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Differential acute phase response due to infection in AIRDs: A cross-sectional multi-centre study based on RA and SLE

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Abstract

Aim: To explore the differences in acute phase responses between infection and disease flare and between viral and bacterial infections.

Methods: The retro-prospective, cross-sectional, multi-centre study considered subjects who had undergone treatment for infection or disease flare between 2019 to 2021. The patients fulfilling the ACR/EULAR 2010 criteria and 2019 EULAR/ ACR criteria for RA and SLE respectively, were recruited from three centers. Patients who did not have autoimmune rheumatic disease or other immune-mediated diseases were considered as controls. The participants were classified into subgroups namely 'overall', 'without autoimmune rheumatic disease', 'SLE' and 'RA'. The infectious and non-infectious groups, and the bacterial and viral disease groups were compared to evaluate the differences in the parameters namely age, gender, total leucocyte count (TLC), neutrophil count(N), lymphocytes count (L) NLR, CRP and procalcitonin. Student t-test was used for the evaluation of continuous data and chi-square test for categorical data. ROC curves were plotted. The cutoff points of variable at 80% and 90% sensitivity and specificity were estimated for each subgroup to differentiate infection and no-infection.

Results: The data of 439 subjects were considered for the analysis of infection vs. non-infection, and that of 218 patients out of 282 in the infection categories for the viral vs. bacterial analysis. Comparison between infection and non-infection groups demonstrated that the parameters TLC, neutrophil, NLR, CRP and procalcitonin were significantly higher in the infection group; whereas, lymphocytes were significantly lower in the infection group. The overall comparison between viral vs. bacterial groups demonstrated significant differences in TLC, lymphocytes and procalcitonin. The receiver operating characteristic (ROC) curve analyses demonstrated that CRP serves as a better indicator than remaining parameters. However, for the RA subgroup, none of the parameters were significant to differentiate infection and flare. Whereas in SLE, the CRP and NLR were able to distinguish infection. The cut-off values for CRP, NLR, TC and procalcitonin at targeted sensitivity and specificity of 90% and 80% varied across the different sub-groups.

Conclusion: TLC, NLR, CRP, and procalcitonin are beneficial in differentiating infections from non-infection in patients without autoimmune disease. CRP is a better indicator of infection in SLE and normal subjects. CRP and procalcitonin in overall group. However, in the presence of inflammatory autoimmune rheumatic diseases, it is paramount to consider the base elevation of these parameters and the skewed inflammatory response while interpreting the parameters.

Keywords: AIRDS, SLE, AS, RA, NLR, CRP, Procalcitonin, inflammatory markers, infection

Introduction

Infection is one of the commonest causes for mortality and morbidity in autoimmune rheumatic diseases (AIRDs). It is often challenging to differentiate symptoms of infections from disease flare. The acute phase reactants (APR) like total leucocyte count, NLR, CRP, and procalcitonin are often used to differentiate systemic immunoinflammatory rheumatic diseases (SIRDs) from infections. The

inflammatory parameters are often non-specific and are elevated in SIRDs due to the altered immune response of pre-existing disease. Many studies have demonstrated the influence of disease activity on expression of APR, especially with reference to rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE).[1,2] Incorporation of the pattern of expression of APR into analytical prediction, especially when used in combination, may enhance the precision of prediction.

Earlier, a preliminary study conducted by the current authors have developed a scoring system pooling all the patients of SIRDs to differentiate the infection from disease flare (IRACON abstract).[3] However, there was a reduction in the sensitivity and specificity in prediction, upon using the same for SLE and RA. Based on these observations, the researchers have proposed to characterize the interplay of these inflammatory parameters in patients with pre-existing SIRD. The literature comparing the aforementioned parameters is limited, especially with reference to RA and SLE. The primary objective of the present study is to understand the differences in acute phase response between infection and disease flare and between viral and bacterial infections in RA and SLE.

Materials and methods

The retro-prospective, cross-sectional, multi-center study included patients who had undergone treatment between 2019 to 2021 for infection or disease flare. The patients were recruited from both records (retrospectively) as well prospectively between the stipulated period. The patients diagnosed with RA and SLE, fulfilling the ACR/EULAR 2010 criteria and 2019 EULAR/ACR criteria respectively, were recruited from three centers (two departments of rheumatology and Immunology and one department of internal medicine).[4,5] Patients who did not have AIRDs or other immune-mediated diseases were considered as controls. The study considered adult patients who presented with fever, malaise and other features suggestive of infectious and disease flare/non-infectious causes or those having features of overlapping infection including cellulitis and abnormal c-reactive protein (CRP). The patients with autoimmune inflammatory syndrome or those with uncertain classification on autoimmune processes like AS, psoriatic arthritis, osteoarthritis and seronegative spondyloarthropathy (SSA) were excluded. However, subjects with these diseases in conjunction with definite AIRD and an overlap infection were included for classification under CTD and other diseases. Other diseases included vasculitis and dermatomyositis. Patients who had been incompletely evaluated and those who did not consent for study participation were excluded. Diagnostic conclusions of disease flare or infections were based on the sole discretion of physician in charge. Data was extracted from the records for even the prospective patients after the resolution of the disease episodes. The study was cleared by institutional ethics committee of ChanRe Rheumatology and Immunology Centre and Research, Bengaluru, India (IEC-CRICR/SN-128/097/2020).

The patient outcomes were categorized as infection, flare or undetermined. The patient outcomes were ascertained based on serology, blood and/or urine culture, viral antibody and antigen tests, as defined under infection. The definitions considered for classifying various infections were as follows: clinically attributable culture from the site of suspected infection and/or those showing definite response to antibiotics or any other signs attributable to bacterial infections like colored pus/discharge and outcome matching to infection were considered as having bacterial etiology. Infections with positive viral serology or PCR like those for H1N1 or with sufficient evidence to conclude viral infections were classified under viral etiology. The infections that could not be ascertained as either due to bacteria or virus, but clinically ascertained as infection, were considered as undetermined infections (which cannot be classified viral/ bacterial infection). Disease flare or activity were concluded based on definition used with reference to flare of SLE and RA.[6,7]

The demographic and APR considered for the study were age, gender, total leucocyte count (TLC), neutrophil count (N), lymphocyte count (L), neutrophil-to-lymphocyte ratio (NLR), CRP and procalcitonin. Total leucocyte counts (TLC), neutrophils and lymphocytes were measured by automated 5-part cell counter, CRP by nephelometry, and procalcitonin by standard PCT-FIA assay using fluorescence technology (SD Biosensor). NLR was estimated. The total leucocyte count was expressed in cells X 10^3 per mm^3, neutrophil and lymphocyte count in percentage, CRP in mg/L, and procalcitonin in ng/dL. The abnormal cut-off values considered for different parameters were as follows: elevated or decreased, total leucocyte counts suggestive of infections by automated hematology analyzers more than 11* 10^3/ mm^3, CRP >12 mg/L, and procalcitonin >0.25 ng/ml.

Statistical analysis: Based on the diagnosis, the participants were classified into subgroups namely ‘without autoimmune rheumatic disease’, ‘SLE’ and ‘RA’. The

combined data of all the three groups were considered as overall group. The patients with CTD and other diseases were not considered for subgroup analysis considering the heterogeneity and smaller sample size. The continuous variables were represented as mean±SD and categorical variables as frequency (percentage). The infectious and disease flare/non-infectious groups were compared to evaluate the differences in the demographic and APR parameters. Similarly, the differences were noted upon comparison between bacterial and viral disease groups. Sensitivity analysis was performed to compare the infection/non-infectious with bacterial/viral dataset. Student t-test was used for the evaluation of continuous data and chi-square test for categorical variable (gender). Statistical analyses were performed and graphs were plotted using python (version: 3.1.0) code in Jupyter notebook (version: 4.8). ROC curves were plotted to verify the discriminatory ability of inflammatory variables with infection vs no infection using EPITOOLS.[8] The cutoff points of variable at 80% and 90% sensitivity were tabulated for the subgroups to differentiate infection and no-infection. P value <0.05 was considered as statistically significant.

Results

A total of 700 patients were recruited and 261 were excluded due to indefinite diagnosis or incomplete information. The data of 439 subjects were considered for the analysis of infection vs. non-infection. The data of only 218 patients out of 282 in the infection categories were used for the viral vs. bacterial analysis, since the remaining data were considered as undetermined infection. The findings of descriptive analysis conducted for infection/no-infection and viral/bacteria groups and the corresponding proportion of subjects noted in the RA, SLE, CTD and other diseases, and patients without autoimmune diseases are given in table 1. The sensitivity analysis showed significantly higher TLC, CRP and procalcitonin and lower lymphocyte in viral/bacterial subjects than infection/non-infection group. No significant difference was noted with regard to age, gender, neutrophil and NLR across the infection/non-infection groups and viral/bacterial groups.

Infection vs. non-infection: Comparison between infection and non-infection groups (Table 2) demonstrated that the parameters namely TLC, neutrophil, NLR, CRP

Table 1: Descriptive analysis and the corresponding proportion of subjects noted in the different subgroups

Variables#		Infection / No-infection (N = 439)	Viral / bacterial N = 218	P-value*
Age (years)		43.18±17.82	49.31±17.19	0.26
Gender: M[F]		90 (20.5) [349 (79.5)]	58 (26.61) [160 (73.39)]	0.05
Total leucocyte count (10^3/ mm^3)		9.88±5.98	10.96±6.35	0.02
Neutrophil (%)		76.72±13.19	78.49±13.29	0.05
Lymphocyte (%)		17.01±10.69	15.27±10.79	0.02
Neutrophil-to-lymphocyte ratio		8.58±10.68	10.42±12.31	0.33
CRP (mg/L)		66.79±73.67	88.47±83.19	<0.01
Procalcitonin (ng/ml)		4.01±13.84	6.64±17.63	0.02
Diagnosis	RA	83 (18.91%)	61 (13.90%)	
	SLE	199 (45.33%)	55 (12.53%)	
	CTD and others disease	71 (16.17%)	44 (10.02%)	
	Patients without autoimmune diseases	86 (19.59%)	58 (13.21%)	

Continuous variables were represented as mean±SD and categorical variables as frequency (percentage)

* Student t-test for the continuous and chi-square test for categorical variable

Table 2: Comparison of parameters between infection and non-infection groups for the categories RA, SLE and normal populations

Predictors#	No-infection (n = 157)	Infection (n = 282)	P-value*
Overall Population (n = 439)			
Age (years)	36.28±15.17	47.04±18.10	< 0.01
Gender: M[F]	16(10.19) [141(89.81)]	74(26.24) [208(73.76)]	< 0.01
Total leucocyte count (10^3/ mm^3)	8.19±4.67	10.83±6.41	< 0.01
Neutrophil (%)	73.51±13.55	78.51±12.66	< 0.01
Lymphocyte (%)	19.42±10.73	15.68±10.44	< 0.01
NLR	6.57±8.53	9.69±11.58	< 0.01
CRP (mg/L)	39.56±49.25	81.95±80.42	< 0.01
Procalcitonin (ng/ml)	1.05±7.98	5.66±15.99	< 0.01
Patients without autoimmune rheumatic disease (n = 86)			
	No-infection (n=12)	**Infection (n = 74)**	
Age (years)	49.08±18.17	55.42±17.77	0.13
Gender: M[F]	2(16.67) [10(83.33)]	45(60.81) [29(39.19)]	< 0.01
Total leucocyte count (10^3/ mm^3)	10.91±7.73	15.00±5.8	0.02
Neutrophil (%)	69.66±10.13	81.15±10.72	< 0.01
Lymphocyte (%)	23.89±10.63	16.29±10.82	0.01
NLR	3.83±2.45	8.73±8.95	0.03
CRP (mg/L)	45.68±60.17	66.59±62.91	0.14
Procalcitonin (ng/ml)	0.49±0.58	12.12±22.03	0.04
Patients with RA (n = 83)			
	No-infection (n = 17)	**Infection (n = 66)**	
Age (years)	55.76±11.95	58.35±11.32	0.2
Gender: M[F]	1(5.88) [16(94.12)]	5(7.58) [61(92.42)]	0.81
Total leucocyte count (10^3/ mm^3)	10.53±4.88	10.74±7.31	0.48
Neutrophil (%)	76.67±9.22	77.71±11.64	0.37
Lymphocyte (%)	14.01±5.92	13.9±8.87	0.48
NLR	6.72±3.32	11.17±14.73	0.11
CRP (mg/L)	81.77±67.04	107.35±92.85	0.15
Procalcitonin (ng/ml)	0.49±0.48	4.81±17.66	0.16
Patients with SLE (n = 199)			
	No-infection (n = 104)	**Infection (n = 95)**	
Age (years)	30.06±9.99	31.61±12.17	0.16
Gender: M[F]	8(7.69) [96(92.31)]	9(9.47) [86(90.53)]	0.65
Total leucocyte count (10^3/ mm^3)	7.18±3.92	7.75±4.22	0.16
Neutrophil (%)	73.35±14.89	77.26±14.43	0.03
Lymphocyte (%)	19.98±11.16	16.31±10.89	0.01
NLR	6.9±9.94	9.62±11.88	0.04
CRP (mg/L)	29.94±41.88	69.14±79.04	< 0.01
Procalcitonin (ng/ml)	1.39±9.80	2.05±8.65	0.31

Continuous variables were represented as mean±SD and categorical variables as frequency (percentage)

* Student t-test for the continuous and chi-square test for categorical variable

Table 3: Comparison of parameters between bacterial and viral infection groups for the categories RA, SLE and normal populations

Predictors#	Viral (n = 60)	Bacterial (n = 158)	P-value*
Overall Population (n = 218)			
Age (years)	46.68±15.73	50.31±17.67	0.08
Gender: M[F]	13(21.67) [47(78.33)]	45(28.48) [113(71.52)]	0.31
Total leucocyte count (10^3/ mm^3)	8.68±4.85	11.83±6.65	< 0.01
Neutrophil (%)	76.95±13.90	79.08±13.05	0.15
Lymphocyte (%)	17.38±12.59	14.47±9.95	0.04
NLR	10.45±15.32	10.41±11.02	0.49
CRP (mg/L)	80.85±82.51	91.37±83.52	0.2
Procalcitonin (ng/ml)	3.21±8.84	7.94±19.85	0.04
Patients without autoimmune rheumatic disease (n = 58)			
	Viral (n = 10)	**Bacterial (n =48)**	
Age (years)	42.7±16.28	57.56±17.48	0.22
Gender: M[F]	4(40) [6(60)]	32(66.67) [16(33.33)]	0.01
Total leucocyte count (10^3/ mm^3)	7.76±5.35	16.64±5.02	<0.01
Neutrophil (%)	75.98±10.90	82.34±11.18	0.05
Lymphocyte (%)	22.27±12.29	14.38±10.09	0.03
NLR	5.64±5.05	10.2±10.44	0.09
CRP (mg/L)	44.75±83.80	77.62±62.75	0.08
Procalcitonin (ng/ml)	1.39±2.9	15.53±25.62	0.04
Patients with RA (n = 61)			
	Viral (n = 16)	**Bacterial (n = 45)**	
Age (years)	56.25±12.06	58.36±11.25	0.27
Gender: M[F]	1(6.25) [15(93.75)]	4(8.89) [41(91.11)]	0.74
Total leucocyte count (10^3/ mm^3)	7.74±4.66	11.0±6.47	0.04
Neutrophil (%)	76.74±11.85	77.67±11.74	0.39
Lymphocyte (%)	14.62±9.78	13.91±8.75	0.39
NLR	12.73±22.49	9.87±9.31	0.24
CRP (mg/L)	75.27±65.25	113.39±96.18	0.07
Procalcitonin (ng/ml)	2.18±6.14	6.24±21.0	0.23
Patients with SLE (n = 55)			
	Viral (n = 13)	**Bacterial (n =42)**	
Age (years)	36.31±14.32	32.95±12.39	0.21
Gender: M[F]	1(7.69) [12(92.31)]	3(7.14) [39(92.86)]	0.95
Total leucocyte count (10^3/ mm^3)	8.56±4.77	7.6±4.34	0.25
Neutrophil (%)	80.74±16.80	75.5±16.60	0.16
Lymphocyte (%)	14.38±14.96	16.23±11.66	0.32
NLR	16.57±18.04	10.41±13.34	0.09
CRP (mg/L)	109.05±126.63	71.92±74.17	0.1
Procalcitonin (ng/ml)	3.16±4.70	3.47±12.61	0.47

Continuous variables were represented as mean±SD and categorical variables as frequency (percentage)

* Student t-test for the continuous and chi-square test for categorical variable

Table 4: ROC cutoffs for the variables at 90% and 80% specificity and sensitivity

Diagnosis	Variables	Cut-off				Area under curve (AUC)	95% CI for AUC
		0.9 target		0.8 target			
		Sensitivity	Specificity	Sensitivity	Specificity		
Overall	Total leucocyte count (10^3/ mm^3)	4.13	13.75	5.43	10.67	0.62	0.57-0.68
	NLR	4.2	35	7.2	28.1	0.62	0.56-0.67
	CRP (mg/L)	5.2	108.7	14.2	78.7	0.69	0.64-0.74
	Procalcitonin (ng/ml)	0.07	1	0.1	0.43	0.69	0.64-0.74
Patients without autoimmune diseases	Total leucocyte count (10^3/ mm^3)	5.8	18	9.52	15.5	0.71	0.52-0.89
	NLR	1.92	7.73	2.34	7.13	0.72	0.59-0.85
	CRP (mg/L)	4.21	18.2	14.2	16	0.82	0.73-0.91
	Procalcitonin (ng/ml)	0.25	0.64	0.39	0.64	0.82	0.72-0.92
RA	Total leucocyte count (10^3/ mm^3)	4.34	18.9	5.43	13.75	0.46	0.32-0.60
	NLR	2.26	12.57	3.38	9.75	0.55	0.41-0.68
	CRP (mg/L)	5.32	184.62	14.2	161	0.56	0.41-0.71
	Procalcitonin (ng/ml)	0.1	1.57	0.1	0.94	0.6	0.47-0.73
SLE	Total leucocyte count (10^3/ mm^3)	2.59	11.44	4.5	9.47	0.53	0.45-0.62
	NLR	2.13	14.67	2.83	8.19	0.61	0.53-0.69
	CRP (mg/L)	3.9	88	10.8	55.5	0.77	0.63-0.77
	Procalcitonin (ng/ml)	0.03	1.4	0.06	0.5	0.57	0.49-0.65

and procalcitonin were significantly higher in the infection group; whereas, lymphocyte were significantly lower in the infection group. The subgroup analysis for normal population demonstrated significant differences in all the parameters except CRP, which could be due to smaller sample size. In RA, none of the values were found to be significantly different between the infection and non-infection groups. In SLE category, neutrophil, lymphocyte, NLR and the CRP were significant, whereas, procalcitonin was not significantly different.

Viral vs. bacterial: The overall comparison between viral vs. bacterial groups (Table 3) demonstrated significant differences in TLC, lymphocytes and procalcitonin. Whereas, neutrophil percentage, NLR and CRP were not significantly different. The subgroup analysis in normal population demonstrated that the TLC, lymphocyte, and procalcitonin were significantly different between the groups. In RA, TLC was significantly different; whereas in SLE, NLR showed some tendency to differentiate the infections.

The receiver operating characteristic (ROC) curve analyses of the data of patients without autoimmune diseases demonstrated that CRP, NLR, TC and procalcitonin have adequate discretion power to differentiate the presence or absence of infection (Table 4) (Graphs given as supplementary file). At 90% sensitivity and specificity, CRP serves as a better indicator than remaining parameters. However, for the RA subgroup, none of the parameters were significant to differentiate infection and flare. Whereas in SLE, the CRP was able to distinguish infection. CRP cut-off 3.9 mg/L and 88 mg/L had 90% sensitivity and specificity to identify infection. In the overall group, CRP and procalcitonin were found to be useful to identify the infections. However, CRP had higher cut-off level of 108 mg/L at 90% specificity. The cut-off values for CRP, NLR, TC and procalcitonin at targeted sensitivity and specificity of 90% and 80% varied across the different sub-groups.

Discussion

The present study has demonstrated that the variation in four commonly used parameters to distinguish infection and inflammation, namely TLC, NLR, CRP, and procalcitonin may

depend on the pre-existing immune-inflammation conditions and the same has been corroborated in the differential responses noted in viral and bacterial infections. CRP could differentiate infection in patients without autoimmune disease and SLE. CRP and procalcitonin were useful in overall group.

In patients without autoimmune diseases, elevated inflammatory parameters from baseline indicate the presence of infections. In the same population, increased levels of TLC and procalcitonin could differentiate bacterial and viral infections. This is not surprising, since these values and reference ranges are defined on the basis of values observed in normal population. Whereas in RA population, the variation was not significant for any of the parameters. In SLE, neutrophil, lymphocyte, NLR and CRP were significantly different between infections and non-infections and only NLR demonstrated some tendency in differentiating between viral and bacterial infection. SLE is a prototype of systemic autoimmune disease, and the inflammatory response is mediated by TH 2 and Interferon; whereas, in RA the response is primarily TH 1 and TNF-alpha driven. This could be one of the reasons for the differences in the relation noted across the four inflammatory parameters. Since, CRP elevation has been observed both in RA flare and infections, it may not be an ideal marker for distinguishing the two. Even the CRP cut-offs to differentiate infections from flare in RA is higher. For example, the specificity is almost 10 times higher in RA than the normal. Hence CRP may be useful when comparing with the previous known values of a patient. Even the TLC changes are not remarkably significant between infection and flare in RA.

Simon et al. (2004) have compared the diagnostic performance of procalcitonin with CRP in identifying bacterial infection in patients with no autoimmune disease and the corresponding sensitivity and specificity noted were 88% vs. 75% and 81% vs. 67% respectively.[9] A meta-analysis by Uzzan B et al. (2006) concluded that the overall accuracy of procalcitonin is significantly higher than CRP in differentiating bacterial and viral infections, and bacterial infections from non-infectious causes of systemic inflammation.[10] The current finding concurs with these previous literature studies validating the superiority of procalcitonin than CRP in identifying bacterial infection from viral in overall population. However, in identifying infection from non-infections, both CRP and procalcitonin were useful. In SLE, CRP demonstrated cut-off 3.9 mg/L and 88 mg/L had 90% sensitivity and specificity, whereas, 10.18 mg/L and 55.5 mg/L had 80% sensitivity and specificity respectively to identify infection. In RA, none of the parameters were found to be useful. In patients without autoimmune disease, the values were 5.2 mg/L and 108 mg/L at 90% sensitivity and specificity and 14.2 mg/L and 78.7 mg/L at 80% sensitivity, suggesting CRP was found to be a better indicator of infection.

On contrary to previous literature findings, the current study has suggested that procalcitonin levels may not be an ideal marker in differentiating infection from flare, and bacterial from viral infections in patients with SLE and RA. There are studies suggesting the significantly elevated procalcitonin levels in patients with SLE flares, especially in the presence of renal activity. Several studies have shown significant rise in the procalcitonin levels in bacterial and fungal infections, in contrast to disease flare and viral infections. Many studies have suggested that the increased procalcitonin cut-off levels have higher specificity in patients with SLE, whereas the sensitivity was significantly low.[11,12] In a meta-analysis involving 668 SLE patients the corresponding sensitivity and specificity noted for procalcitonin in detecting bacterial infections were 66.8% (95% CI 60.0-73.2) and 89.8% (95% CI 86.6-92.4), respectively, and that of CRP were 81.3% (95% CI 75.3-86.3) and 63.0% (95% CI 58.5-67.5).[13] Akin to these findings, the present study also indicates that 90% specificity had higher cut-off for procalcitonin in SLE patients and it also had higher cut-off in comparison to those without AID (1.4 vs. 0.64).

The present study has corroborated that the inflammatory parameters namely CRP, NLR, TLC and procalcitonin have adequate discretion power to differentiate infection in normal subjects, and CRP is superior than remaining parameters in SLE. A prospective study by Kim et al. has suggested that CRP at a cut-off value of 13.5 mg/L had 100% sensitivity and 90% specificity in detecting bacterial infection in SLE patients and it is superior to S100A8/A9 and procalcitonin.[14] In contrast, Tamaki et al. have concluded that increased serum procalcitonin level has 97.1% specificity in diagnosing bacterial infection in patients with active SLE, irrespective of the dosage of corticosteroids and immunosuppressants.[15] Wang et al. have compared the clinical characteristics of various serum biomarkers and concluded CRP as the sole effective marker for detecting infection in SLE patients and also recommended procalcitonin as a predictive marker of SLE activity.[16] Broca-Garcia et al. have concluded that CRP along with NLR is beneficial in identifying SLE patients with non-viral infection.[17] Similarly, Kim et al. have concluded that NLR with a cut-off value of 5.70 has significant specificity (98%) than CRP in

diagnosing infection in SLE patients.[18] A meta-analysis by Wang et al. has found that NLR was significantly high in SLE patients as opposed to controls, thereby suggesting its use as an indicator for disease activity monitoring.[19]

In RA, none of the values were found to be significant upon comparison between the infection and non-infection, however increased TLC differentiated bacterial from viral infection. Literature review shows that there are very few studies evaluating the role of inflammatory markers in diagnosing infections in RA patients. Nagai et al. have concluded on the potential of post-NLR/pre-NLR ratio as surrogate marker for predicting bacterial infection in patients with RA receiving tocilizumab.[20] In concurrence with these findings, an observational study involving 489 subjects carried out by Chandrashekara et al. has reported that NLR may serve as a cost-effective marker for inflammation in RA, in contrast to traditional markers. Moreover, it has comparable efficacy as that of CRP.[21] Sato et al. have suggested high serum procalcitonin level (≥ 0.5 ng/ml) as a specific marker for detecting bacterial infection in RA patients as opposed to CRP, ESR or WBC.[22]

Patients recruited from multiple centers are one of the major strengths of the current study. Total leucocyte count, NLR, CRP, and procalcitonin are markers that could be readily obtained from laboratory reports of patients. One of the major limitations of the present study is limited sample size, especially with reference to RA sub-group. Further research should focus on the scoring and correlation of these markers for standardizing the cut-off values for various clinical scenarios. It is also important to evaluate the potential use of ratios of these parameters for differentiating infections and flare. As not all the inflammatory components alter in the same manner, developing an algorithm will be beneficial in differentiating infection vs. flare.

Conclusion

In conclusion, the inflammatory markers namely TLC, NLR, CRP, and procalcitonin assist in differentiating infections from non-infection in patients without autoimmune disease. CRP is a better indicator of infection in SLE and normal subjects, and CRP and procalcitonin in overall group. However, in the presence of inflammatory autoimmune rheumatic diseases, the base elevation of these parameters and the skewed inflammatory response need to be considered, while interpreting the parameters. This pilot study opens up new avenues in defining newer scoring systems considering the pre-existing inflammatory autoimmune rheumatic diseases.

Competing interests

The authors declare that they have no competing interests.

Contribution

All the authors have contributed equally to the conceptualization, data capturing and developing the content.

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References

1. Lv F, Song LJ, Li XF. Combined measurement of multiple acute phase reactants to predict relapse of rheumatoid arthritis. Int J Rheum Dis. 2015 Sep;18(7):725-30.
2. Ospina FE, Echeverri A, Zambrano D, Suso J-P, Martínez-Blanco J, Cañas CA, et al. Distinguishing infections vs flares in patients with systemic lupus erythematosus. Rheumatology. 2017 April; 56(suppl_1): i46–i54.
3. Chandrashekara S, Renuka P, Anupama KR, Devaraj, Prakruti J, Veena R. Scoring system based on inflammatory parameters to screen for infection and disease flare and bacterial versus viral infections in the background of inflammatory rheumatic disease. Indian J Rheumatol. 2019 (suppl):S111-12.
4. Kay J, Upchurch KS. ACR/EULAR 2010 rheumatoid arthritis classification criteria. Rheumatology. 2012 Dec 1;51(suppl_6):vi5–9.
5. Aringer M, Costenbader K, Daikh D, Brinks R, Mosca M, Ramsey-Goldman R, et al. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. Ann Rheum Dis. 2019 Sep;78(9):1151–9.
6. Bingham CO, Pohl C, Woodworth TG, Hewlett SE, May JE, Rahman MU, et al. Developing a standardized definition for disease "flare" in rheumatoid arthritis (OMERACT 9 Special Interest Group). J Rheumatol. 2009 Oct;36(10):2335–41.
7. Petri M, Kim MY, Kalunian KC, Grossman J, Hahn BH, Sammaritano LR, et al. Combined oral contraceptives in women with systemic lupus erythematosus. N Engl J Med. 2005 Dec 15;353(24):2550–8.
8. Epitools. [Internet]. 2021 [cited 2022 Feb 18]. Available from: https://epitools.ausvet.com.au/
9. Simon L, Gauvin F, Amre DK, Saint-Louis P, Lacroix J. Serum procalcitonin and C-reactive protein levels as markers of bacterial infection: a systematic review and meta-analysis. Clin Infect Dis. 2004 Jul 15;39(2):206–17.
10. Uzzan B, Cohen R, Nicolas P, Cucherat M, Perret G-Y.

Procalcitonin as a diagnostic test for sepsis in critically ill adults and after surgery or trauma: a systematic review and meta-analysis. Crit Care Med. 2006 Jul;34(7):1996–2003.
11. Bador K, Intan S, Hussin S, Gafor A. Serum procalcitonin has negative predictive value for bacterial infection in active systemic lupus erythematosus. Lupus. 2012 Oct 1;21(11):1172–7.
12. Shin KC, Lee YJ, Kang SW, Baek HJ, Lee EB, Kim HA, et al. Serum procalcitonin measurement for detection of intercurrent infection in febrile patients with SLE. Ann Rheum Dis. 2001 Oct;60(10):988–9.
13. Song GG, Bae S-C, Lee YH. Diagnostic accuracies of procalcitonin and C-reactive protein for bacterial infection in patients with systemic rheumatic diseases: a meta-analysis. Clin Exp Rheumatol. 2015 Apr;33(2):166–73.
14. Kim H-A, Jeon J-Y, An J-M, Koh B-R, Suh C-H. C-reactive Protein Is a More Sensitive and Specific Marker for Diagnosing Bacterial Infections in Systemic Lupus Erythematosus Compared to S100A8/A9 and Procalcitonin. The Journal of Rheumatology. 2012 Apr 1;39(4):728–34.
15. Tamaki K, Kogata Y, Sugiyama D, Nakazawa T, Hatachi S, Kageyama G, et al. Diagnostic accuracy of serum procalcitonin concentrations for detecting systemic bacterial infection in patients with systemic autoimmune diseases. J Rheumatol. 2008 Jan;35(1):114–9.
16. Wang J, Niu R, Jiang L, Wang Y, Shao X, Wu M, et al. The diagnostic values of C-reactive protein and procalcitonin in identifying systemic lupus erythematosus infection and disease activity. Medicine (Baltimore). 2019 Aug;98(33):e16798.
17. Broca-Garcia BE, Saavedra MA, Martínez-Bencomo MA, Montes-Cortes DH, Jara LJ, Medina G, et al. Utility of neutrophil-to-lymphocyte ratio plus C-reactive protein for infection in systemic lupus erythematosus. Lupus. 2019 Feb 1;28(2):217–22.
18. Kim H-A, Jung J-Y, Suh C-H. Usefulness of neutrophil-to-lymphocyte ratio as a biomarker for diagnosing infections in patients with systemic lupus erythematosus. Clin Rheumatol. 2017 Nov 1;36(11):2479–85.
19. Wang L, Wang C, Jia X, Yang M, Yu J. Relationship between Neutrophil-to-Lymphocyte Ratio and Systemic Lupus Erythematosus: A Meta-analysis. Clinics (Sao Paulo). 2020;75:e1450.
20. Nagai Y, Yokogawa N, Shimada K, Sugii S. Utility of the neutrophil-to-lymphocyte ratio for predicting bacterial infection in patients with rheumatoid arthritis receiving Tocilizumab. Rheumatol Int. 2020 Dec 1;40(12):2039–46.
21. Chandrashekara S, Mukhtar Ahmad M, Renuka P, Anupama KR, Renuka K. Characterization of neutrophil-to-lymphocyte ratio as a measure of inflammation in rheumatoid arthritis. Int J Rheum Dis. 2017 Oct;20(10):1457–67.
22. Sato H, Tanabe N, Murasawa A, Otaki Y, Sakai T, Sugaya T, et al. Procalcitonin is a specific marker for detecting bacterial infection in patients with rheumatoid arthritis. J Rheumatol. 2012 Aug;39(8):1517–23.