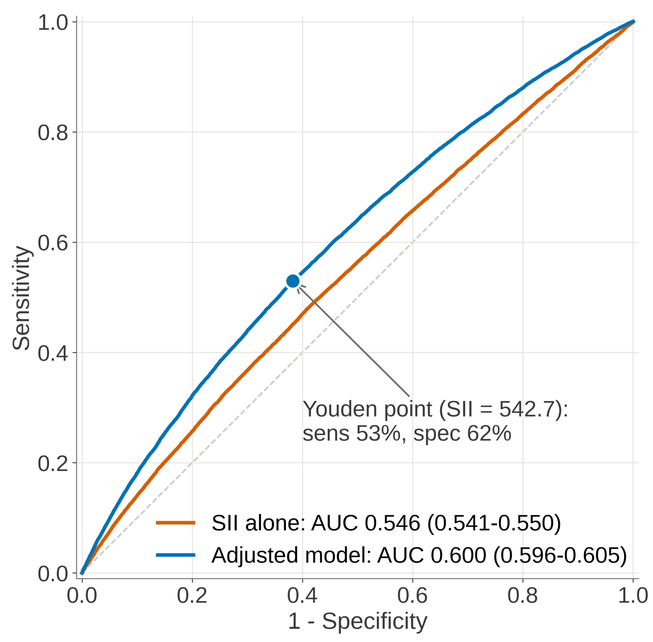


Figure 2. ROC curves, LDA vs active disease (N = 63,968).

SII Cut-Off Performance

SII ≥	Source	Sens	Spec	PPV	NPV	J
305.6	RA vs healthy [3]	87%	15%	55%	51%	0.02
542.7	This study (Youden)	59%	47%	57%	50%	0.06
578.2	Lit: NHANES [5]	56%	51%	57%	50%	0.06

Univariate classification of active disease (positive = SII at or above cut-off). No threshold performed adequately (best J = 0.06); the Youden criterion was nearly flat from SII 340 to 1,150. The abstract's 53%/62% is the adjusted-model operating point.

How Our Cut-Off Compares

Study	Setting	Cut-off	AUC	Sens/Spec
Satis 2021 [4]	Clinical (DAS28)	574.2	0.643	56% / 46%
Aci 2024 [6]	Clinical (DAS28)	611.5	0.717	58% / 61%
Liu 2023 [5]	NHANES survey, US*	578	n/r	n/r
This study	**US EHR, N = 63,968**	**542.7**	**0.600†**	**53% / 62%**

**Prevalence study: 578 is a risk-inflection point for having RA; no activity AUC reported (n/r). †Covariate-adjusted model, operating point mapped to SII. Operating characteristics converge across very different settings; none reach clinically useful discrimination.*

Results: Dose Response

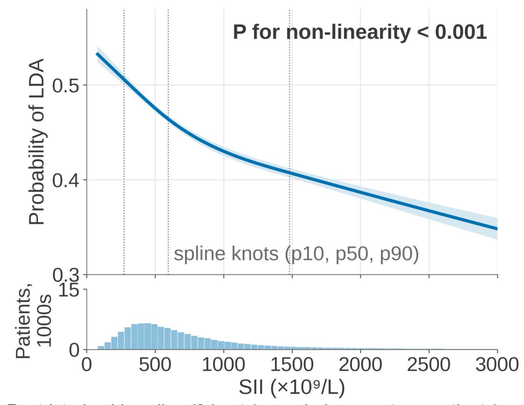


Figure 3. Restricted cubic spline (3 knots), one index event per patient (n = 100,336).

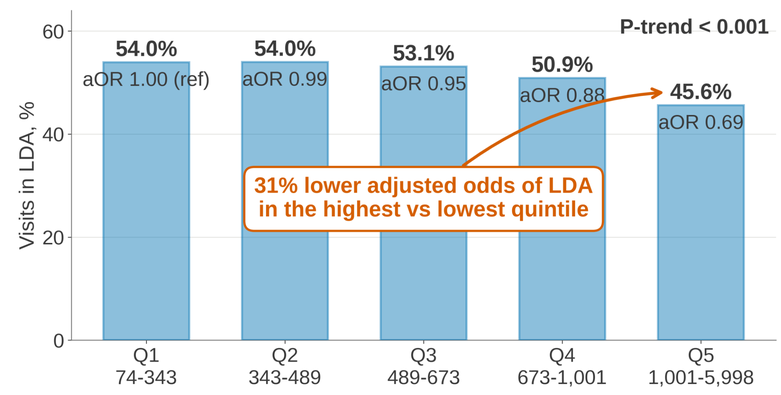


Figure 4. LDA by SII quintile: 454,955 visits, 100,336 patients. aORs vs Q1 (fully adjusted); 95% CIs: Q2 0.96-1.01, Q3 0.93-0.98, Q4 0.86-0.90, Q5 0.68-0.71.

Robustness of the Q5 vs. Q1 Effect

Specification	aOR (95% CI)
Primary (visit-level logistic)	0.69 (0.68-0.71)
Patient-clustered robust SEs	0.69 (0.67-0.72)
GEE, exchangeable correlation	0.68 (0.67-0.70)
Clinical exclusions (370,246 visits)	0.69 (0.67-0.71)

Sensitivity cohort (N = 49,882) unchanged on all endpoints: median SII 592, r = 0.09, AUC 0.601.

Conclusions

In one of the largest real-world evaluations of SII in RA, SII tracked disease activity in a robust, non-linear dose-response but discriminated only marginally: it is not a substitute for CDAI. SII may still have value as a low-cost adjunct where CDAI is not recorded, but it should not replace clinician-scored assessment.

Future Directions

- Assess whether within-patient SII change tracks CDAI change
- Combine with CRP/ESR and related indices (PIV, SIRI) [6,7]

Limitations

- Cross-sectional main analyses: no causal inference; CBC within ±7 d selects lab-monitored patients
- Covariate missingness (chiefly insurance, 27%); complete-case models; residual confounding
- Predominantly White, non-Hispanic, US South cohort

References: 1. Hu B, et al. Clin Cancer Res 2014;20:6212-22. 2. Yin X, et al. Sci Rep 2024;14:15129. 3. Wu Y, et al. Front Immunol 2025;16:1621209. 4. Satis S. Curr Health Sci J 2021;47(4):553-7. 5. Liu B, et al. Arthritis Res Ther 2023;25:34. 6. Aci R, et al. Reumatologia 2024;62(6):439-46. 7. Dervisevic A, et al. Medeniyet Med J 2024;39(3):183-91. 8. Aletaha D, Smolen J. Clin Exp Rheumatol 2005;23(5 Suppl 39):S100-8.

Abbreviations: CBC complete blood count; CDAI Clinical Disease Activity Index; GEE generalized estimating equations; J Youden index; LDA low disease activity; PIV pan-immune-inflammation value; SIRI systemic inflammation response index.

Disclosures: All authors are employees of OM1, Inc. De-identified EHR data (OM1 Real-World Data Cloud).