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Diagnostic accuracy of different blood cells-derived indexes in rheumatoid arthritis

A cross-sectional study

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Abstract

To evaluate the performance of different blood cells-derived indexes in the diagnosis of rheumatoid arthritis (RA).

Neutrophil-to-lymphocyte ratio (NLR), lymphocyte to monocyte ratio, platelet to lymphocyte ratio (PLR), systemic inflammation response index (SIRI), and aggregate inflammation systemic index were calculated in 199 consecutive RA patients and 283 sex and age-matched controls (147 healthy donors and 136 patients with other rheumatic diseases). Area under the curve (AUCs), sensitivity and specificity were calculated to evaluate the accuracy of indexes in discriminating between RA and controls. Association between indexes and RA variables was explored by multiple linear regression analyses.

Blood cells-derived indexes did not demonstrate good accuracy in differentiating RA from controls with lymphocyte to monocyte ratio, the index with the best diagnostic performance, having 63.6% of sensitivity and 65.3% specificity [AUC (95%CI) = 0.67 (0.62–0.72]. The accuracy of the indexes in differentiating RA from healthy donors was significantly higher than that (AUCs < 0.6 for all comparisons) differentiating RA from rheumatic diseases. In RA, SIRI and aggregate inflammation systemic index showed significant association with C-reactive protein and erythrocyte sedimentation rate.

Our results do not support the use of blood cells-derived indexes for the diagnosis of RA, suggesting that they might reflect chronic inflammatory burden in rheumatic diseases rather than, specifically, in RA.

Abbreviations: ACR/EULAR = American College of Rheumatology/European League against Rheumatisms, AISI = aggregate inflammation systemic index, AUC = area under the curve, CRP = C-reactive protein, HD = healthy donors, LMR = lymphocyte to monocyte ratio, NLR = neutrophil-to-lymphocyte ratio, PLR = platelet to lymphocyte ratio, RA = rheumatoid arthritis, RDs = other rheumatic diseases.

Keywords: neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, rheumatoid arthritis, sensitivity, specificity

1. Introduction

Rheumatoid arthritis (RA) is an autoimmune disease characterized by chronic inflammation. RA affects synovial joints leading to bone damage, disability and excess of cardiovascular events and cardiovascular mortality.[1] In Western countries prevalence of RA is about 0.5% to 1% of the adult population.[2] Etiology of RA is unknown, and its pathogenesis is thought to be the result of an environmental-driven autoimmune process in genetically susceptible subjects[3]

Diagnosis of RA is mainly based on clinical grounds and remains a very challenging process of differential diagnosis. The recently defined 2010 American College of Rheumatology/European League against Rheumatisms (ACR/EULAR) classification criteria for RA[4] represent an international effort to increase the chance of early diagnosis and treatment of RA. Accordingly to the 2010 ACR/EULAR classification criteria, the classification of disease is strongly based on the positivity of rheumatoid factor and anti-cyclic citrullinated peptide antibodies, as well as on the presence of high levels of C-reactive protein (CRP) and/or erythrocyte sedimentation. Unfortunately, despite high sensitivity the 2010 ACR/EULAR classification criteria are characterized by low to moderate specificity (0.34–0.96).[5] Therefore, there is still the unmet need of developing

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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routinely available biomarkers that could facilitate early and accurate diagnosis of RA.

Different cells, such as neutrophils, lymphocytes and platelets are proven to be involved in the regulation of inflammatory process and to play a role in the immune-mediated pathways of several neoplastic and chronic diseases.[6,7] Apart from lymphocytes, neutrophils are shown to activate antigen-presenting cells[8,9] and to trigger adaptive immune response by neutrophil extracellular traps.[10] Furthermore, platelets are thought to boost leukocyte recruitment into the RA synovial vascular compartment.[11]

The evidence of the specific role of neutrophils, lymphocytes and platelets as mediators of systemic and articular inflammation in RA has led to the study of blood-cells based indexes as diagnostic biomarkers of RA.

Recently, several studies[12–23] and 2 meta-analyses[24,25] have reported a significant association between the neutrophil to lymphocyte ratio (NLR), the platelet to lymphocyte ratio (PLR) and the presence of RA.

Moreover, apart from NLR and PLR, new blood-cell-derived indexes, such as the derived NLR (dNLR)[26] and the lymphocyte to monocyte ratio (LMR)[17] have gained interest in recent years, as potential diagnostic tools in RA. Conversely, no data are available about the performance of the systemic inflammation response index (SIRI) and the aggregate inflammation systemic index (AISI) in RA.

Therefore, we sought to comprehensively evaluate, in a case controlled cross-sectional study, the diagnostic accuracy of NLR, dNLR, PLR, LMR, SIRI and AISI for RA.

2. Materials and methods

2.1. Patients and controls

Consecutive unselected RA patients satisfying the 2010 ACR/EULAR classification criteria[4] enrolled in the "BIOmarkers of subclinical atherosclerosis in RA–The Bio-RA study" between October 2015 and November 2018 were included. We furthermore enrolled an age- and sex-matched control group comprising healthy blood donors (HD) referred to the blood bank of the University hospital (AOU) of Sassari (Italy), as well as consecutive patients with "other than RA" rheumatologic conditions (other rheumatic diseases, RDs) treated and followed-up in the rheumatology outpatient's clinic of the University hospital (AOU) of Sassari (Italy).

In RA patients, demographic and medical history information, disease specific scores and descriptors, as well as clinical and treatment data were collected upon enrollment in the Bio-RA study and analyzed. In particular, data regarding the steroid treatment; daily steroid dose; treatment with synthetic or biological disease-modifying anti-rheumatic drugs; blood CRP levels; erythrocyte sedimentation rate; Disease Activity Score-28; Health Assessment Questionnaire, (HAQ); positivity for rheumatoid factor, and anti-citrullinated cyclic peptide antibodies were registered.

According to the local procedures of the blood donors bank, only demographic data and hemograms were available for analysis in the HD group, while hemograms and complete clinical data were available for analysis in patients with other rheumatologic conditions.

The Bio-RA study was approved by the Ethics Committee of Azienda ASL 1 of Sassari (Italy) (2219/CE-2015) and was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all individual participants.

2.2. Blood cells-based indexes calculation

Fasting morning blood samples were prospectively collected following standard procedures and protocols dictated by current national guidelines, and analyzed in a certified laboratory by automatic systems. Laboratory technicians were blinded to clinical diagnosis. The following indexes were derived from the absolute leucocyte (W), neutrophil (N), lymphocyte (L), monocyte (M), and platelet (P) counts:

(1) the neutrophil to lymphocyte ratio (NLR) = N/L,
(2) the derived neutrophil to lymphocyte ratio (dNLR) = N/(W-L),
(3) the LMR = L/M,
(4) the platelet to lymphocyte ratio (PLR) = P/L,
(5) the systemic inflammation response index (SIRI) = (N × M)/L, and
(6) the AISI = (N × M × P)/L.

The diagnosis of RA according to 2010 ACR/EULAR classification criteria[4] was the standard reference. Diagnosis

Table 1

Demographic and clinical characteristics of RA and controls.

Variable	RA n = 199	Controls n = 283	*P*	HD n = 147	Other RDs n = 136	All RDs n = 335	RA vs HD *P*	RA vs other RDs *P*	All RDs vs HD *P*
Age, years	55.5 ± 7.5	55.6 ± 9.8	.86	55.1 ± 5.3	56.2 ± 13.0	55.8 ± 10.1	.57	.56	.34
Female, n (%)	123 (61.8)	198 (70)	.07	100 (68)	98 (72.1)	221 (66)	.23	.06	.65
Disease duration, years	9.48 ± 8.1	–	–	–	–	–			
DAS-28	3.5 ± 1.1	–	–	–	–	–	–	–	–
HAQ	0.62 ± 0.5	–	–	–	–	–	–	–	–
CRP, mg/dL	1.9 ± 6.7	–	–	–	–	–	–	–	–
ESR, mm/h	27.4 ± 20	–	–	–	–	–	–	–	–
Steroid use, n (%)	119 (59.8)	–	–	–	83 (61)	202 (60.3)	–	.82	–
Steroid dose, mg/day	2.28 ± 3.4	–	–	–	3.91 ± 9	2.88 (6.8)	–	.07	–
DMARDs, n (%)	144 (72.4)	–	–	–	70 (51.5)	214 (63.9)	–	**<.001**	–
TNFi, n (%)	48 (24.1)	–	–	–	32 (23.5)	80 (23.9)	–	.9	–

All RDs = sample including patients with RA and other RDs, CRP = C-reactive protein, DAS-28 = Disease Activity Score-28 joints, DAS-28 = Disease Activity Score-28 joints, DMARDs = disease-modifying anti-inflammatory drugs, ESR = erythrocyte sedimentation rate, HAQ = Health Assessment Questionnaire, HD = healthy donors, Other RDs = patients with rheumatic diseases other than RA, RA = rheumatoid arthritis, TNFi = tumor necrosis factor alpha inhibitors. Comparisons were made with t-test and chi-square test. In **bold** significant *P*.

Table 2

Blood cell count indexes across groups.

Variable	RA n = 199	Controls n = 283	RA vs Controls *P*	HD n = 147	Other RDs n = 136	All RDs n = 335	RA vs HD *P*	RA vs other RDs *P*	All RDs vs HD *P*
NLR	2.42 ± 1.2	2.06 ± 1.4	**.004**	1.74 ± 0.7	2.41 ± 1.9	2.42 ± 1.5	**<.001**	.91	**<.001**
dNLR	1.67 ± 0.9	1.53 ± 0.8	.08	1.43 ± 0.5	1.63 ± 1.0	1.65 ± 0.9	**<.01**	.73	**<.01**
LMR	4.07 ± 1.6	5.58 ± 5.6	**<.001**	6.01 ± 2.6	5.13 ± 7.6	4.50 ± 5.0	**<.001**	.06	**<.01**
PLR	148 ± 69	128 ± 62	**<.01**	115 ± 34	142 ± 80	146 ± 74	**<.001**	.44	**<.001**
SIRI	1.28 ± 1.0	0.99 ± 1.3	**.009**	0.68 ± 0.3	1.33 ± 1.8	1.30 ± 1.4	**<.001**	.77	**<.001**
AISI	343 ± 331	247 ± 318	**<.01**	157 ± 100	343 ± 331	344 ± 372	**<.001**	.98	**<.001**

AISI = aggregate inflammation systemic index, All RDs = sample including patients with RA and other RDs, dNLR = derived NLR, HD = healthy donors, LMR = lymphocyte to monocyte ratio, NLR = neutrophil to lymphocyte ratio, Other RDs = patients with rheumatic diseases other than RA, PLR = platelet to lymphocyte ratio, RA = rheumatoid arthritis, SIRI = systemic inflammation response index. Comparisons were made with t-test and chi-square test. In **bold** significant *P*.

of RA and other RDs was made by a senior rheumatologist (GLE).

2.3. Statistical analysis

Results are expressed as means (mean ± SD) or absolute numbers and percentages [n(%)]. Statistical differences between groups were assessed using unpaired Student *t*-test or Mann–Whitney rank sum test, as appropriate. Differences between categorical variables were investigated with the chi-squared test or the Fisher exact test, depending on the numerosity of samples.

Correlations between variables were assessed by Pearson correlation or Spearman correlation. Multiple linear regression analysis was used to evaluate independent associations between baseline characteristics and blood-cells derived indexes, including into the models biologically plausible and significantly correlated (at the univariate linear regression analysis) variables.

The ability of the different indexes to discriminate between RA and controls, and between RA, RDs, and HD, was assessed using receiver operating characteristics curve analysis and expressed as area under the curve (AUC) with 95% confidence intervals (95%

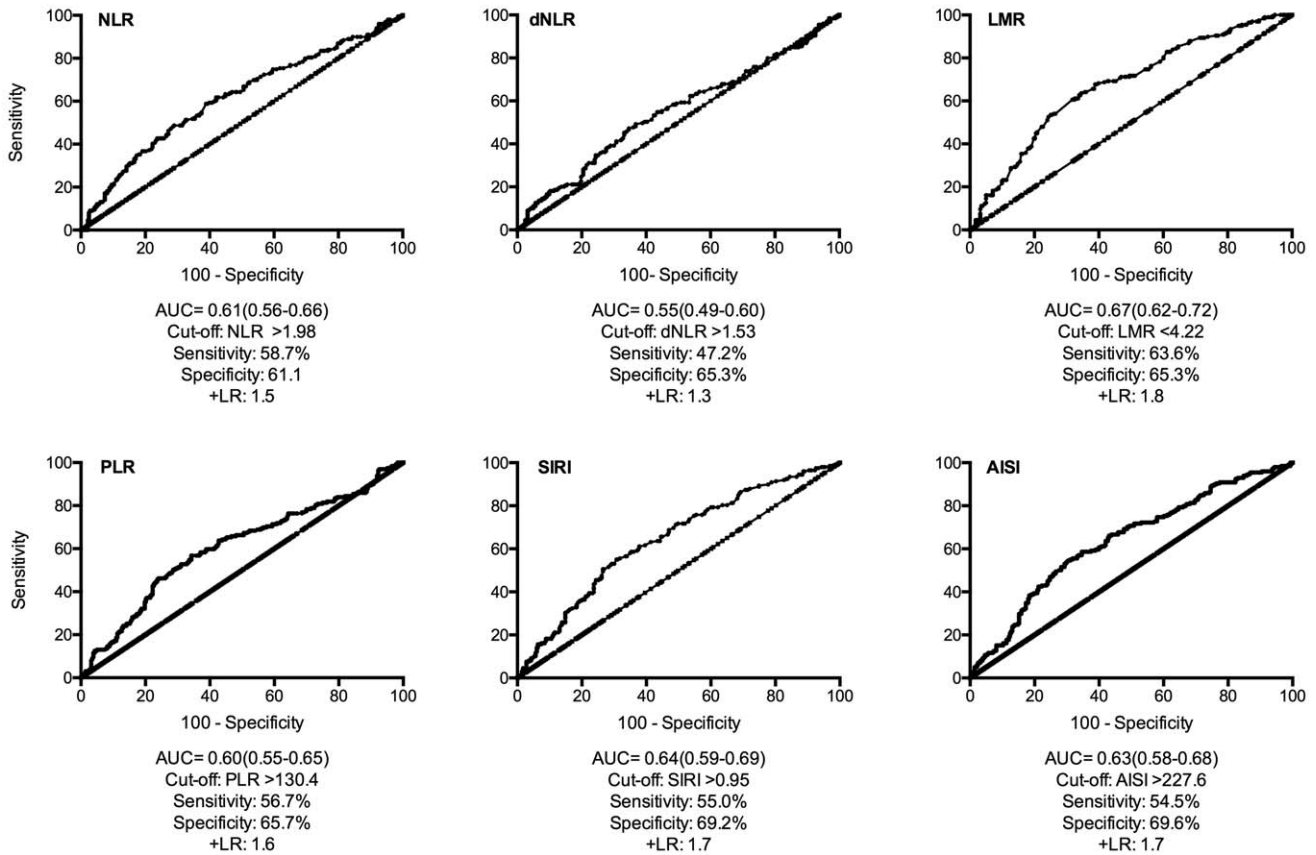

Figure 1. Blood-cell derived indexes in RA vs controls. ROC curves of NLR (neutrophil to lymphocyte ratio). ROC curves of NLR (neutrophil to lymphocyte ratio), dNLR (derived NLR), LMR (lymphocyte to monocyte ratio), PLR (platelet to lymphocyte ratio), SIRI (systemic inflammation response index), and AISI (aggregate inflammation systemic index) were plotted to determine area under the curve of each index in separating rheumatoid arthritis (RA) from controls. +LR = positive likelihood ratio, ROC = receiver operating characteristics.

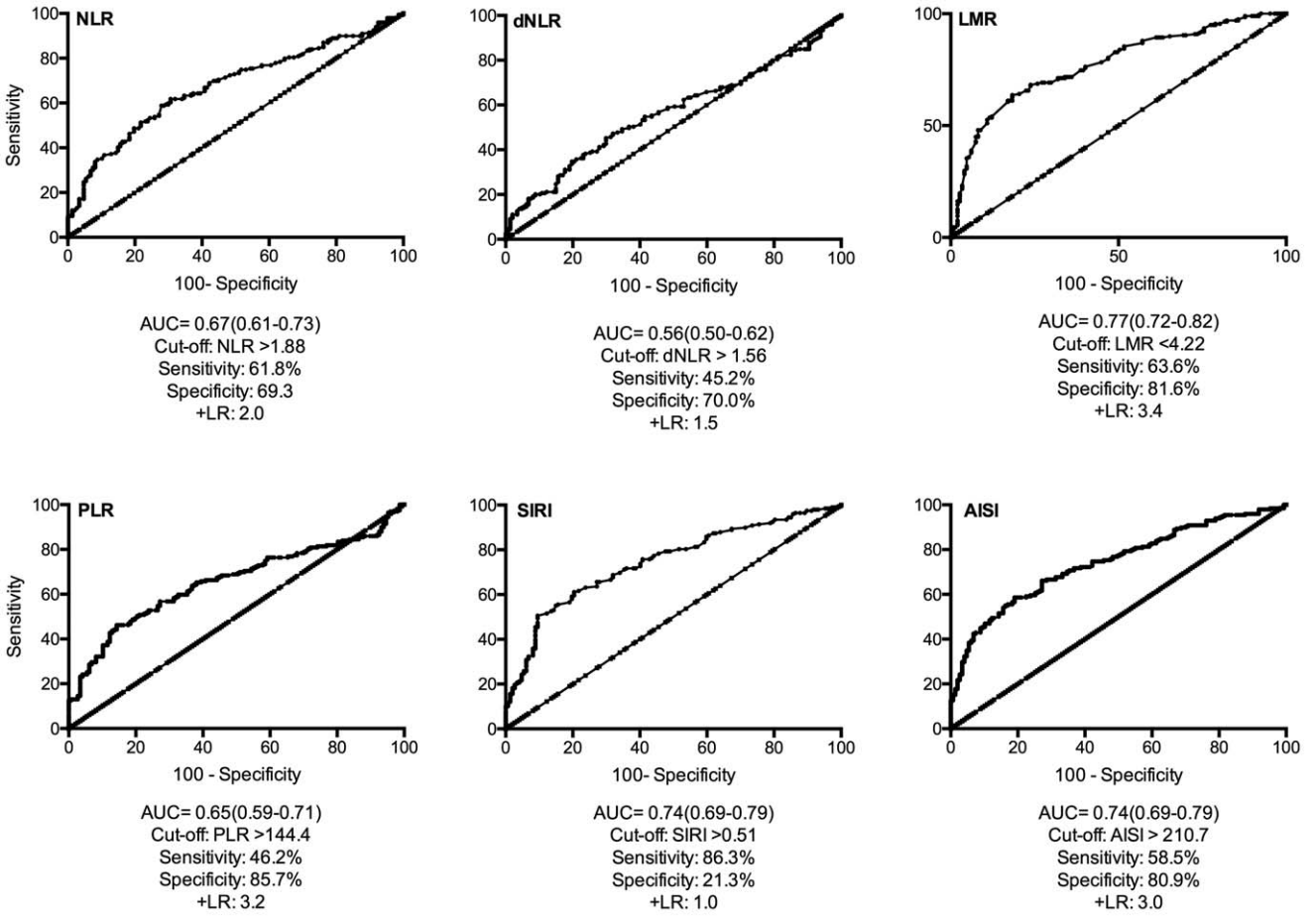

Figure 2. Blood-cell derived indexes in RA vs HD. ROC curves of NLR (neutrophil to lymphocyte ratio), dNLR (derived NLR), LMR (lymphocyte to monocyte ratio), PLR (platelet to lymphocyte ratio), SIRI (systemic inflammation response index), and AISI (aggregate inflammation systemic index) were plotted to determine area under the curve of each index in separating rheumatoid arthritis (RA) from heathy donors (HD). +LR, positive likelihood ratio, ROC = receiver operating characteristics.

CI). Optimal cut-offs for sensitivity and specificity were calculated using the Youden test. Positive likelihood ratios (+LR) were also calculated.

Analyses were performed using SPSS 20 (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp). Graphs were created using GraphPad Prism 7 (GraphPad Software 7825, Fay Avenue, Suite 230, La Jolla, CA 92037 USA). A $P \leq .05$ was considered statistically significant.

3. Results

3.1. Patients and controls (Table 1)

A total of 199 RA patients and 283 controls (147 HD and 136 patients with other rheumatic diseases) were studied. The subgroup of RDs included 29 patients with psoriatic arthritis, 25 with systemic sclerosis, 20 with systemic lupus erythematosus, 16 with Sjogren syndrome, 16 with ankylosing spondylitis, 11 with undifferentiated connective tissue disease, 4 with mixed connective tissue disease, 5 with polymyalgia rheumatica, 4 with vasculitis and 4 with myositis.

As expected, according to the RA epidemiology, the female gender was the prevalent one. Age and gender distribution were similar between patients and control groups by matching as per protocol (Table 1). RA patients had a relatively long mean disease duration (mean 9.48 years), moderate mean disease activity (Disease Activity Score-28 = 3.5 ± 1.1) and were mostly under immunosuppressive and anti-inflammatory treatment at the time of assessment (Table 1).

There were no significant differences in pharmacological treatment between RA patients and subjects with other rheumatic disease with the exception of a higher disease-modifying anti-rheumatic drugs use in the sub-group of other rheumatic diseases (Table 1).

3.2. Performance of blood cells-derived indexes in RA vs controls (Table 2 and Fig. 1)

All indexes, with the exception of dLNR, were significantly different in RA patients compared to controls (Table 2). However, receiver operating characteristics curves showed poor accuracy of the indexes in discriminating RA from controls with AUC (95%CI) ranging from 0.55 (0.49–0.60) for dNLR to 0.67 (0.62–0.72) for LMR (Fig. 1).

LMR showed the best diagnostic performance with a value <4.22 having a sensitivity of 63.6%, a specificity of 65.3% and a +LR of 1.8 (Fig. 1).

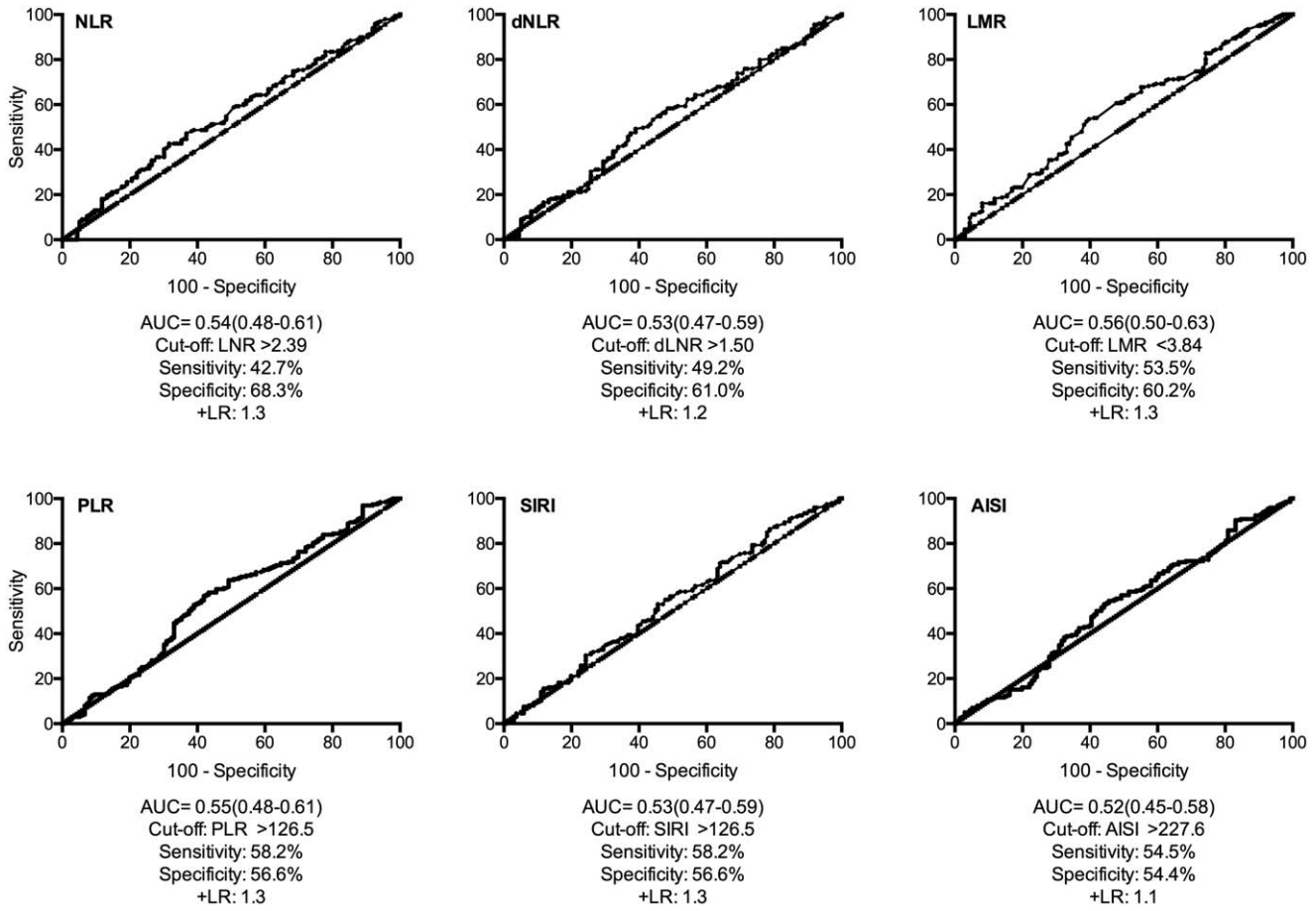

Figure 3. Blood-cell derived indexes in RA vs other RDs. ROC curves of NLR (neutrophil to lymphocyte ratio), dNLR (derived NLR), LMR (lymphocyte to monocyte ratio), PLR (platelet to lymphocyte ratio), SIRI (systemic inflammation response index), and AISI (aggregate inflammation systemic index) were plotted to determine area under the curve of each index in separating rheumatoid arthritis (RA) from rheumatic diseases (RDs). +LR, positive likelihood ratio, ROC = receiver operating characteristics.

3.3. Performance of blood cells-derived indexes in RA vs HD (Table 2 and Fig. 2)

All indexes were significantly different in RA compared to HD ($P < .001$ for all comparisons, Table 2), and showed moderate to good accuracy in differentiating RA from HD with AUC (95% CI) ranging from 0.55 (0.50–0.62) for dNLR to 0.77 (0.72–0.82) for LMR (Fig. 2). A value of LMR < 4.22 differentiated RA from HD with a sensitivity of 63.6% and a specificity of 81.6% (+LR = 3.4).

3.4. Performance of blood cells-derived indexes in RA vs other RDs (Table 2 and Fig. 3)

There were no significant differences in the studied indexes between RA patients and subjects with other RDs (Table 2). AUCs ranged from 0.52 (0.49–0.58) for AISI to 0.56 (0.50–0.63) for LMR (Fig. 3).

3.5. Performance of indexes between all RDs vs HD (Table 2 and Fig. 4)

Comparing a sample including RA patients and other RDs (All RDs) with HD showed significant differences in blood cells-derived indexes ($P < .01$ for all comparisons) and moderate accuracy, with AUCs ranging from 0.54 (0.49–0.5) for dLNR to 0.74 (0.70–0.79) for LMR, in separating patients with rheumatic diseases from healthy subjects. A value of LMR < 4.22 distinguished patients with rheumatic diseases from healthy subjects with a sensitivity of 58.9% and a specificity of 81.6% (+LR = 3.2).

3.6. Multiple regression analysis (Table 3)

In multiple regression analysis LMR showed significant association with female gender while SIRI and AISI were associated with the male gender (Table 3). Furthermore, both SIRI and AISI were significantly associated with increasing concentrations of CRP, a marker of systemic inflammation, shorter disease duration and younger age.

4. Discussion

In this study we performed a comprehensive performance evaluation of different blood cells-derived indexes in distinguishing RA from control subjects. Despite the fundamental role of circulating blood cells, especially neutrophils and lymphocytes, in the regulation of inflammatory, innate and adaptive immune responses the use of indexes that include multiple components of

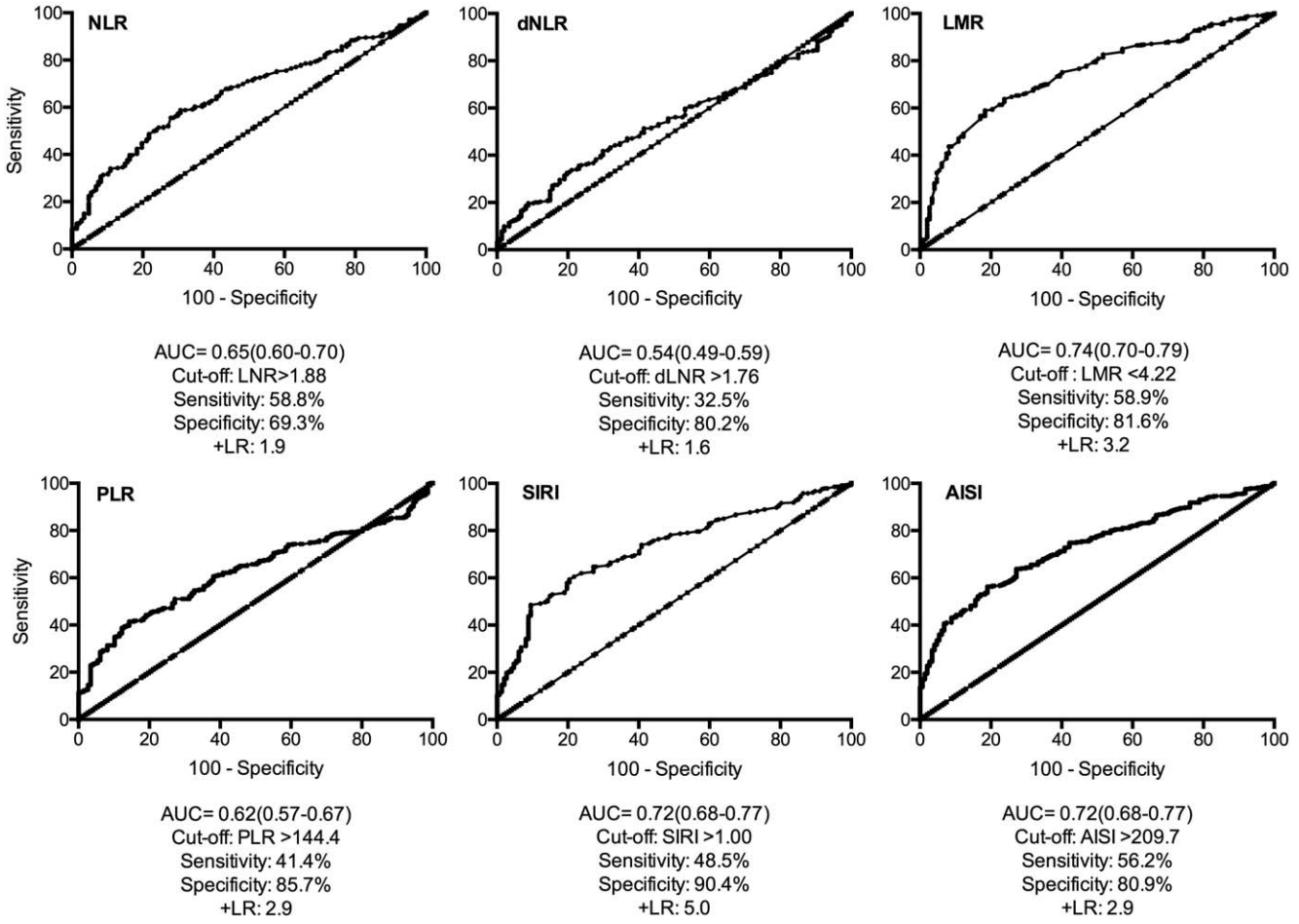

Figure 4. Blood-cell derived indexes in all RDs vs HD. ROC curves of NLR (neutrophil to lymphocyte ratio), dNLR (derived NLR), LMR (lymphocyte to monocyte ratio), PLR (platelet to lymphocyte ratio), SIRI (systemic inflammation response index), and AISI (aggregate inflammation systemic index) were plotted to determine area under the curve of each index in separating all rheumatic diseases (RDs) from healthy donors (HD). +LR, positive likelihood ratio, ROC = receiver operating characteristics.

Table 3

Factors associated to blood cells-based indexes in RA patients.

	LMR		SIRI		AISI	
	Beta	***P* value**	**Beta**	***P* value**	**Beta**	***P* value**
Age	/		–0.17	.012	–0.21	.003
Gender	–0.25	<.001	0.32	<.001	0.28	<.001
Disease duration	/		–0.16	.008	–0.13	.027
CRP	/		0.48	<.001	0.37	<.001
ESR	/		/		0.21	.002
DAS-28	/		/		/	
Steroid use	/		/		/	
DMARDs use	–0.168	.017	/		/	
TNFi use	/		/		-0.13	0.033
R^2	0.09	.33	0.31			

A linear regression for multiple variables (stepwise method) was performed including into the model biologically plausible variables and variables showing significant association ($P < 0\ 05$) with the dependent variables (LMR, SIRI and AISI) at the univariate regression analysis. / = variable removed from the model, AISI = aggregate inflammation systemic index, CRP = C-reactive protein, DAS-28 = Disease Activity Score-28 joints, DMARDs = disease-modifying anti-inflammatory drugs, ESR = erythrocyte sedimentation rate, LMR = lymphocyte to monocyte ratio, SIRI = systemic inflammation response index, TNFi = tumor necrosis factor alpha inhibitors. R^2, coefficient of multiple determination. Gender classification: 0 female, 1 male.

the complete blood count, in order to further improve diagnosis and prognostic classification of RDs, has not been investigated until recently.[24,25]

Moreover, there is no information regarding the discriminatory power of NLR, PLR, dNLR, and LMR when distinguishing RA from a control population that includes subjects with other inflammatory rheumatic diseases. For the first time, we extended the analysis to two novel indexes, SIRI and AISI, not yet investigated in RA. The SIRI and AISI indexes, calculated including multiple blood cells, have been recently proposed as markers of systemic inflammation with prognostic relevance in patients undergoing major surgery and oncological therapy.[27–29]

When compared with a control population including healthy controls and patients with rheumatic diseases other than RA, all indexes showed relatively poor accuracy as diagnostic tests for RA (AUCs < 0.7 for all comparisons). The LMR showed the highest accuracy (AUC = 0.67) for the diagnosis of RA. Similarly, in a previous retrospective study the LMR demonstrated a slightly better accuracy in differentiating RA from controls (AUC = 0.70).[15] However, in this study controls were represented by patients with osteoarthritis, a condition characterized by a lower inflammatory state.

Of note, the low accuracy of blood cells-derived indexes for the diagnosis of RA in our study was related to their poor discriminatory value in separating RA from other inflammatory diseases (AUCs < 0.6 for all comparisons) whereas we confirmed their moderate to good accuracy in distinguishing RA and other rheumatic diseases from healthy subjects.

In multiple regression analysis in the RA population, when adjusting for the use of steroids and immunosuppressive drugs, the two novel indexes, SIRI and AISI, were significantly association with systemic inflammation but not with RA disease activity. Therefore, it is possible that SIRI and AISI reflect a chronic inflammatory state rather than RA-specific (pathogenetic) pathways.

The main limitation of this study is related to the fact that the majority of RA (and other RDs) received pharmacological treatment at the time of assessment. Therefore, the potential impact of specific immunosuppressive drugs (non-steroidal anti-inflammatory drugs, glucocorticoids, synthetic and biologic disease modifying anti-rheumatic drugs) on blood cells-derived indexes, even after correction in the regression analysis, could be not completely ruled out. We not prospectively collected data about comorbidities of participants enrolled in the study, therefore we were not able to completely rule out the possibility that differences in blood cells-derived indexes may, at least in part, be attributable to concomitant conditions.

Moreover, we were not able to assess the correlation between blood cells-derived indexes and conventional systemic inflammatory markers in patients with other RDs, that could have provided insights about their potential role as alternative biomarkers of inflammation.

There is good evidence that RA patients develop early endothelial dysfunction and accelerated arterial wall stiffening, predisposing them to fatal cardiovascular events and sudden death.[1,30–32] Therefore, easy to use and affordable biomarkers of accelerated atherosclerosis may be of high value in the management of patients with RA. Even if not addressed in this study, previous findings suggest that blood cells-derived biomarkers may be linked to increased cardiovascular disease burden and risk of future cardiovascular events in the general population.[33–35] Therefore, future prospective studies are needed to explore the value of blood cells-derived indexes as markers of cardiovascular disease burden in the RA population.

5. Conclusions

Blood cells-derived indexes accurately separate patients with rheumatic diseases from healthy subjects but appear of limited value in differentiating between RA patients and other rheumatic diseases. The value of blood cells-derived indexes as a measure of systemic inflammatory burden in RA and other rheumatic diseases should be further evaluated in larger studies.

Author contributions

Conceptualization: Gian Luca Erre, Angelo Zinellu, Panagiotis Paliogiannis
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