Systemic inflammation response index as an emerging biomarker in osteoarthritis patients: a bibliometric and large sample retrospective investigation

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Abstract

Objective

To determine the value of the whole-blood inflammatory response index as an emerging biomarker for the assessment of disease activity in osteoarthritis (OA).

Methods

Extensive analysis of the literature on OA and whole-blood inflammatory indicators were provided through a bibliometric approach. Clinical characteristics and indicators of OA patients and healthy controls (HC) were retrospectively analysed. Four whole-blood inflammatory response indices – neutrophil/lymphocyte count (NLR), platelet/lymphocyte count (PLR), monocyte/lymphocyte count (MLR), and systemic inflammation response index (SIRI), as well as clinical traits like the OA patient's self-perception and immune-inflammatory indicators were analysed for correlations. Cut-off values were determined using receiver operating characteristic (ROC) curves, and they were subsequently employed in logistic regression models to work out whole-blood inflammatory indices and disease activity.

Results

The pathophysiology of osteoarthritis has received most of the spotlight in literature studies of OA and whole-blood inflammation indicators. The "inflammation", "osteoarthritis" and "disease activity" were the top 3 key word clusters. Retrospective analysis showed that MLR, NLR, PLR, and SIRI were markedly higher in OA subjects compared to HC subjects. ROC curve consequences manifested that SIRI and NLR could separate OA from healthy controls. NLR, PLR, MLR, and SIRI proved to be related to immune-inflammatory markers, visual analogue scale (VAS) scores, and short-form (SF)-36 scores with regard to correlation analysis and association criteria. Logistic regression manifested that SIRI, NLR, and C-reactive protein (CRP) forecasted disease activity, however, the model that combined SIRI and CRP was superior to CRP alone.

Conclusion

SIRI may serve as a non-invasive, appropriate biomarker to correlate with disease activity.

Key words

systemic inflammation response index, osteoarthritis, bibliometrics, biomarkers, inflammation

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Introduction

Osteoarthritis (OA) is a prevalent chronic systemic autoimmune disease with clinical signs such as joint swelling, pain, and impaired mobility (1). Ultimately, it can reduce the wellbeing of people in the form of depression, functional loss, and financial hardship, along with increased medical costs (2, 3). Therefore, effective auxiliary tools for the early management of OA deserve attention.

Current treatment modalities are mainly chondroprotective agents and nonsteroidal anti-inflammatory drugs, with arthroplasty eventually being considered for patients with advanced knee osteoarthritis (4). Unable to accurately classify disease activity in patients, clinicians face significant difficulties in deciding how to apply current medications. We highlight the emerging concept of early osteoarthritis that will permit the identification of patients at high risk of osteoarthritis progression and to initiate early treatment interventions (5). In addition, early treatment improves long-term outcomes and provides the greatest benefit.

The use of patient reported outcomes (PROs), such as the visual analogue scale (VAS) (6) and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (7) score, is recommended by current practice standards. Their boundedness includes patient subjectivity and failure to capture the effects of extra-articulate representations. Imaging-based methods such as Kellgren-Lawrence (KL) (8) grading have similar limitations. For example, x-rays can only demonstrate structural features and have inconsistencies between readers (9). Most importantly, it can take up to a decade after the onset of signs and symptoms for abnormalities to be detected. Molecular markers in OA have been the object of growing attention due to their potential usefulness in developing early diagnosis, in assessing disease activity and severity (10). Favero *et al.* (11) summarised the most recent biomarkers in erosive hand OA, mainly including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) (12), interleukin-2 receptor, clusterin concentration, visfatin concentration, cartilage metabolites, etc. Kalogera *et al.* (13) investigated the overall biomarkers of extracellular matrix remodeling in serum and SF in OA. The ESR and CRP, regrettably, are two non-specific biomarkers of inflammation that can be susceptible to a variety of conditions, such as infection or acute stressors (14). In addition, there is a lack of large studies validating the association between these biomarkers and PROs with OA. As a result, using these biomarkers alone to gauge disease activity is incomplete, along with additional markers of inflammation associated with PROs must be identified.

Immuno-inflammatory mechanisms are increasingly implicated in the pathogenesis of OA (15). In the onset and progression of OA, the immunological and inflammatory systems are activated, with platelets, neutrophils, lymphocytes, and monocytes playing significant roles (16). As an emerging indicator of inflammation with easy detection, low cost, and availability through the blood routine, it has been applied as a useful tool for disease activity in diseases with an inflammatory component, including systemic lupus erythematosus (17), ankylosing spondylitis (18), gout (19) and rheumatoid arthritis (20). Previous studies have identified the blood neutrophil/lymphocyte count (NLR) (21), platelet/lymphocyte count (PLR), and mean platelet volume (MPV) (22) as promising markers of inflammation indicating the severity of Knee OA. Some preliminary studies also suggest that PLR and MPV may have certain practicability as novel inflammatory markers of OA in the Turkish population (21, 22). Some smaller observational studies have also found monocyte/lymphocyte count (MLR) to be of elevated diagnostic value for Knee OA in Chinese populations (23). Previous studies, however, have not examined the link between these emerging biomarkers such as NLR, PLR, MPV, MLR and patient reported outcomes or assessed the utility of these new biomarkers in comparison to existing biomarkers like ESR or CRP.

Through bibliometrics and visualisation analysis, this study first understood

the knowledge structure, research status, and development trend of whole blood inflammatory response indexes in OA, such as NLR, PLR, MLR, and systemic inflammation response index (SIRI). The role of whole-blood inflammatory response indicators in the onset of OA and their potential as emerging biomarkers are explored. Next, we assessed retrospectively the usefulness of whole blood inflammatory response indices (NLR, PLR, MLR, and SIRI) as biomarkers in subjects with OA. The purpose of the study was to ascertain whether whole-blood inflammatory response indices correlate with current biomarkers of disease activity and whether they are linked to patient reported outcomes and disease activity status (as defined by VAS).

Materials and methods

Materials

- Sources and retrieval methods of literature

The literature research was collected from the Web of Science Core Set (WoSCC) and analysed visually by bibliometrics (24). The WoSCC database contains all article related information including key words, abstracts, and citation information. Literature searches were performed within one day to avoid bias. The search terms are as follows: (TS= osteoarthritides OR osteoarthrosis OR osteoarthroses OR osteoarthrosis deformans OR osteoarthritis) AND TS= (neutrophil OR neutrophil-lymphocyte ratio OR lymphocyte OR monocyte lymphocyte ratio OR platelet lymphocyte ratio). Reviews and articles in English were the only ones reviewed. A total of 583 articles from 2001 to 2023 were ultimately included in the analysis. Table I presents the results of the combined screening.

Table I. TS search queries and refinement procedures.

Set	Results	Refinement
1	553	TOPIC: (TS = (Osteoarthritides OR Osteoarthrosis OR Osteoarthroses OR (Osteoarthrosis Deformans) OR osteoarthritis) AND TS = (neutrophil OR lymphocyte OR neutrophil-lymphocyte ratio OR monocyte lymphocyte ratio OR platelet lymphocyte ratio)) Indexes = SCI-EXPANDED
2	550	Refined by LANGUAGES: (ENGLISH)
3	538	Refined by DOCUMENT TYPES: (ARTICLES OR REVIEW ARTICLES)

- Clinical patient information

This study gathered medical records from OA (25) patients who were admitted to the First Affiliated Hospital of Anhui University of Chinese Medicine's rheumatology and immunology Department between March 2009 and February 2023. The hospital information system (HIS) database includes basic information on patients, such as body mass index (BMI), age, gender, comorbidities, and disease duration. Further exclusion criteria include severe infections, serious diseases of the circulatory, respiratory, and hematopoietic systems, and other autoimmune diseases. The Charlson Comorbidity Index (CCI) assesses the comorbidities of patients with OA at diagnosis (26). It is a weighted scale of 19 comorbidities expressed as a sum (27). In the CCI each condition is assigned different scores, ranging from 1 point for each of myocardial infarction, congestive cardiac failure, peripheral artery disease, dementia, cerebrovascular disease, chronic lung disease, connective tissue disease, ulcer, chronic liver disease, diabetes; 2 points for each of hemiplegia, kidney disease, diabetes with end-organ damage, tumor, leukemia, lymphoma; 3 points for moderate or severe liver disease; and 6 points for tumor metastasis or Acquired Immune Deficiency Syndrome(AIDS).

In all, 7,068 osteoarthritis patients took part in the study. Meanwhile, 880 healthy volunteers recruited for regular check-ups at the same hospital's medical examination center were selected for the research. It was unnecessary to obtain informed consent for this retrospective and observational study. The personal information of the subjects was masked prior to any analysis. Research protocols at the hospital were approved by the ethics committee, and all procedures were conducted in accordance with the principles of the Declaration of Helsinki (Review no. 2022MCZQ01).

Methods

- Bibliometric analysis

The CiteSpace software is a Web-based Java application that uses the information contained in this article to predict trends in the field (28). To assist in the visual review of knowledge areas and emerging trends, CiteSpace (v. 6.1.R5) utilised the usage of the key word co-occurrence analysis, cluster analysis, timeline or time zone views, and references (29). Cluster analysis could classify and summarise key words and discover the correlation between OA and whole-blood inflammatory response indices. The time period is set to be from January 2001 to December 2023, the time slice is one year, the threshold item is "Top N", and the data of the top ten high-frequency nodes are chosen for each time slice in the CiteSpace software parameter setting. "Pathfinder" is chosen as the cutting connection method to streamline the network architecture and draw attention to crucial components.

- Laboratory examination and index calculation

A routine blood analyser was used to check the subject's blood routine. The index based on blood cells is calculated as follows: (1) MLR = monocyte count/lymphocyte count; (2) NLR = neutrophil count/lymphocyte count; (3) PLR = platelet count/lymphocyte count; (4) SIRI (20) = neutrophil count × monocyte count/lymphocyte count. The biochemical analyser detects erythrocyte sedimentation rate (ESR), immunoglobulin A (IGA), C-reactive protein (CRP), ferritin, immunoglobulin G (IGG), complement component 4 (C4), immunoglobulin M (IGM), and complement component 3 (C3). Specific situations are tested on an individual basis.

- Patient reported outcomes (PROs)

Clinical assessments were performed, including the VAS (30) and the short

form-36 Health Survey (SF-36). The EuroQol visual analogue scale (EQ-VAS) is a pain rating scale that assess the quality of life (31). Scores are based on self-reported measures of symptoms that are recorded with a single handwritten mark placed at one point along the length of a 10-cm line that represents a continuum between the two ends of the scale -"no pain" on the left end (0 cm) of the scale and the "worst pain" on the right end of the scale (10 cm) (32).The SF-36 contains the following eight subscales: role-emotional (RE), bodily pain (BP), general health (GH), social function (SF), vitality (VT), physical function (PF), role-physical (RP), and mental health (MH) (33). It is recommended that SF-36 be utilised as an essential psychosocial outcome domain in clinical trials of pain therapies and as a crucial component in the study of individuals with chronic pain (34). It has been commonly applied to self-assessment in patients with rheumatism (35). We used the median to classify all outcome measurements as critical.

- Association rules

As one of the most influential algorithms for mining the frequent items of Boolean association rules, Apriori has gained considerable popularity (36). Association rules are defined as the relationship between X and Y, in which X and Y are called the antecedent (left-hand-side, LHS) and the subsequent (right-hand-side, RHS), respectively. M denotes the total number of items in the sample, whereas X and Y each represent a certain set of items. The corresponding formulas for support, confidence, and lift are as follows:

$$(1) \quad \text{Support}(X) = \frac{X}{M}$$

$$(2) \quad Confidence(X \rightarrow Y) = \frac{Support(X \cup Y)}{Support(X)}$$

$$(3) \quad Lift(X \rightarrow Y) = \frac{Confidence(X \rightarrow Y)}{Support(Y)} = \frac{Support(X \cup Y)}{Support(X) \square Support(Y)}$$

Statistical analysis

We used SPSS 22.0 (Chicago, IL, USA) software to perform statistical analyses and plots. The normality of the data was checked using the Shapiro-Wilk method. The mean± standard deviation is utilised to express continuous variables with a normal distribution. For a non-normal distribution, the median (P25-P75) is utilised. Categorical variables are presented as numbers (percentages). The Mann-Whitney test, Student's t-test, Wilcoxon signed-rank test, or chi-square test (depending on the situation) were all conducted to determine statistical significance. The correlation between NLR, MLR, PLR, SIRI, and additional metrics in normal and non-normal distribution data is assessed using Spearman's or Pearson's correlation analysis, respectively. To evaluate the capability of NLR, MLR, PLR, and SIRI to differentiate among individuals with osteoarthritis, receiver operating characteristic (ROC) curves were established, with the area under the curve (AUC) regarded as 95% confidence intervals (CI), specificity, and sensitivity. Jorden's test is used to determine the optimal critical value. In order to evaluate the statistical relationships between the outcomes of interest (NLR, MLR, PLR, and SIRI) and patient characteristics as well as immune-inflammatory indicators, logistic regression models were constructed. The model was simplified through a backward stepwise procedure until the model contains solely variables with $p<0.05$. Model-estimated odds ratios (ORs) and p-values with a significance level of 0.05 are presented.

The absolute value of the t-statistic for each model parameter was applied to compare the relative weights of each predictor in the logistic regression models. The larger the T-statistic, the more significant the predicted variable, since the significance of parameter estimation depends on the T-distribution, which is generally expressed in terms of p-values. The logistic regression model was assessed using the McFadden R^2 (37) and Hosmer-Lemeshow goodness-of-fit test. In general, a McFadden pseudo-R^2 value between 0.2 and 0.4 indicates excellent fit, whereas values close to 0 indicate weak fit (38). Model selection was carried out using both the Akaike Information Criterion (AIC) and Bayesian Information Criteria (BIC) (39). We introduced R4.2.0 software, rms, and media packages to construct a nomogram diagnostic diagram, prediction model, and decision curve.

Results

Global publication output and citation trends

In total, 538 publications that met the study's inclusion criteria were analysed by CiteSpace, including 475 original articles (88.29%) and 53 review articles (9.85%). The number of publications and citations in a particular period can objectively and quantitatively reflect the overall trend of an area. Annual circulation and citations of publications related to OA and the whole-blood inflammatory response index are shown in Figure 1A. It peaked in 2017 and 2020 with 61 papers (11.34%). Overall, the field as a whole has seen a steady upward trend in annual publication volumes, although there have been some years of volatile pullbacks. In Figure 1B, a polynomial fit curve is shown for the overall annual growth trend. According to the time curve, the cumulative global number of publications in this field is expected to continue to rise over the next decade ($R_2 = 0.5614$). In addition, the frequency of citations to these publications has shown an increasing trend year on year (Fig. 1A), with a total of 15,144 citations (14,806 after self-citations), an average of 28.15 citations, and an overall h-index of 55. These data indicate that the study of OA, which has been widely studied by scholars, has shown a flourishing trend in recent years and has become a major new hot spot in research related to the whole blood inflammatory response index in OA.

Analysis of co-citation references

We highlighted research topics closely related to the field of OA-whole blood inflammatory response index by evaluating 538 literature co-citation networks. We selected 45 references (with a minimum number of 10 citations) to map the co-citation analysis network. Cluster analysis reveals the knowledge structure of the studied regions. It forms unequal intensity clusters based on the links where items co-occur, and there is significant homogeneity between items

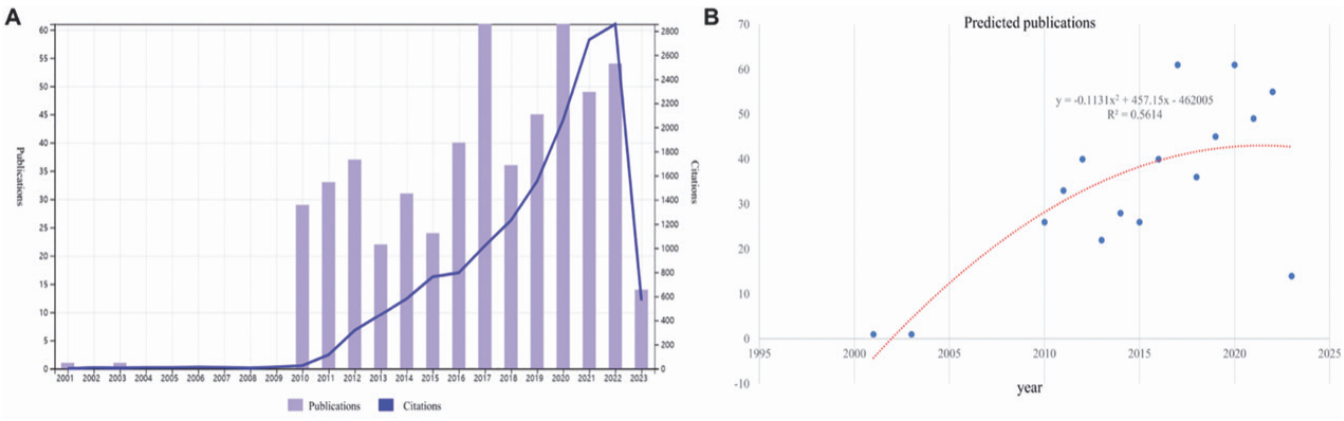

Fig. 1. **A**: Number of publications per year *versus* number of citations. **B**: Curve fitting of the overall annual growth trend in publications.

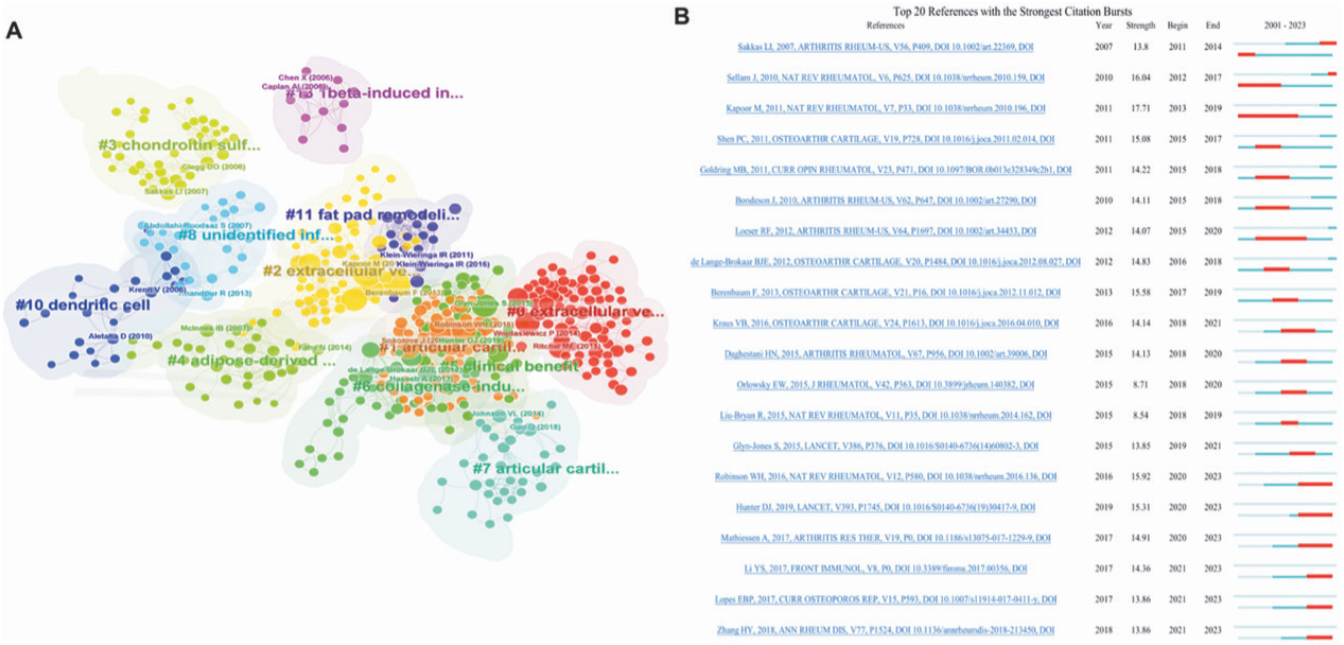

Fig. 2. **A**: Clustering of co-cited references; **B**: The top 20 references with strong citation bursts.

in the clusters. The literature clusters were divided using various node colours (Fig. 2A). In all, there were 14 clusters. The main research hotspots are extracellular vesicles, articular cartilage, cell-derived exosomes, chondroitin sulfate, adipose-derived mesenchymal stem cells, clinical benefits, collagenase-induced osteoarthritis, articular cartilage repair, unidentified inflammatory mediators, dendritic cells, fat pad remodeling, and 1 beta-induced inflammation. Based on clustering, we noticed that the majority of studies concentrated on the osteoarthritis pathogenesis, specifically connected to inflammatory mediators and cartilage metabolism.

Citation bursts are a reflection of citations that have been used repeatedly by scholars on a particular topic over time. The top 20 citations with strong citation bursts are highlighted in detail in Figure 2B, where the blue line represents the time period and the red cross section indicates the strong citation burst. The research report by Kapoor *et al*. (40) (17.71), which garnered the most citations over the course of seven years, had the strongest citation burst value among all of these. This article was published in 2011 in *Nature Reviews Rheumatology*, entitled "Role of proinflammatory cytokines in the pathophysiology of osteoarthritis". Their article describes the function of pro-inflammatory cytokines in the pathophysiology of OA and explores the possibility of treating the condition with anti-cytokine therapy. The first citation burst, which started in 2011 and lasted for four years, was published in *Arthritis Rheum* (USA) by Sakkas *et al*. The function of T lymphocytes in the aetiology of osteoarthritis was discussed in this article (41). It is worth noting that while most of the citation bursts have ended, several are still ongoing, indicating that these research topics have been receiving attention in recent years. Articles that have exploded in recent years, such as Li *et al*. (42) emphasise the role of T cell subtypes in the pathogenesis of OA. Synovitis, complement activation, cytokines, and immune cell populations were investigated by Lopes *et al*. (43) in relation to OA. Zhang *et al*. (44) investigated

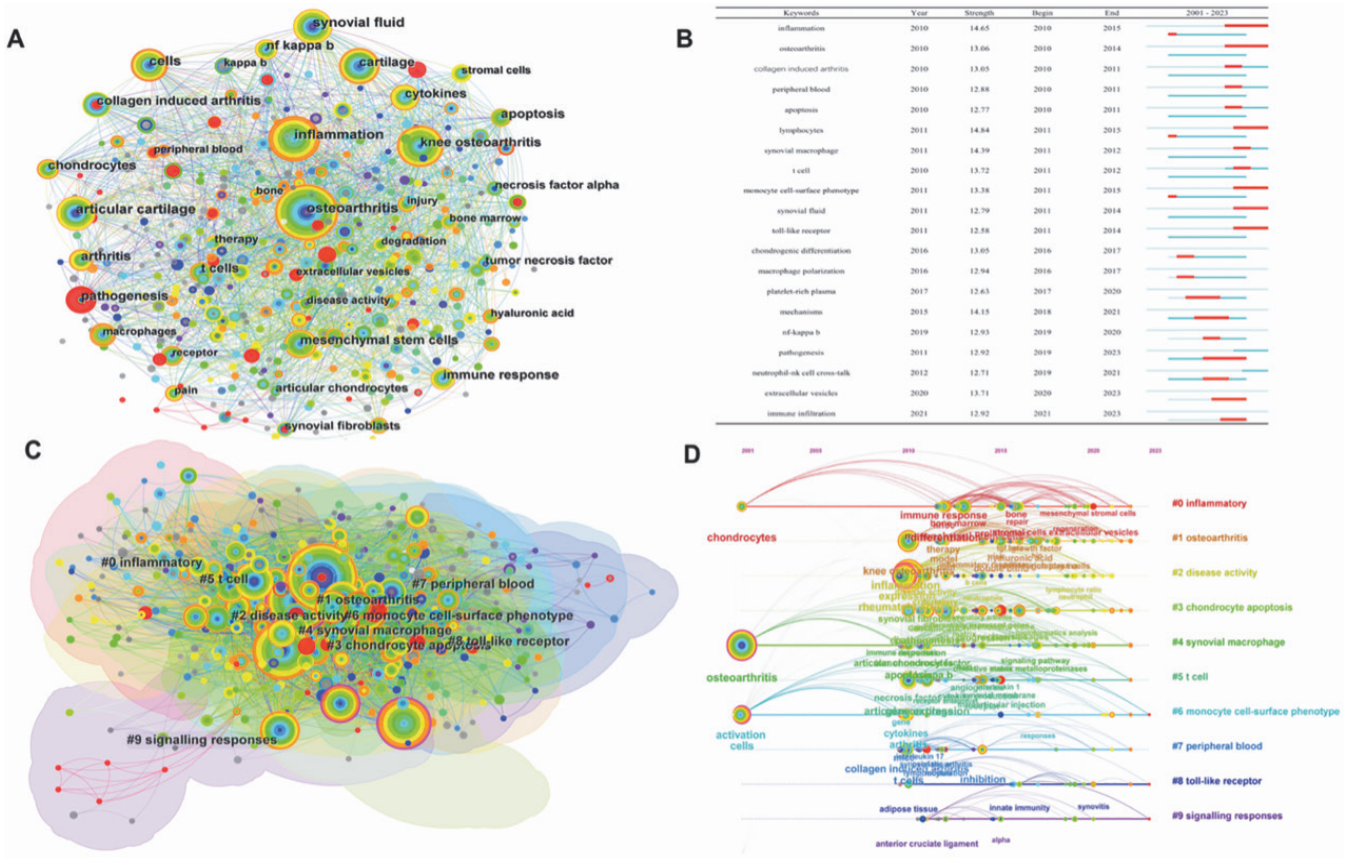

Fig. 3. **A**: Key word co-occurrence network; **B**: The top 20 key words with the most significant bursts of citations; **C**: Clustered view of key words; **D**: Time zone view of key words.

the role and regulatory mechanisms of synovial macrophage polarisation in the progress of osteoarthritis.

In summary, highly co-cited references shed light on the course of OA from multiple perspectives. The pathophysiology of OA is profoundly affected by chronic low-grade inflammation, which also contributes to increased symptom severity, joint dysfunction, and cartilage loss. T cells and macrophages are involved in the chronic inflammatory immune response to OA.

Analysis of co-cited key words

In addition to citations, co-occurrence and burst analysis of key words can also help identify research topics and hot trends in publications. Key word co-occurrence analysis is a key word analysis provided by the authors in the dataset. A total of 438 key words were found using CiteSpace software, and key words related to osteoarthritis – whole blood inflammatory response index are listed in the network diagram (Fig. 3A). The top 10 high-frequency key words included inflammation, osteoarthritis, collagen-induced arthritis, peripheral blood, apoptosis, lymphocytes, synovial macrophage, T-cell, monocyte cell surface phenotype, synovial fluid, etc. In addition, we conducted a burst of the top 20 strongest key words in the literature through CiteSpace software (Fig. 3B). Among them, the longest burst was *inflammation* (2010–2015), and *lymphocytes* had the strongest burst (14.84). At the same time, we found that *immune infiltration*, *extracellular vesicles*, *neutrophil-NK cell cross-talk*, and *pathogenesis*, were the most popular key words in Figure 3B in the last 3 years.

The cluster analysis of key words is carried out (Fig. 3C), and the clustering time graph is constructed to show the evolution process of high-frequency key words (Fig. 3D). Key words are located in the year of their first appearance. The results showed that there are 10 main categories: inflammatory, osteoarthritis, disease activity, chondrocyte apoptosis, synovial macrophage, t-cell, monocyte cell-surface phenotype, peripheral blood, toll-like receptors, signalling response, and macrophage polarisation. These suggest that studies related to osteoarthritis and whole blood inflammatory response indices have focused on inflammation and disease activity.

NLR, MLR, PLR, and SIRI increased in OA patients

Age, sex, or BMI between OA patients and healthy controls did not differ significantly. In comparison to the healthy group, OA patients had significantly higher levels of NLR, MLR, PLR, and SIRI (Table II). Individuals with OA had increased neutrophil counts, monocyte counts, and platelet counts, but decreased lymphocyte counts. ESR, CRP, ferritin, IGA, and IGG levels of immunological inflammation were substantially greater in individuals with OA than in the control group.

ROC curves separating NLR, MLR, PLR, and SIRI

NLR, MLR, PLR, and SIRI had an excellent specificity (p<0.01) in sepa-

Table II. Demographic, clinical, and laboratory characteristics.

Variables		OA (n=7,068)	HC (n=880)	*p*-value
Baseline characteristics	Age(year)	60.591 ± 13.011	63.282 ± 11.601	0.432
	Male (%)	1,602 (22.67)	191 (16.19)	0.343
	BMI	23.411 ± 2.242	22.341 ± 3.142	0.312
	Symptom duration (years)	17.001 ± 9.090	NA	/
	CCI	1.251 ± 1.031	NA	/
Laboratory index	Neutrophil count ($\times10^9$/L)	4.432 (2.231,7.671)	2.342 (1.871,3.012)	< 0.001
	Lymphocyte count ($\times10^9$/L)	1.581 (1.061,1.932)	2.090 (1.461,2.412)	0.034
	Monocyte count ($\times10^9$/L)	0.762 (0.211,1.762)	0.371 (0.281,0.440)	0.025
	Platelet count ($\times10^9$/L)	344.201 (169.011,478.452)	157.701 (126.251,230.012)	< 0.001
	MLR	0.321 (0.201,0.482)	0.171 (0.111,0.214)	< 0.001
	NLR	3.192 (1.761,4.712)	1.232 (0.771,1.432)	< 0.001
	PLR	161.381 (106.621,225.672)	93.94 (76.512,116.633)	< 0.001
	SIRI	1.991 (0.651,2.782)	0.423 (0.321,0.664)	< 0.001
	ESR (mm/h)	27 (17,42)	9 (1,14)	< 0.001
	CRP (mg/L)	21.252 (2.461,38.995)	0.851 (0.213,2.031)	< 0.001
	Ferritin (pg/mL)	177.263 (69.231,286,796)	56.143 (40.112,106.172)	< 0.001
	IGA(g/L)	2.381 (1.781,4.110)	1.091 (0.561,2.451)	< 0.001
	IGM(g/L)	1.111 (0.812,1.632)	0.562 (0.312,1.862)	0.651
	IGG(g/L)	13.231 (10.252,16.543)	7.511 (6.121,12.712)	< 0.001
	C3(g/L)	1.101 (0.921,2.282)	0.342 (0.123,0.674)	0.341
	C4(g/L)	0.252 (0.191,0.424)	0.132 (0.021,0.223)	0.452
PROs	VAS (cm)	5.5 (5.0,7.5)	/ /	
	SF-36			
	RE (score)	9.011 ± 2.423	/ /	
	BP (score)	24.581 ± 10.581	/ /	
	SF (score)	31.613 ± 10.921	/ /	
	PF (score)	21.971 ± 11.421	/ /	
	RP (score)	11.511 ± 6.673	/ /	
	GH (score)	22.670 ± 11.261	/ /	
	VT (score)	30.161 ± 12.041	/ /	
	MH (score)	47.511 ± 12.352	/ /	

BMI: body mass index; CCI: Charlson comorbidity index; MLR: monocyte/lymphocyte count; NLR: neutrophil/lymphocyte count; PLR: platelet/lymphocyte count; SIRI: systemic inflammation response index; VAS: visual analogue scale; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; IGA: immunoglobulin A; IGG: immunoglobulin G; IGM: immunoglobulin M; C3: complement component 3; C4: complement component 4; SF-36: short form-36 health survey; RE: role-emotional; BP: bodily pain; SF: social function; PF: physical function; RP: role-physical; GH: general health; VT: vitality; MH: mental health.

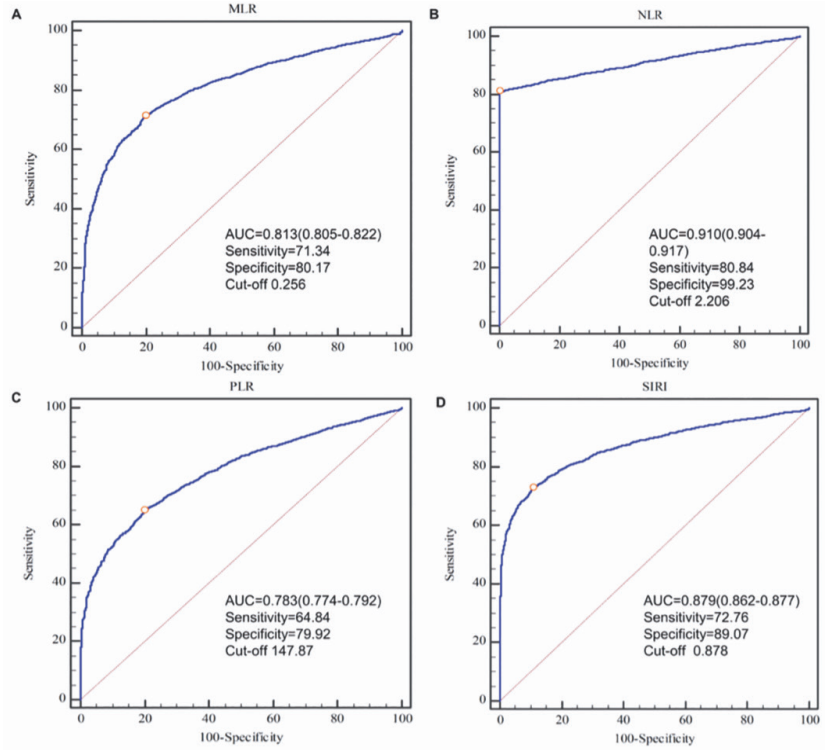

Fig. 4. ROC curve analyses of NLR, MLR, PLR, and SIRI.

rating those suffering from OA from healthy individuals, according to the ROC analysis (Fig. 4). With an ideal cut-off of 2.206 and 0.878, respectively, NLR and SIRI showed the highest sensitivity and specificity in differentiating performance among these metrics, with AUCs (95% CI) of 0.910 (0.904–0.917) and 0.879 (0.862–0.877), respectively. The PLR cut-off was 147.87, and the MLR cut-off was 0.256.

Connections between immuno-inflammatory markers, PROs, and NLR, MLR, PLR, and SIRI

Correlation analysis was constructed to verify the association of NLR, MLR, PLR, and SIRI with age, symptom duration, BMI, immune-inflammatory measures, and PROs (Table III). The consequences revealed that NLR, MLR, PLR, and SIRI were emphatically correlated with age and symptom duration. It was positively correlated with immune-inflammatory indicators such

Table III. Correlations of NLR, MLR, PLR, and SIRI with immune-inflammatory indicators.

Variables	MLR		NLR		PLR		SIRI	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Baseline characteristics								
Age	0.645	<0.001	0.681	<0.001	0.684	<0.001	0.679	<0.001
Symptom duration	0.639	0.001	0.659	<0.001	0.686	<0.001	0.649	<0.001
BMI	-0.010	0.384	-0.013	0.276	-0.013	0.276	-0.016	0.173
CCI	-0.112	0.244	-0.021	0.145	-0.023	0.206	-0.114	0.231
Laboratory index								
Ferritin	0.021	0.991	0.638	0.011	0.690	<0.001	0.018	0.236
CRP	0.664	<0.001	0.678	<0.001	0.746	<0.001	0.674	<0.001
ESR	0.668	<0.001	0.676	<0.001	0.743	<0.001	0.671	<0.001
C3	0.639	0.001	0.680	<0.001	0.622	<0.001	0.776	<0.001
C4	0.669	0.001	0.681	<0.001	0.642	<0.001	0.675	<0.001
IGA	0.651	<0.001	0.672	<0.001	0.643	<0.001	0.676	<0.001
IGG	0.656	<0.001	0.676	<0.001	0.648	<0.001	0.616	<0.001
IGM	0.018	0.135	0.015	0.223	0.003	0.830	0.011	0.377
PROs								
VAS	0.637	0.002	0.616	0.013	0.631	0.011	0.623	0.003
SF-36								
RE	-0.603	0.042	-0.017	0.292	-0.007	0.914	-0.611	0.011
BP	-0.643	0.007	-0.026	0.105	-0.008	0.626	-0.025	0.118
SF	-0.534	0.035	-0.020	0.215	0.054	0.387	-0.024	0.134
PF	0.002	0.891	0.013	0.428	0.004	0.795	0.002	0.983
RP	-0.020	0.126	-0.023	0.076	-0.629	0.027	-0.024	0.071
GH	-0.005	0.767	0.008	0.623	-0.005	0.770	0.002	0.975
VT	-0.007	0.640	0.001	0.995	0.000	0.981	0.010	0.546
MH	-0.006	0.720	0.002	0.915	0.019	0.225	-0.005	0.758

MLR: monocyte/lymphocyte count; NLR: neutrophil/lymphocyte count; PLR: platelet/lymphocyte count; SIRI: systemic inflammation response index; BMI: body mass index; CCI: Charlson comorbidity index; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; C3: complement component 3; C4: complement component 4; IGA: immunoglobulin A; IGG: immunoglobulin G; IGM: immunoglobulin M; PROs: patient reported outcomes; VAS: visual analogue scale; SF-36: short form-36 health survey; RE: role-emotional; BP: bodily pain; SF: social function; PF: physical function; RP: role-physical; GH: general health; VT: vitality; MH: mental health.

Table IV. Association rules of SIRI, NLR, MLR, PLR, and immunoinflammatory indicators.

Items (LHS ⇨ RHS)	Support (%)	Confidence (%)	Lift
SIRI ⇨ CRP	78.891	62.410	1.029
NLR ⇨ CRP	78.881	61.298	1.033
MLR ⇨ CRP	78.991	59.056	1.015
PLR ⇨ CRP	80.891	51.453	1.057

LHS: left-hand-side; RHS: right-hand-side; MLR: monocyte/lymphocyte count; NLR: neutrophil/lymphocyte count; PLR: platelet/lymphocyte count; SIRI: systemic inflammation response index; CRP: C-reactive protein.

as CRP, ESR, C3, C4, IGG, and IGA, as well as VAS scores. NLR and PLR are also emphatically correlated with ferritin. The MLR was also negatively correlated with RE, BP, and SF. PLR is negatively correlated with RP. SIRI is negatively correlated with RE.

Association rules

We assessed the degree of improvement in SIRI, NLR, MLR, and PLR with immuno-inflammatory markers using the optimal cut-off values established by the ROC curve, where the minimum support is adapted to be 70% and the minimum confidence is adopted to be 50%. Each item was ranked according to the highest confidence score. The data demonstrated that SIRI, MLR, PLR, and NLR were all deeply correlated with CRP. The above correlation details improvement degree is >1 (Table IV, Fig. 5).

NLR, PLR, MLR, and SIRI as independent predictors of OA: univariate and multivariate regression analysis

The ROC curve was used to define the optimal cut-off values for NLR, MLR, PLR, and SIRI, and the critical values for the other variables were defined based on the medians. Logistic regression models were constructed to describe the association between NLR, MLR, PLR, SIRI, ESR, CRP, immunoinflammatory indicators, and disease activity (as classified by VAS ≥5.5). In univariate regression analysis, SIRI (OR=1.812, p=0.001), NLR (OR=1.911, p=0.005), MLR (OR=1.405, p=0.012), and PLR (OR=1.316, p=0.016) were independent risk factors for OA disease activity. ESR (OR=1.211, p=0.038) and CRP (OR=2.204, p=0.027) were significantly linked with OA disease activity (Fig. 6). A multivariate logistic regression model including control factors was implemented to work out the odds of the outcome variable (active disease). Consistently, a stronger correlation was observed in multivariate logistic regression analysis controlling for sex, age, disease duration, and BMI (Table V). SIRI (OR=2.784, p=0.008), NLR (OR=2.409, p=0.014) and CRP (OR=1.196, p=0.025) remained independent predictors of OA disease activity. In the multivariate model, ESR (OR=1.105, p=0.061) failed to perform as an independent predictor of disease activity. As variables of interest, laboratory values (NLR, SIRI, and CRP) were compelled into the multivariate simplified model. To ascertain if NLR and SIRI were associated with disease activity after taking CRP into account, NLR and SIRI were also examined while adjusting for CRP. When accounting for CRP, SIRI (+CRP) (OR=3.432, p<0.001) continued to be a significant predictor of active disease in addition to the previously mentioned control variables. AIC and BIC demonstrate that models including SIRI and CRP outperform models including CRP alone.

A Hosmer-Lemeshow goodness-of-fit test shows that the model provides a perfect fit (Chi-Square=10.139, DF=8, p=0.225). McFadden's R_2=0.214, which is outside the range of 0.2–0.4, represents a good model fit. The logistic regression model, therefore, exhibits a strong model fit. In the nomogram, we selected three predictors, NLR, SIRI, and CRP, as the best variables to predict disease activity in OA (Fig.

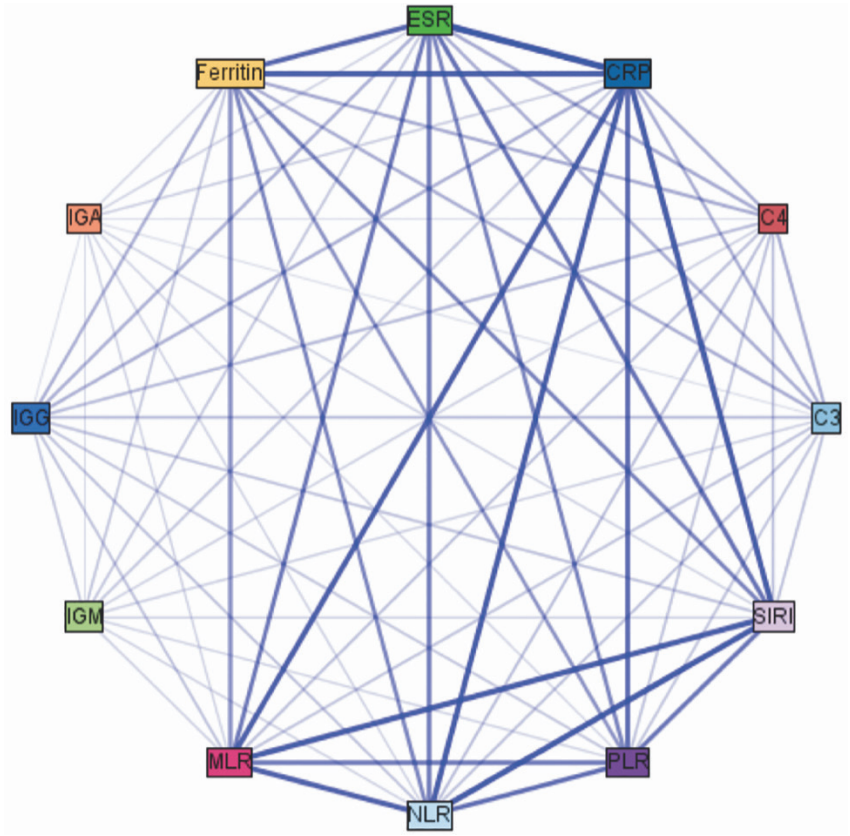

Fig. 5. Visual network diagram of the association rules. Note: The strength of the interaction between terms is shown by the thick, thin, and dashed lines. The maximum number of links that can be presented is 80, and strong links are thicker. A strong link has a lower limit of 50 and a higher maximum of 25, and the link size varies continuously.
MLR: monocyte/lymphocyte count; NLR: neutrophil/lymphocyte count; PLR: platelet/lymphocyte count; SIRI: systemic inflammation response index; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; C3: complement component 3; C4: complement component 4; IGA: immunoglobulin A; IGG: immunoglobulin G; IGM: immunoglobulin M.

Variables	OR(95%CI)	t-stat	*p*-value
Age			
<60	Reference	Reference	Reference
≥60	1.723(0.109-4.418)	1.505	0.233
Gender	Reference	Reference	Reference
Female	2.087(0.875-4.229)	1.938	0.144
Male	Reference	Reference	Reference
BMI≥24	1.731(0.407-3.313)	-0.636	0.294
Symptom duration	1.339(0.701-3.315)	1.667	0.105
NLR≥2.206	1.911(1.201-4.622)	48.397	0.005**
MLR ≥0.256	1.405(1.103-4.661)	20.066	0.012**
PLR ≥147.87	1.316(1.001-3.421)	20.615	0.016**
SIRI ≥0.878	1.812(1.101-3.232)	26.243	0.001**
Baseline ESR↑	1.211(1.011-3.322)	11.627	0.038*
Baseline CRP↑	2.204(1.023-3.401)	15.949	0.027*
Baseline Ferritin↑	0.991(0.837-3.172)	1.875	0.912
Baseline IGA↑	1.181(1.012-3.480)	0.693	0.150
Baseline IGM↑	0.920(0.623-2.953)	-0.327	0.436
Baseline IGG↑	1.124(1.017-3.305)	2.612	0.127
Baseline C3↑	1.118(0.964-3.296)	2.043	0.140
Baseline C4↑	0.990(0.826-3.187)	-0.258	0.916

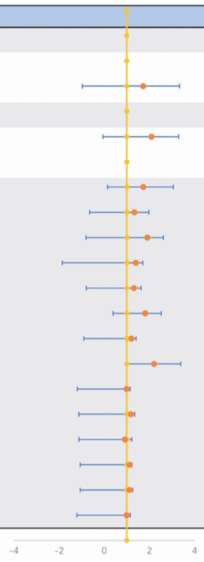

Fig. 6. Univariate logistic regression analysis of the influence of relevant parameters on osteoarthritis pain. *p<0.05. **p<0.01.
BMI: body mass index; MLR: monocyte/lymphocyte count; NLR: neutrophil/lymphocyte count; PLR: platelet/lymphocyte count; SIRI: systemic inflammation response index; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; C3: complement component 3; C4: complement component 4; IGA: immunoglobulin A; IGG: immunoglobulin G; IGM: immunoglobulin M.

7A). The calibration curve shows good consistency in the discriminant performance of the column graph (Fig. 7B). The decision curve analysis (DCA) of the data set showed that patients could obtain a satisfactory net benefit from the prediction model (Fig. 7C).

Discussion

This project began with a bibliometric and visual analysis to understand the structure of knowledge, and trends in the whole blood inflammatory response index in OA. The statistical and fitting analysis of 538 articles showed that the study of the OA- whole blood inflammatory response index is attracting researchers' interest and developing rapidly (Fig. 1). Furthermore, the growth trend appears to be prospective. Highly co-cited references shed light on the pathogenesis of OA from multiple perspectives (Fig. 2). OA patients typically exhibit inflammatory infiltration of the synovial membrane by macrophages, T cells, mast cells, B cells, plasma cells, natural killer cells, dendritic cells, and neutrophils (42). The top 5 high-frequency key words related to the OA-whole blood inflammatory response index are inflammation, osteoarthritis, collagen-induced arthritis, peripheral blood, and apoptosis. Key word clustering can characterise the intrinsic knowledge architecture and reveal academic frontiers. Cluster analysis revealed the existence of 10 major clusters in the OA - whole blood inflammatory response index field (Fig. 3), with the top 3 clusters being: inflammatory, osteoarthritis, and disease activity. These results suggest that whole blood inflammatory indices in OA might be involved in the inflammatory response and probably correlated with disease activity.

Pain, limited movement, and worsening joint function are all symptoms of OA, a disease that is endemic throughout the world. Gender (45), age, and obesity (46) are all probable risk factors for OA. The VAS, ESR, and CRP are routine assessment tools for assessing OA information and disease activity. However, these tools are basic, non-specific and non-differential, and can lead to bias in disease assessment. Furthermore, radiography (47)

Table V. Multivariate logistic regression assessing for the association of various laboratory values and active disease, defined by VAS≥ 5.5.

Laboratory variable (critical value)	Odds ratio (95% CI)	t-stat	*p*-value	AIC	BIC
NLR (2.206)	2.409 (1.112-4.893)	20.073	0.014	562.341	504.231
MLR (0.256)	1.275 (1.105-5.602)	6.473	0.053	Not performed	Not performed
PLR (147.87)	1.119 (1.101-4.181)	6.630	0.064	Not performed	Not performed
SIRI (0.878)	2.784 (1.001-3.532)	25.451	0.008	378.591	269.421
ESR (27)	1.105 (0.913-3.251)	7.627	0.061	Not performed	Not performed
CRP (21.252)	1.196 (1.047-3.343)	11.949	0.025	608.120	532.450
SIRI (+CRP)	3.432 (2.421-5.341)	26.001	<0.001	211.670	207.910
NLR (+CRP)	1.549 (1.023-3.678)	8.435	0.058	467.452	434.252

For each model, gender, age, symptom duration, and BMI were all controlled. After adding CRP to the model, the final models (+ CRP) examined for connections between SIRI, NLR, and disease activity (defined by VAS ≥ 5.5).
CI: confidence interval; AIC: Akaike information criteria; BIC: Bayesian information criteria; NLR: neutrophil/lymphocyte count; MLR: monocyte/lymphocyte count; PLR: platelet/lymphocyte count; SIRI: systemic inflammation response index; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.

and MRI can accurately reflect the informative state of a joint, but these are complex and require specialised techniques. Hence, there is an urgent need for a sensitive and specific tool to detect disease activity and assess treatment efficacy. As an innate immune system (48), complete blood counts, including neutrophil, monocyte, lymphocyte, and platelet counts (49), are crucial in the onset of OA. The presence of neutrophils contributes to the progression of OA through a variety of pro-inflammatory and degenerative mechanisms (50-52), resulting in a general decline in patient quality of life (53). Neutrophils control the immune response through cell-cell contacts and participate in the cytokine and chemokine cascades that follow inflammation (54). Neutrophils have the largest cytotoxic potential of the cells involved in the pathophysiology of OA, due to their ability to release oxidising enzymes and reactive oxygen species (54). Inflammation and immune system responses in osteoarthritis are also profoundly affected by platelets (55). Activated platelets can result in increased adhesion of neutrophils and monocytes, which stimulates neutrophils in the neutrophil extracellular trap (NET) network, to be involved in the process of platelet and apoptotic cell death (55). Hence, whole blood cell analysis of OA provides new therapeutic targets and diagnostic methods.

Utilising clinical patients with OA to test the feasibility of NLR, MLR, PLR, and SIRI as inflammatory biomarkers, our study tackles a topic of importance and utility. We observed significantly higher levels of NLR, MLR, PLR and SIRI in OA patients than in healthy volunteers (Table II), suggesting that they may be involved in the onset and development of the disease. Furthermore, NLR and SIRI have outstanding discriminatory power in OA and are of diagnostic value (Fig. 4). We additionally highlighted that age and symptom duration were associated positively with NLR, MLR, PLR, and SIRI. There were correlations with multiple immune-inflammatory markers (CRP, ESR, C3, C4, IGG, IGA, and ferritin), suggesting that NLR, MLR, PLR, and SIRI have similar effects on inflammatory markers. It was correlated with VAS, RE, BP, RP and SF in PROs (Table III), indicating that the whole blood inflammation index was correlated with OA activity and patient reported outcomes. To find relevant associations or connections between sets of items from a huge amount of data, one of the most popular methods for mining similar sets of items for Boolean association rules is the Apriori algorithm. Similarly, the association rule results again support the high correlation between SIRI, MLR, PLR, NLR and CRP. The support was all 78% and the model's suggestive power was all greater than 1 (Table IV, Fig. 5). This indicates that the association rule makes sense. SIRI, NLR, MLR, PLR, ESR and CRP have

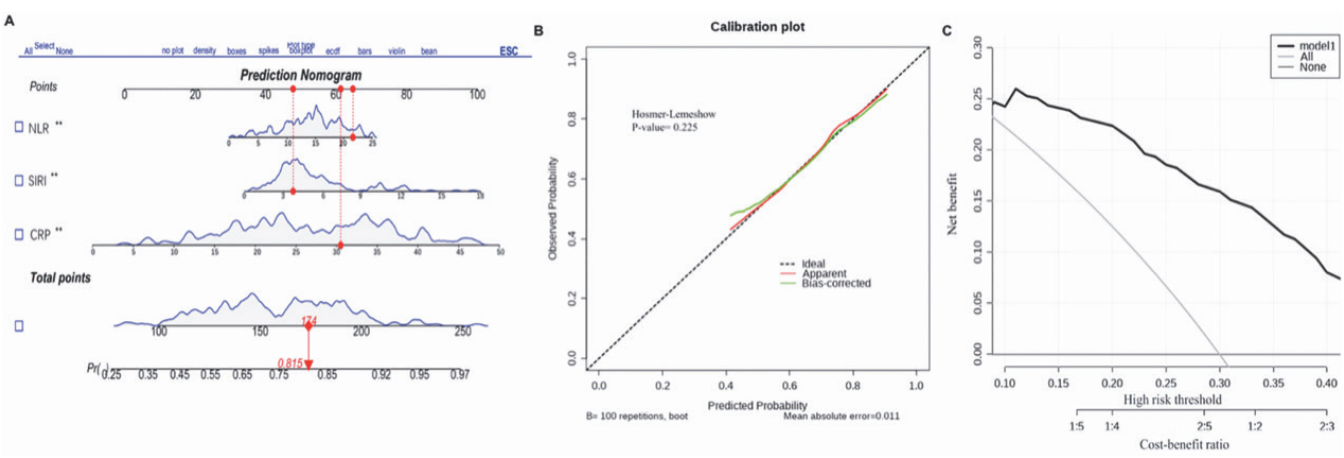

Fig. 7. A: Nomogram of the logistic regression model. Three predictors make up the nomogram. The top points on each predictor are added by finding their top score. The percent likelihood is represented by the total number of points projected onto the underlying scale. Find the top points of each predictor and add them together. The total number of points projected onto the bottom scale represents the % probability.
B: Calibration curve of the logistic regression model. **C**: DCA of the logistic regression model.

been identified as independent risk variables for OA disease activity via univariate regression analysis (Fig. 6). Only SIRI (OR=2.784, p=0.008), NLR (OR=2.409, p=0.014), and CRP (OR=1.196, p=0.025) persisted as independent predictors of OA disease activity in multivariate logistic regression. Models with SIRI alone outperform models with NLR and CRP only, as assessed by AIC and BIC. Furthermore, we noticed that the inclusion of the SIRI cut-off in a model controlled for CRP increased OR, while reducing AIC and BIC, implying a more accurate model for identifying active disease. It is fascinating to point out that in our multivariate model, NLR and CRP did not reach statistical significance (Table V). The resulting optimal model is controlled for CRP and incorporates SIRI. These results further demonstrate the utility of SIRI for disease activity prediction and prediction as defined by VAS. It is important to note that our results imply that SIRI may improve, rather than replicate, existing biomarker models when added to them.

In patients with Knee OA, previous cross-sectional surveys have assessed the diagnostic utility of MLR, NLR, and PLR. In comparison to KL1-3 patients, MLR and NLR were considerably higher in KL4 patients (23). PLR and mean platelet volume (MPV) in the blood have been verified by Taşolu (21) *et al*. to be promising novel markers that may characterise the severity of Knee OA. Whereas, no studies have examined the effectiveness of SIRI in the assessment of OA. SIRI reflects the intricate interactions and potential synergistic effects between neutrophils, monocytes, and lymphocytes. As a result, SIRI rather than NLR and PLR may more accurately represent the interaction between inflammatory and immunological responses. Our study demonstrates for the first time that SIRI is an insightful marker of disease activity in OA. Nevertheless, SIRI is implicated in inflammatory processes in OA has not yet been demonstrated. Further studies on the discriminatory effectiveness of SIRI and NLR in OA versus other rheumatic diseases are needed. In summary, SIRI can be utilised as an adjuvant inflammatory biomarker to speed up diagnosis and has excellent discriminative properties between OA patients and healthy controls, but it is not yet appropriate for the diagnosis of OA.

Limitations and strengths

The current study has several advantages. Firstly, it is literature-based research and a large-sample investigation, and the results are quite reliable. Secondly, this is the first real-life research to evaluate the diagnostic and prognostic utility of SIRI in OA patients.

Thirdly, we prove that, in a variety of scenarios, SIRI outperforms NLR, MLR, and PLR as a tool. Fourth, SIRI is cutting-edge, affordable, easy to use, and non-invasive compared to conventional assessment instruments. Our study does have certain drawbacks, though. First, because it was a retrospective study and lacked longitudinal monitoring, selection bias could be present. Second, because our study was restricted to real-world patients, we were not able to examine or rule out the effect of treatment on SIRI, which could have caused confounding biases. Finally, PROs were not available for healthy controls. Future multicentre prospective studies are therefore anticipated to support our findings.

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