Original Research Article

Systemic inflammatory index a simple marker of thrombo-inflammation and prognosis in severe COVID-19 patients

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ABSTRACT

Background: COVID-19 pandemic has challenged the healthcare resources globally, inspiring the need for identifying simple, economical biomarkers. COVID-19 is an immune-inflammatory disorder and systemic inflammatory index (SII) derived from the peripheral blood has been proposed as a marker.
Methods: Retrospective study of severe COVID-19 hospitalized patients (total N=154 including diabetic subset N=57). Data regarding hematological variables such as absolute neutrophil count (ANC), absolute lymphocyte count (ALC), platelet count along with thrombo-inflammatory proteins, D-dimer, C-reactive protein (CRP) were extracted from medical records. SII was calculated from ANC×platelets/lymphocyte count. Clinically applicable cut-offs were derived using the receiver operating characteristic curve (ROC) analysis for SII, CRP and D-dimer. Correlations between hematological parameters and D-dimer, CRP were analyzed to validate them as biomarkers of thrombo-inflammation and as predictors of clinical outcome.
Results: Among 154 severe COVID-19 patients, significant association with mortality was seen with respect to ANC (p<0.001), SII (p=0.01), CRP (p=0.004) and D-dimer (p=0.001). In the total COHORT, based on ROC curve, applicable cut-off for outcome prediction were for SII 14.85×10^5 (area under curve (AUC)-0.691, sensitivity-67%, specificity-64%, odds ratio (OR)-3.44), CRP 19.7 mg/l (AUC-0.718, OR-5.71), D-dimer 0.285 mcg/ml (AUC-0.773, OR-6.94) respectively. In the diabetic subset, the cut-offs for SII 14.85×10^5 (AUC-0.68, sensitivity-80%, specificity-54%, OR-4.7), CRP 52.5 mg/l (AUC-0.723, OR-5.36) and D-dimer 0.285 mcg/ml (AUC-0.771, OR-11.3) respectively.
Conclusions: Clinically applicable thresholds for SII serve as reliable biomarkers of thrombo-inflammation and prognosis in severe COVID-19 patients. Diabetic patients with similar thresholds had higher risk and prediction for mortality. In the resource constrained health care settings, who might not afford D-dimer, SII may serve as an economical bio-maker.

Keywords: Systemic inflammatory index, Severe COVID-19, Thrombo-inflammation, Diabetes mellitus

INTRODUCTION

COVID-19 (Coronavirus Disease 2019) pandemic has adversely affected the health care settings globally, with an explosive rise in the severe cases requiring intensive care, it posed a huge economic burden on the already meagre healthcare resources, especially of the developing countries.[1,2] Exploring simple biomarkers which can help in the management is the need of the hour.

Severe COVID-19 infection is now recognized as an immune-inflammatory vascular disorder resulting in critical illness comprising severe pneumonia, acute respiratory distress syndrome (ARDS), which can progress to cytotoxic storm and death.[3] Elderly patients and those with co-morbid conditions like diabetes mellitus, coronary artery disease, COPD have higher mortality.[4] Simple inflammatory biomarkers of inflammation may predict the clinical outcome of these patients. Hematological parameters such as neutrophil lymphocyte ratio (NLR),

platelet lymphocyte ratio (PLR), red cell distribution width (RDW), in certain studies have been shown to be prognostic markers in COVID-19 patients.[5] The role of TLC, ANC, derived neutrophil lymphocyte ratio (DNLR) and their predictive value in severe COVID-19 have also been reported.[6] SII, derived based on peripheral blood neutrophil, lymphocyte and platelet counts has been proposed as a novel indicator of the immune-inflammatory status.[7] Studies have indicated SII to be predictive of the prognosis of tumors and inflammatory diseases.[8] SII has been proposed to be a prognostic indicator to assess the in-hospital mortality and the development of ARDS in patients with COVID-19 and help for clinical risk assessment.[9,10]

We evaluated the role of the easily accessible peripheral blood-derived SII in hospitalized patients with severe COVID-19 as an immuno-inflammatory procoagulant marker in predicting the clinical outcome.

METHODS

We analyzed retrospective patient data of hospitalized patients with severe COVID-19.

After appropriate institutional ethics committee clearance, patients admitted with RT-PCR confirmed severe COVID-19, from 1 September to 30 September 2020 were included in our study.

Inclusion criteria

Severe patients were defined[11] as severe pneumonia (respiratory rate >30 /min, SpO_2 <90% at room air, <94% with O_2 supplementation), patients with ARDS and septic shock were included in the study.

Exclusion criteria

Patients with hematological malignancies, immune-deficiency states, receiving renal replacement therapy were excluded from the study.

The demographic, clinical and laboratory admission data of 154 patients were extracted from the medical case records including 57 diabetic patients. Baseline data of the hematological parameters from peripheral blood samples such as TLC, ANC, absolute lymphocyte count, platelet counts at hospital admission were collected.

SII was calculated using the formula,

$$SII = \frac{platelet\ count \times absolute\ neutrophil\ count}{absolute\ lymphocyte\ count}.$$

SII was correlated with mortality and evaluated as a prognostic marker.

In order to strengthen the validity of SII as a biomarker for thrombo-inflammation and as a prognosticator of the clinical outcome in severe COVID-19, correlation studies between SII and the immune-inflammatory protein-CRP and procoagulant protein D-dimer were done.

Statistical analysis

Continuous variables were expressed as appropriate mean±SD. Categorical variables were summarized as the frequencies and percentages. For categorical variables, Chi-square test and for continuous variables, independent t test was applied. A ROC curve analysis was used to determine the clinically applicable cut-off of SII for predicting mortality. The OR for mortality above this cut-off was calculated. The correlation of SII with immune-inflammatory proteins such as CRP and D-dimer was analyzed using Pearson's correlation co-efficient.

Similar analyses were performed among the diabetic subsets. P<0.05 was recognized as statistically significant. All statistical analyses were performed using SPSS v21.0 software.

RESULTS

Age

In our study, the total cohort comprised 154 patients, among which the diabetic subset included 57 patients. 43 of 154 patients (27.9%) expired, with the mean age being 63.81 years, while 111 patients (72%) recovered.

Among the diabetic subset, 21 of 57 (36.8%) patients expired with a mean age of 64.95 years, while 36 of 57 (63.1%) patients recovered with a mean age of 56.03 years. (Table 1).

Gender

In the total cohort among 154 patients, mortality was seen in 24% (12/50) females, while in males, the mortality was 29.8% (31/104) (p=0.452). Among diabetics, mortality was seen in 46.7% (7/15) females, while in males it was 33.3% (14/42) (p=0.358) (Table 1).

TLC

The mean TLC of the patients in the total cohort (N=154) was 10250 cells/mm^3 while among diabetics (N=57) it was 10500 cells/mm^3 (Table 1).

ANC

Mean absolute polymorph count of the patients in total cohort (N=154) was 7881 cells/mm^3 while among diabetics (N=57) was 8378 cells/mm^3 (Table 1).

Absolute lymphocyte counts

The mean absolute lymphocyte count in the total cohort (normal range=800-5000 cells/mm^3) was 2079 cells/mm^3, while in the diabetic subset was 1429 cells/mm^3 (Table 1).

Platelet count

The mean platelet count in the total cohort (normal range=1.5×10^5-4×10^5) was 2.87×10^5, while in the diabetic subset 3.04×10^5 (Table 1).

PLR

In the total cohort, PLR showed no significant association with mortality (p=0.792). Similar results were also observed in the diabetic subset (p=0.264) (Table 1).

SII

A statistically significant association of SII with mortality both in total (OR=3.44, p=0.01) and in the diabetic subset (OR=4.7, p=0.017) was seen.

In the total cohort (N=154) mean SII of the patients was 19×10^5, while among the diabetic subset (N=57) it was 26×10^5 (Table 1).

Using Younden's index for deriving the highest sensitivity (67%) and specificity (64%) in the ROC curve, with an AUC of 0.691, an applicable cut off for the SII in the total cohort was 14.85×10^5, which had an OR of 3.44 in predicting the mortality (Table 2) (Figure 1).

In the diabetic subset, an AUC for SII was 0.68, with similar cut-offs of SII at a sensitivity of 80% and specificity of 54% diabetics had a similar odds ratio of 4.7 in predicting the mortality (Table 2) (Figure 2).
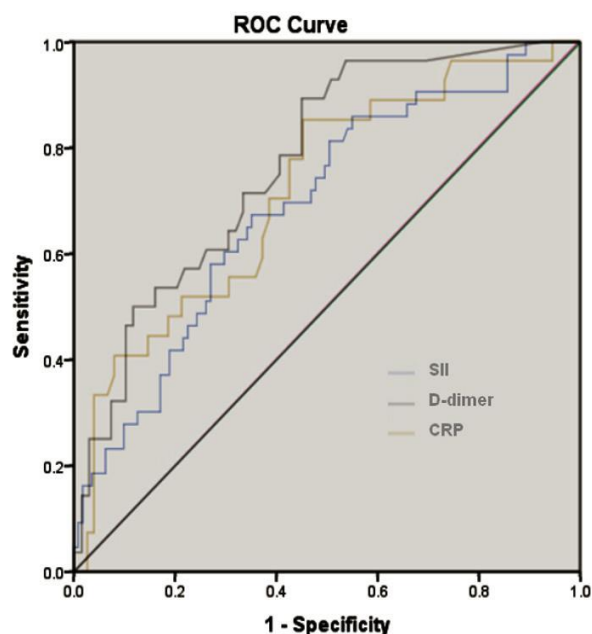

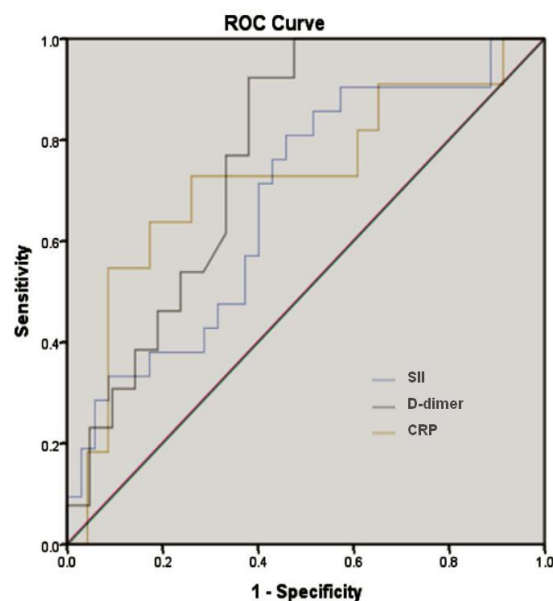**Figure 1: ROC curve analysis of total cohort including SII, (AUC=0.691), CRP (AUC=0.718) and D-dimer (AUC=0.773).**

Figure 2: ROC curve analysis for diabetic cohort, including SII, (AUC=0.68), CRP (AUC=0.723) and D-dimer (AUC=0.771).

CRP

CRP has a positive correlation with mortality, which was statistically significant (p=0.004). For total cohort cut-off from ROC curve with AUC 0.718 with a sensitivity of 85% and specificity of 54.6% was 19.7mg/l (Table 2).

In the diabetic subset, CRP has a positive correlation with mortality, which was statistically significant (p=0.045). The mean CRP in the diabetic cohort 74.72 mg/l, while among those who expired, it was 116.3mg/l, while among those who survived, it was 54.78mg/l (Table 1) (Figure 1).

For diabetic cohort cut-off from ROC curve with AUC 0.723 with a sensitivity of 72.72% and specificity 73.91% was 52.5 mg/l (Table 2) (Figure 2).

D-dimer

D-dimer has a positive correlation with mortality, which was statistically significant (p=0.001). The mean D-dimer in the total cohort 1.04 mcg/ml. While among the expired D-dimer was 1.87 mcg/ml and among those who recovered was 0.7 mcg/ml (Table 1).

For the total cohort cut-off from the ROC curve with AUC 0.773 with a sensitivity of 89.2% and specificity, 55% was 0.28 mcg/ml for predicting mortality with an OR of 6.94 (Table 2) (Figure 1).

Table 1: Demographic and hematological parameters and their association with mortality in total cohort and diabetic subset.

Variables	Total (N=154)		DM (N=57)	
	Mean±SD	P* value	Mean±SD	P* value
Age	52.73	<0.01	59.31	0.009
Sex (male)	67.5%	0.452	73%	0.358
TLC	10250	<0.001	10500	0.002
ANC	7881	<0.001	8378	0.001
Eosinophils	263	0.051	251.3	0.194
Monocytes	394.1	0.598	385.96	0.913
Lymphocytes	2071	0.413	1429.2	0.803
Platelets	2.87×10^5	0.838	3.04×10^5	0.804
PLR	232.54	0.161	300	0.282
SII	19×10^5	0.01	26×10^5	0.017
CRP	50.65	0.004	74.72	0.045
D-dimer	1.04	0.001	1.24	0.042
Admission random glucose	235	0.078	291	0.236

*P value indicating a statistically significant association with mortality.

Table 2: AUC and applicable cut-offs with sensitivity, specificity and OR for mortality derived from the ROC curve for statistically significant hematological variables.

Variables	cohort	AUC	Cut-off	Sensitivity	Specificity	OR
SII	Total	0.691	14.85×10^5	67	64	3.44
	Diabetes mellitus	0.68	14.85×10^5	80	54	4.7
CRP	Total	0.718	19.7	85	54	5.71
	Diabetes mellitus	0.723	52.5	72.7	73.9	5.36
D-dimer	Total	0.773	0.285	89.2	55	6.94
	Diabetes mellitus	0.771	0.285	92.3	61.9	11.3

Table 3: Correlation of SII with thrombo-inflammatory proteins.

Parameters		r value	P value
CRP	Total	0.389	0.004
	Diabetes mellitus	0.373	0.045
D-dimer	Total	0.380	<0.001
	Diabetes mellitus	0.563	0.03

In the diabetic subset, the mean D-dimer was 1.24 mcg/ml, which was statistically significant with mortality (p=0.042). Cut-off from ROC curve with AUC 0.771 with a sensitivity of 92.3% and specificity 61.9% was 0.28 mcg/ml for predicting mortality with an OR of 11.3 (Table 2) (Figure 2).

Correlating SII with thromboinflammatory proteins

CRP and D-dimer

CRP versus SII

In the total cohort, SII was statistically significant with CRP (p=0.004) and a positive co-relation by Pearson's correlation coefficient (r=0.389) was seen. Similar results were also observed with the diabetic subset (p=0.045 and r=0.373) (Table 3).

D-dimer versus SII

In the total cohort, SII was highly statistically significant with D-dimer (p<0.001) and a positive co-relation by Pearson's correlation coefficient (r=0.380) was seen. In the diabetic subset also a significant association was seen (p=0.003, r=0.563) (Table 3).

Admission plasma glucose

Admission plasma glucose did not show any statistical significance with mortality in total (p=0.078) and diabetic subset (p=0.236) (Table 1).

There was also no statistically significant correlation with SII, CRP or D-dimer in both total and diabetic subset (Table 1).

DISCUSSION

SII is a novel immuno-haematological parameter studied as a biomarker, which comprehensively summarizes the balance of host immune-inflammatory and procoagulative status, calculated with the formula,

$$SII = \frac{platelet\ counts \times neutrophil\ counts}{lymphocyte\ counts}.$$

It was suggested to be a prognostic biomarker in sepsis patients and in certain lung, gastro-intestinal malignancies and coronary artery disease.[12-14] Similarly, Fois et al showed that SII on admission independently predicts in-hospital mortality in COVID-19 patients and may assist with early risk stratification in this group.[9] In contrast, our study focused on SII in severe COVID-19, from a resource constraint hospital setting including a diabetic subset and its correlation with inflammatory and procoagulant proteins.

In our study, the total cohort comprised of 154 patients, among which the diabetic subset included 57 patients. 27.9% (43 of 57 patients) in the total cohort and 36.8% (21 of 57) patients in the diabetic subset expired suggesting that diabetic patients had a higher mortality.

Peripheral blood cell count abnormalities such as neutrophilia and lymphopenia are associated with disease severity and mortality in severe COVID-19 patients reported elsewhere.[15] Whereas in our study, more than 50% of the deceased among both groups had leukocytosis and a significant number of patients also had normal leukocyte counts. In line with other studies, our study showed neutrophilia with a mean absolute neutrophil count of 7881 cells/mm^3 (normal range=2500-6000 cells/mm^3), but there was no lymphocytopenia, showing a mean absolute lymphocyte count of 2070 cells/mm^3 (normal range=800-5000 cells/mm^3).

In the host, as part of the initial immunological defense against infection, polymorphonuclear leucocytes took the lead.[16] Neutrophil phagocytosis and extracellular trap formation result in bactericidal and fungicidal actions; however, their role in viral infection is less clear.[17] Reactive oxygen species released from activated leucocytes induce cell DNA and incite a response resulting in antibody-dependent cell-mediated cytotoxicity.[18]

SARS-COV-2 infects T cells through the CD147-spike protein and angiotensin-converting enzyme 2 (ACE2) receptors, resulting in a decreased population of CD3+, CD4+ and CD8+ T lymphocytes and an increased number of regulatory T cells.[19] Lymphocytes and endothelial cells produce virus-related inflammatory factors such as interleukin-6 and interleukin-8, tumor necrosis factor-alpha (TNF-alfa) and granulocyte colony-stimulating factor (G-CSF) and interferon-gamma factors (IGFs), activating neutrphils.[20] This immune-inflammatory vasculitis cascade triggers pro-inflammatory and procoagulant proteins resulting in extensive microvascular dysfunction and widespread organ damage.[21] Type 2 diabetes is a chronic metabolic disorder associated with inflammation as a key pathophysiologic process involving various systems such as adipose tissue, pancreatic beta cell, gut microbiota, skeletal muscle, neural system. In addition immune-inflammatory cells such as T cells, B cells, monocyte-macrophages and NK cells play an active role along with adipocytokines in aggravating the inflammation.[22] Diabetes is also a procoagulant state and SII, which measures immune dysregulation and platelet function has not yet been studied in diabetes. Our study highlighted the role of SII as a marker of thrombo-inflammation in diabetics with severe COVID-19.

PLR

The role of platelets in inflammation is important. Retrospective analysis showed that about one-third of the study population suffered thrombocytopenia, which suggested organ dysfunction and physiological disorder.[23] Clinically, Yang et al indicated that the nadir platelet counts were related to an increased risk of in-hospital mortality and the lower platelet count has a greater risk of death.[24]

The shift in platelet and lymphocyte counts prevailing in acute inflammatory and pro-thrombotic states is reflected by the PLR which has also been studied as a sensitive indicator of the degree of cytokine storm in COVID-19.[25] But in contrast to this finding, no significant association was seen between PLR and mortality in our study in both total (p=0.792) and diabetic cohorts (p=0.264).

SII

However, SII is an indicator of the combined inflammatory response due to neutrophil, lymphocyte and platelet counts. Our study analyzed correlative data of SII as a thrombo-inflammatory prognostic marker in patients with severe COVID-19. A remarkable finding of our study is that a diabetic subset (N=57) was separately analyzed, as diabetes itself being an inflammatory disorder, was the commonest co-morbidity in COVID-19 patients.[26] And an interesting finding was that the diabetic subset had a higher mean SII 21×10^5, compared to total cohort which was 19×10^5.

Applicable cut-offs of SII for predicting mortality by ROC curves

Fois et al with an AUC cut-off of 0.625, predicted prognostic accuracy for survival with a sensitivity and specificity of 55% and 75%, respectively though not statistically significant.[9] However, in our study in the total cohort, an SII at a cut-off of 14.85×10^5 (AUC=0.691, the sensitivity of 67% and specificity of 64%) had an OR of 3.44 in predicting the mortality.

In the diabetic subset, an SII at a similar cut-off (AUC=0.68, the sensitivity of 80% and specificity of 54%), diabetics had an OR of 4.7 in predicting the mortality. It was interesting to note that though diabetic patients had a higher mean SII (21×10^5 versus 19×10^5), with similar cut-offs in both groups (14.85×10^5) diabetics had a greater OR for mortality. This suggested that the risk of thrombo-inflammation was higher in diabetics and early recognition and appropriate intervention may result in favorable outcomes.

In order to strengthen the validity of SII as a biomarker of thrombo-inflammation and clinical outcome, the correlations between SII with CRP and D-dimer were assessed.

Inflammatory markers and their correlations with mortality and SII

CRP and mortality

CRP is an inflammatory marker, and its levels often correlate with the severity of the infection. CRP levels can activate the complement and enhance phagocytosis.[27] Based on ROC curve analysis CRP at a cut off 19.7mg/l in the total cohort (AUC=0.718, sensitivity=85%, specificity=54% with an OR=5.71) and 52.5mg/l in diabetic subset (AUC=0.723, sensitivity=72.7, specificity=73.9% with an OR=5.36) correlated well and predicted mortality.

SII and CRP correlation

SII had a statistically significant positive correlation with CRP (total cohort p=0.004, r=0.389, in diabetic subset p=0.045, r=0.373), suggesting it to be a simple biomarker of inflammation.

D-dimer and mortality

Severe COVID-19 is a major cause of morbidity and mortality because of thrombotic complications. They appear to be a result of the interplay between inflammation and the coagulation system or thrombo-inflammation. Abnormal coagulation parameters such as elevated D-dimer level and fibrin degradation products results in a hypercoagulable state.[28] D-dimer is a fibrin degradation product (FDP), contains two D fragments of the fibrin protein joined by a cross-link as a result of fibrinolysis.[29] D-dimer concentration in serum is a marker of thrombo-embolic disease.[30] A four-fold increase in this protein is a strong predictor of mortality in those suffering from COVID-19.[31]

D-dimer at a cut off (ROC curve analysis) in total cohort of 0.285 mcg/ml (AUC=0.773, sensitivity=92.3%, specificity=61.9% with an OR=6.94) and 0.285 mcg/ml in diabetic subset (AUC=0.771, sensitivity=92.3%, specificity=61.9%, OR=11.3) correlated with mortality.

SII and D-dimer correlation

SII also had a statistically significant correlation with D-dimer (total cohort p<0.001, r=0.380), in diabetic subset (p=0.003, r=0.563) suggesting it to be a simple biomarker of thrombo-inflammation.

These findings from our study validate SII as a simple, reliable biomarker of thrombo-inflammation from the pathophysiologic perspective and its role in predicting the clinical outcome of the hospitalized severe COVID-19 patients.

Admission plasma glucose

Correlation with admission plasma glucose

At admission, random plasma glucose levels were not shown to have any significant correlation with SII, CRP, D-dimer in both the total and diabetic subset (p=0.078 and p=0.236, respectively) (Table 1). It was to be noted that for the diabetic subset, the inclusion criteria were confirmed history of diabetes and history of anti-diabetic medication usage. This was not a comparison study between diabetics and non-diabetics. HbA1c could not be done for all patients due to resource limitations during the COVID-19 pandemic. The combination of various factors such as the diabetic subsets inclusion, few cases of de-novo diabetes mellitus, stress hyperglycemia, COVID-19 related hyperglycemia could explain the mean plasma glucose (235 mg/dl) (Table 1).

The limitations of the study were its retrospective nature and its relatively small sample size. Prospective studies with a larger patient base across different health care settings may establish SII as a simple and economical tool in the treatment of COVID-19 patients.

CONCLUSION

Clinically applicable thresholds for SII derived from an easily accessible peripheral blood sample can serve as an economical biomarker of thrombo-inflammation and prognosis, in severe COVID-19 infection. Diabetic patients had higher mean SII levels and the risk of thrombo-inflammation and death are high even with similar cut-offs in predicting mortality.

The significant correlation between SII and D-dimer validates its role as a simple, economical tool in early identification of procoagulant inflammatory status especially in the resource-constrained health care settings who may not be able to afford D-dimer assessments in the setting of severe COVID-19.

SII may become a powerful tool in early risk stratification and effective management with widespread clinical usage.

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