Original Article

Influence of laboratory biomarkers on inflammatory indices for assessing severity progression in COVID-19 cases

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Abstract

Background and Objective: This study explored the role of various laboratory biomarkers on inflammatory indices for predicting disease progression toward severity in COVID-19 patients.**Methods:** This retrospective study was conducted on 1233 adults confirmed for COVID-19. The participants were grouped undermild, moderate, and severe grade disease. Serum bio-inflammatory index (SBII) and systemic inflammatory index (SII) were calculated and correlated with disease severity. The study variables, including clinical details and laboratory variables, were analyzed for impact on the inflammatory indices and severity status using a sequential multiple regression model to determine the predictors for mortality. Receiver operating characteristics defined the cut-off values for severity. **Results:** Among the study population, 56.2%, 20.7%, and 23.1% were categorized as mild, moderate, and severe COVID-19 cases. Diabetes with hypertension was the most prevalent comorbid condition. The odds for males to have the severe form of the disease was 1.6 times (95% CI = 1.18–2.18, $P = 0.002$). The median (inter-quartile-range) of SBII was 549 (387.84–741.34) and SII was 2097.6 (1113.9–4153.73) in severe cases. Serum urea, electrolytes, gamma-glutamyl transferase, red-cell distribution width-to-hematocrit ratio, monocytopenia, and eosinopenia exhibited a significant influence on the SpO_2, SBII, and SII. Both SBII ($r = -0.582$, $P < 0.001$) and SII ($r = -0.52$, $P < 0.001$) strongly correlated inversely with SpO_2 values [Figures 3a and 3b]. More than 80% of individuals admitted with severe grade COVID-19 had values of more than 50th percentile of SBII and SII. The sensitivity and specificity of SBII at 343.67 for severity were 81.4% and 70.1%, respectively. SII exhibited 77.2% sensitivity and 70.8% specificity at 998.72. **Conclusion:** Serial monitoring of the routinely available biomarkers would provide considerable input regarding inflammatory status and severity progression in COVID-19.

Keywords: Hemogram, ROC curve, routine biomarkers, serum bio-inflammatory index, systemic inflammatory index

Introduction

The pandemic of novel coronavirus disease of 2019 (COVID-19) has led to numerous losses of life globally. Early diagnosis by evaluation of critical biomarkers at an early stage might be lifesaving.

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Received: 08-10-2021 **Revised:** 07-12-2021
Accepted: 16-12-2021 **Published:** 14-05-2022

Access this article online

Quick Response Code:

Website: www.jfmpc.com

DOI: 10.4103/jfmpc.jfmpc_2014_21

Studies have been conducted to identify critical biomarkers that can predict disease severity and survival outcome. Various biomarkers and radiological markers have been identified that can predict the adverse effect. However, these specialized investigations can only be performed in higher institutes and highly equipped laboratories. This holds back the criteria for early diagnosis in remote areas that lack such infrastructure resulting in increased mortality.

Previous studies reflected that a deranged renal function test (RFT) profile, dyselectrolemia, hyperbilirubinemia, deranged

How to cite this article: Prasad S, Patel S, Behera AK, Sahu D, Shah S, Nanda R, *et al*. Influence of laboratory biomarkers on inflammatory indices for assessing severity progression in COVID-19 cases. J Family Med Prim Care 2022;11:2056-72.

liver enzymes, and hypoproteinemia substantially influence the critical outcome.[1–5] Similarly, anemia, leucocytosis, leucopenia, neutropenia, thrombocytopenia, and eosinophilia have also been worse prognoses.[6–10]

A moderate and severe rise in inflammatory markers like high-sensitivity C-reactive protein (hs-CRP), lactate dehydrogenase (LDH), and ferritin were associated with mortality.[11–15] Understanding the relationship between these biomarkers would be crucial to early assessing severity in rural settings with limited facilities in developing countries like India to prevail timely intervention. The study results would enable the primary care physicians to evaluate the patients based on the basic investigations that can be performed in their set-up.

There are limited studies that explored the routinely investigated parameters in predicting the COVID-19 disease severity in an Indian setup. Therefore, the study aimed to explore the role of various laboratory biomarkers as predictors of inflammatory status and disease severity in COVID-19 confirmed cases and their dynamicity with relation to the inflammatory markers.

Materials and Methods

Study subjects

A retrospective observational study was conducted on one thousand two hundred thirty-three (N = 1233) adults of more than 18 years old admitted to our institute for the treatment of COVID-19. All confirmed cases for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) by reverse transcriptase polymerase chain reaction (RT-PCR) were included for the study. The study duration was for 4 months and started after ethical approval from the institute ethics committee. A consent waiver was approved for this study, and the participants' identification remains coded. The investigators followed Helsinki's guidelines for good clinical practice. The study participants were grouped as mild, moderate, and severe as per the oxygen saturation (SpO_2) by pulse oximetry of the finger-tip values at the time of admission. Patients with SpO_2 values above 94% were considered as mild grade COVID-19. Those with SpO_2 values of 91% to 94% were grouped as moderate grade, and those with SpO_2 less than equal to 90% were grouped as severe grade cases.

COVID-19 severity score was assessed as per classification approved by the Clinical Management Protocol for COVID-19, Government of India, Ministry of Health and Family Welfare, Directorate General of Health Services.[16]

Clinical and laboratory data collection and inclusion-exclusion criteria

The investigators collected details of the patient's demography and clinical presentation from the medical record section of the institute. The laboratory parameters investigated within 24 h of admission were noted. Only RT-PCR confirmed cases were included in the study. Patients with incomplete data (clinical and laboratory reports), pregnant and lactating females, and who had blood transfusions in the last 12 weeks were excluded from the study.

After entering the completed clinical data, according to the numbers of clinical signs, symptoms, and associated comorbidity, the investigator assigned a comorbidity score and a total clinical severity (TCS) score to each patient.

The inflammatory markers considered for analysis in this study were hs-CRP, LDH, and ferritin. The complete blood count (CBC) parameters consisted of blood hemoglobin (Hb), hematocrit (Hct), red blood cell (RBC) count, mean corpuscular volume (MCV), mean corpuscular Hb (MCH), mean corpuscular Hb concentration (MCHC), red cell distribution width (RDW), total leucocyte count (TLC), neutrophil count (NC), lymphocyte count (LC), monocyte count (MC), eosinophil count (EC), platelet count (PC), erythrocyte sedimentation rate (ESR), prothrombin time (PT), international normalized ratio (INR), and activated plasma thromboplastin time (APTT).

Although not reported, the investigators calculated the following ratios for analysis purposes:

Serum glutamate-oxaloacetate transaminase-to-serum glutamate-pyruvate transaminase (SGOT/SGPT), albumin-to-globulin (AGR), CRP-to albumin ratio(CAR), RDW-to-Hct, (RDW/Hct), Hb-to-RDW (Hb/RDW), neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio(LMR), and platelet-to-lymphocyte ratio(PLR).

The inflammatory status in the study population was calculated by using two indices, serum bio-inflammatory index (SBII) and systemic inflammatory index (SII). SBII was calculated as = [sum the serum values of all the three inflammatory markers (hs-CRP, LDH, and ferritin)]/(three). The formula used for SII was = (PC*NC)/LC.

Statistical analysis

All statistical analyses were performed in SPSS software version 20 (IBM Corp.). The distribution of comorbid conditions was presented in percentages and compared between the groups using the Chi-square test. The continuous variables were tabulated for mean with standard deviation and median with interquartile range. A dual depiction of the data would better understand the distribution pattern in the COVID-19 cases. The first quartile and third quartile values were referred to as IQR. Analysis of variance (ANOVA) test for parametric variables and Kruskal-Wallis one-way ANOVA for the nonparametric test were applied to compare data subsets.

The relationship of the study variables with the inflammatory index and severity of the disease was analyzed by univariate and multivariate regression analyses. Individual predictor variable for the inflammatory and severity status in the study population was established using sequential multiple regression model. Receiver

operating characteristics (ROC) with area-under-curve (AUC) and cut-off values were analyzed for the severity of the disease. A *P* value less than 0.05 was considered for statistical significance.

Results

Demographic variables and clinical details in the study population

Among the study population (N = 1233), 56.2% (n = 693), 20.7% (n = 255), and 23.1% (n = 285) were grouped under mild, moderate, and severe forms of COVID-19, respectively. As depicted in [Table 1], nearly 43% of admitted patients had no associated comorbidities. Diabetes mellitus with hypertension (17%) was most prevalent in the study population.

Table 1: Percentage distribution of comorbidities associated with COVID-19 patients

Comorbidities	Counts	Percentage
None	539	43.7
Cancer	5	0.4
CAD	14	1.1
DM	156	12.7
DM, HTN	210	17
CAD, COPD	2	0.2
CKD	2	0.2
COPD	5	0.4
Asthma	2	0.2
CKD, DM, HTN	10	0.8
DM, CAD	10	0.8
DM, CKD	3	0.2
HTN	175	14.2
HTN, CAD	14	1.1
HTN, CKD	4	0.3
DM, COPD	5	0.4
DM, CVA	1	0.1
DM, HTN, CAD	34	2.8
DM, HTN, COPD	3	0.2
DM, HTN, CAD, CKD	1	0.1
DM, HTN, CAD, TB	2	0.2
DM, HTN, CVA	1	0.1
Tuberculosis	5	0.4
DM, HTN, TB	1	0.1
DM, TB	3	0.2
HTN, COPD	7	0.6
HTN, TB	2	0.2
DM, Cancer Bone	1	0.1
DM, Hypothyroidism	1	0.1
HTN, Renal transplant	2	0.2
Hepatitis-B	1	0.1
HTN, Cancer Breast	1	0.1
Hypotension	1	0.1
Hyperthyroidism	1	0.1
Hypothyroidism	3	0.2
SCD	3	0.2
SCD, GDM	1	0.1
TB, CKD, Hepatitis-B	1	0.1
Thalessemia major	1	0.1

Almost 49% of individuals admitted with mild COVID-19 had no associated comorbidities [Figure 1], whereas 28.8% severe cases had a score of 2. The number of males was more in each group as depicted in [Figure 2] (χ^2 = 13.03, *P* = 0.001). The odds for being admitted with severe grade disease in males was 1.6 times (95% CI = 1.18–2.18, *P* = 0.002).

Comparison of study variables in the study population

As illustrated in [Table 2], the mean age of 56.4 (12.9) years in severe cases was significantly higher than the other two (*P* < 0.001). The duration of hospital stay were lowest in mild cases (*P* < 0.001) with a median of 6 days. The TCS score in moderate and severe groups was higher than the milder group. All three serum inflammatory markers depicted a significant increase from mild to severe cases. The median (IQR) of urea was 50 (34–78.5) mg/dl, which was significantly raised than the mild and moderate cases (*P* < 0.001). Both sodium and potassium levels were significantly raised in severe grade COVID-19 cases. Serum liver enzymes, SGOT, SGPT, and ALP, were found to be greatly elevated in severe cases than the other groups (*P* < 0.001). Serum gamma-glutamyl transferase (GGT) was found raised in both moderate and severe cases than the milder form (*P* < 0.001). Total protein, albumin, and AGR showed a significant reduction trend from mild to severe grade disease, whereas the globulin values were higher in the moderate group than in mild cases (*P* = 0.014). CAR values showed an increasing trend (*P* < 0.001).

The hematocrit indices, Hb, RBC count, MCV, MCH, and MCHC were quite comparable between the groups. The median RDW of 14.1% was considerably higher in severe grade disease than the mild forms. Total leucocytes, neutrophils, NLR, PLR, and SII showed a sequential increase from mild to severe form of COVID-19. On the contrary, LC, MC, and EC depicted a reducing trend in these groups (*P* < 0.01). PT was substantially increased higher in moderate and severe cases than mild ones (*P* = 0.001).

Correlation of the inflammatory indices with SpO_2 in the study population

The correlation graphs depicted in [Figures 3a and 3b] indicated the significant inverse association between the

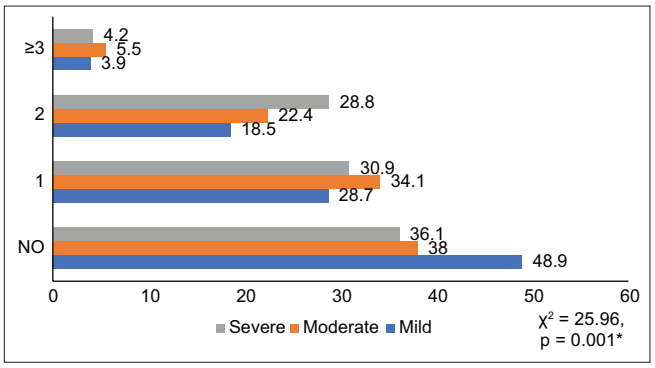

Figure 1: Frequency percentages of comorbidity score among the study groups

Table 2: Comparison of Mean (SD) and Median (IQR) values of the variables in the study groups (*n*=1233)

Variables (Units)	Mild *n*=693 (56.2%)		Moderate *n*=255 (20.7%)		Severe *n*=285 (23.1%)	
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
SpO_2 (%)	97.2 (1.5)	97 (96-98)	92.38 (1.5)	93 (91-94)	79.07 (10.3)	82 (72-87)
Age (years)	50.66 (16.7)	53 (36-64)	57.9 (14.5)*	59 (48-68)*	56.4 (12.9)^	57 (48-65.75)^
DOH (days)	7.04 (3.9)	6 (5-9)	8.86 (5.5)*	7 (5-11)*	9.83 (7.4)^	9 (5-12)^
TCS score	2.31 (1.6)	2 (1-3)	2.85 (1.4)*	3 (2-4)*	3.07 (1.3)^	3 (2-4)^
hs-CRP (mg/L)	30.46 (43.6)	11 (2-43)	70.27 (57.7)*	59 (19-108)*	96.98 (66.2)^#	93 (36-150)^#
LDH (U/L)	473.6 (238.4)	424.5 (290.8-593)	625.7 (282.1)*	562 (418-775)*	790.24 (320.4)^#	756 (525-988.5)^#
Ferritin (ng/mL)	277.1 (359.5)	153 (66-317.5)	489.14 (418.9)*	367 (202-647)*	852.3 (535.5)^#	771 (419-1239)^#
SBII	260.27 (172.03)	214.67 (147.67-320)	395.05 (202.39)*	355.67 (253.67-490.67)*	579.84 (250.18)^#	549 (387.84-741.34)^#
Urea (mg/dL)	30.79 (26.9)	24 (18-32.5)	51.99 (48.03)*	37 (24-59)*	69.1 (58.5)^#	50 (34-78.5)^#
Creatinine (mg/dL)	1.3 (1.4)	1.1 (0.9-1.2)	1.49 (1.8)	1.1 (0.9-1.4)	1.65 (2)^	1.1 (0.9-1.4)^
Uric Acid (mg/dL)	4.78 (1.8)	4.6 (3.6-5.7)	5.09 (2.5)	4.5 (3.5-5.9)	4.88 (2.8)	4.1 (3.1-5.8)
Na^+ (mmol/L)	137.92 (4.9)	139 (136-141)	137.73 (5.9)	138 (135-141)	139.25 (7.9)^#	138 (135-142)
K^+ (mmol/L)	4.05 (0.58)	4 (3.7-4.4)	4.3 (0.71)*	4.2 (3.8-4.7)*	4.46 (0.8)^#	4.4 (3.9-4.9)^#
Cl^- (mmol/L)	103.8 (4.5)	105 (101-107)	103.59 (5.6)	104 (100-106)	103.3 (7.3)	102 (99-106)
TBil (mg/dL)	0.75 (0.8)	0.6 (0.45-0.8)	0.82 (0.9)	0.63 (0.47-0.86)	0.93 (0.73)^#	0.73 (0.5-1.03)^#
DBil (mg/dL)	0.21 (0.43)	0.14 (0.1-0.2)	0.27 (0.6)	0.11 (0.25)	0.32 (0.39)^	0.2 (0.15-0.34)^
SGOT (U/L)	44.32 (71.7)	30 (22-43)	48.45 (50.6)	37 (26-56)	83.54 (160.1)^#	43 (28-71)^#
SGPT (U/L)	38.03 (48.5)	25 (15-42)	45.38 (44.2)	32 (20-51)	79.2 (145.6)^#	40 (26-73)^#
SGOT/SGPT	1.39 (0.7)	1.26 (0.92-1.69)	1.34 (0.8)	1.15 (0.88-1.67)	1.24 (0.7)^	1.12 (0.7-1.5)^
ALP (U/L)	87.71 (67.1)	72 (60-94)	81.59 (48)	71 (55-95)	103.5 (57.6)^#	89 (67.5-121)^#
GGT (U/L)	43.55 (54.9)	29 (18.5-47)	67.93 (89.5)*	43 (26-75)*	82.33 (87.4)^	60 (33-94)^
Total Protein (gm/dL)	6.99 (0.8)	7 (6.6-7.4)	6.71 (0.78)*	6.8 (6.3-7.2)*	6.39 (0.87)^#	6.4 (5.8-7)^#
Albumin (gm/dL)	3.81 (0.57)	3.9 (3.5-4.2)	3.4 (0.55)*	3.47 (3.1-3.8)*	3.12 (0.5)^#	3.15 (2.8-3.5)^#
Globulin (gm/dL)	3.17 (0.65)	3.1 (2.8-3.5)	3.3 (0.55)*	3.3 (2.9-3.7)*	3.3 (0.6)	3.3 (2.9-3.7)
AGR	1.24 (0.29)	1.24 (1.1-1.4)	1.06 (0.24)*	1.05 (0.9-1.2)*	0.98 (0.21)^#	0.97 (0.85-1.1)^#
CAR	0.89 (1.4)	0.28 (0.06-1.2)	2.19 (1.9)*	1.8 (0.5-3.1)*	3.2 (2.4)^#	2.9 (1.2-4.8)^#
Hb (gm/dL)	12.51 (2.01)	12.7 (11.3-13.8)	12.25 (2.1)	12.7 (11-13.7)	12.54 (2.44)	12.8 (11.2-14)
Hct (%)	38.09 (5.8)	38.4 (34.7-41.7)	37.3 (6)	37.9 (34.9-41)	38.5 (7.4)	38.9 (34.6-42.4)
RBC ($\times 10^{\wedge 6}$/L)	4.52 (0.76)	4.53 (4.11-4.99)	4.48 (0.77)	4.5 (4.05-4.9)	4.56 (0.95)	4.6 (4.01-5.13)
MCV (fL)	84.89 (8.3)	85.3 (80.3-89.9)	83.83 (9.03)	83.9 (79.1-89.6)	85.1 (8.9)	85.1 (79.6-89.9)
MCH (pg)	27.93 (3.5)	28.2 (26.1-30.1)	27.6 (3.7)	27.9 (25.8-29.7)	27.8 (3.4)	28 (25.7-30)
MCHC (gm/dL)	32.84 (1.6)	33 (31.9-34)	32.79 (1.6)	32.9 (31.8-33.8)	32.6 (1.7)	32.7 (31.5-33.8)
RDW (%)	14.3 (2.3)	13.8 (13-15)	14.61 (2.5)	14.1 (13-15.5)	14.87 (2.8)^	14.1 (13.3-15.6)^
RDW/Hct	0.39 (0.12)	0.36 (0.32-0.42)	0.41 (0.16)	0.37 (0.33-0.44)	0.41 (0.21)	0.36 (0.32-0.44)
Hb/RDW	0.89 (0.2)	0.93 (0.78-1.04)	0.87 (0.21)	0.9 (0.72-1.01)	0.87 (0.2)	0.9 (0.7-1.02)
TLC ($\times 10^{\wedge 3}$/L)	6.88 (3.3)	6.1 (4.7-8.2)	8.89 (4.7)*	7.9 (5.5-10.9)*	12.34 (7.2)^#	10.6 (7.3-15.8)^#
NC (%)	60.23 (14.2)	60 (50.2-70)	72.57 (12.9)*	73 (63.2-82.9)*	79.83 (12.4)^#	83 (74-89)^#
LC (%)	28 (12.5)	27 (19-35.7)	18.04 (10.6)*	17 (10-24.9)*	12.08 (9.5)^#	10 (5-16)^#
MC (%)	8.44 (3.7)	8 (6-10)	7.28 (3.6)*	7 (4.8-9.9)*	6.21 (3.7)^#	5.2 (3.6-8.7)^#
NLR	3.34 (4.4)	2.24 (1.4-3.7)	7.48 (8.9)*	4.4 (2.6-8.1)*	13.41 (14.3)^#	8.04 (4.6-16.8)^#
LMR	3.96 (2.7)	3.39 (2.2-4.8)	3.06 (2.9)*	2.29 (1.4-3.6)*	2.24 (1.7)^#	1.7 (1.01-2.9)^#
EC (%)	3.2 (2.3)	3 (1.7-5)	2.3 (2.2)*	2 (0.6-3.9)*	1.76 (1.9)^#	1.1 (0-2.6)^#
PC ($\times 10^{\wedge 3}$/L)	237.7 (98.6)	225 (166-281.5)	263.78 (122.7)*	250.5 (176.8-325)*	266.66 (136.2)^	248 (170.5-328)^
PLR	12.11 (14.8)	8.04 (5.4-13.1)	23.39 (22.47)*	15.22 (8.1-31.37)*	38.48 (40.4)^#	26.1 (14.5-46.3)^#
SI index	846.48 (1370.3)	472.81 (276.5-869.3)	1914.4 (2124.4)*	1057.7 (528-2596.2)*	3329.3 (3816.5)^#	2097.6 (1113.9-4153.73)^#
ESR (mm/hr)	60.41 (49.9)	45 (20-90.5)	82.2 (51.8)*	70 (40-130)*	74.9 (50.8)^	60 (32.5-115)^
PT (seconds)	10.88 (1.3)	10.7 (10.2-11.3)	11.14 (1.4)	10.9 (10.3-11.5)	11.76 (3.4)^#	11.2 (10.5-12)^#
INR	1.02 (0.14)	1 (0.9-1.1)	1.03 (0.15)	1 (1-1.1)	1.1 (0.4)^#	1 (1-1.1)^#
APTT (seconds)	29.97 (10.8)	28.9 (26.9-31.5)	31.45 (6.1)	30.4 (27.9-33.4)	32.37 (8.9)^	30.2 (28.1-33.9)^

*P<0.05 between mild and moderate cases; ^P<0.05 between mild and severe cases; #P<0.05 between moderate and severe cases. The full names are mentioned in the abbreviation section

inflammatory indices, SBII (r = −0.582, $P < 0.001$) and SII (r = −0.52, $P < 0.001$) with SpO_2 values. The SpO_2 level at admission was significantly low in individuals with higher SBII and SII. The SBII and SII values were categorized into four percentiles [Table 3]. Nearly 89% of the individuals admitted under severe grade COVID-19 had SBII values more than the 50th percentile (>288.67); 61.1% of severe cases had SBII of more than 476.18 (percentile group 4) [Figure 4a]. Similarly, almost 84% of severe cases depicted SBII more than the 50th percentile value of SII (>758.53), and 54.4% of

Table 3: Distribution of SpO_2% values within the percentile groups of the two inflammatory indices

Inflammatory indices	Percentile group	Mild	Moderate	Severe	Chi Square df, (*P*)
SBII	1 (<179.17)	271 (39.1)	27 (10.6)	10 (3.5)	423.856 (<0.001*)
	2 (179.18-288.67)	225 (32.5)	63 (24.7)	21 (7.4)	
	3 (288.68-476.17)	130 (18.8)	98 (38.4)	80 (28.1)	
	4 (476.18-1208.33)	67 (9.7)	67 (26.3)	174 (61.1)	
SII	1 (<363.98)	257 (37.1)	39 (15.3)	12 (4.2)	325.236 (<0.001*)
	2 (363.99-758.52)	227 (32.8)	47 (18.4)	34 (11.9)	
	3 (758.53-1878.04)	142 (20.5)	83 (32.5)	84 (29.5)	
	4 (1878.05-33847)	67 (9.7)	86 (33.7)	155 (54.4)	

Chi-Square df denotes Chi-Square value with degree of freedom; 1 denoted values below 25th percentiles, 2 denoted values between 25th to 50th percentiles, 3 denoted values between 50th to 75th percentiles and 4 denoted values between 75th to 100th percentiles

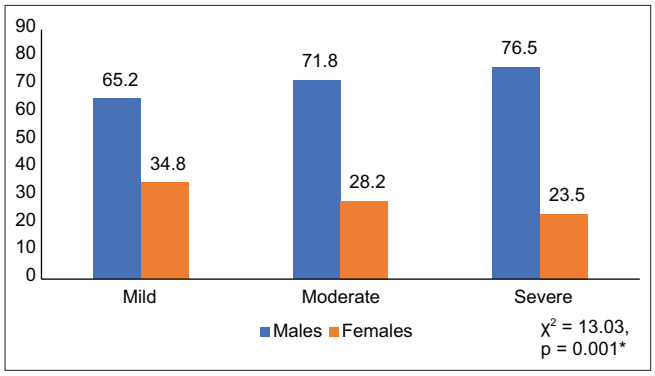

Figure 2: Gender distribution within the study groups

individuals were under percentile group 4 (>1878.05) [Table 4 and Figure 4b].

Univariate and multivariate regression analysis of the variables with inflammatory indices and severity status in the study population of COVID-19 cases [Table 4]

SBII

Age, comorbidity score, TCS score, and serum variables except for creatinine, total protein, and albumin revealed a significant positive relationship with the SBII. Total protein, albumin, and AGR noted an inverse association. Unlike the correlation with SpO_2, hematological indices like MCV, MCH, MCHC, RDW, RDW/Hct, TLC, NC, NLR, PLR, ESR, PT, INR, and APTT showed a positive association. However, RBC count, Hb/RDW, LC, MC, LMR, and EC correlated inversely with SBII.

SII

Similar to SBII. In agreement with SBII, SII showed a significant positive correlation with RDW and a negative correlation with Hb/RDW. The leucocyte, platelets, and other hematological indices demonstrated a similar association to that of SII.

The multivariate analysis recorded a significant relationship among TCS score, inflammatory markers, serum urea, and electrolytes with SpO_2. Liver markers failed to show a substantial degree of effect on SpO_2 except for serum GGT (0.013). Similarly, except for RDW/Hct ($P < 0.001$), TLC ($P < 0.001$),

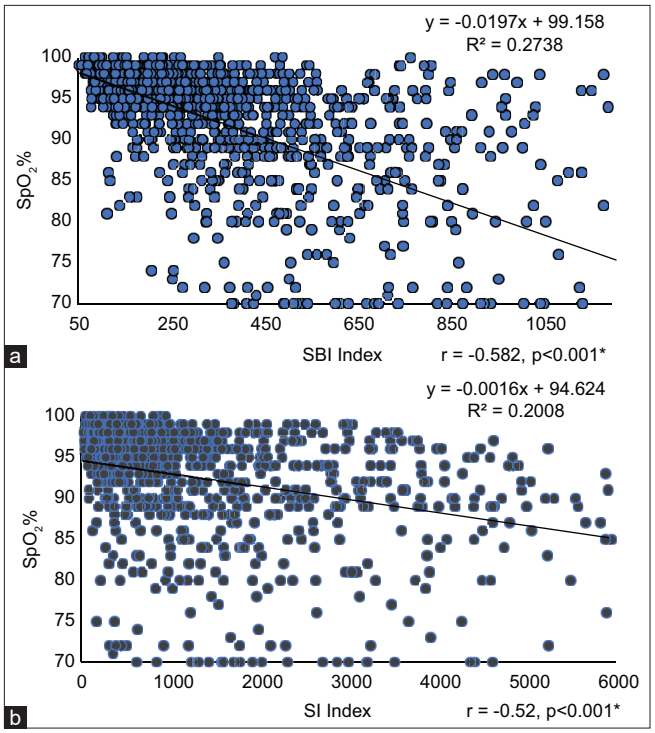

Figure 3: (a) Correlation between SpO_2% and SBII. (b) Correlation between SpO_2% and SII

NLR ($P = 0.021$), and ESR (0.031), other indices did not show any considerable impact on SpO_2. Both NLR ($P = 0.025$) and PLR ($P = 0.019$) revealed a significant influence on SBII. The leucocyte and platelet values were used for the calculation of SII, and hence, a significant correlation was observed. After adjusting all other variables, the study variables failed to exhibit any significant effect on SII as an independent predictor.

SpO_2

The grade of severity of the disease at the time of admission was assessed by the SpO_2 values. With an increase in age, SpO_2 levels were significantly lowered. Similarly, comorbidity, TCS, and inflammatory markers depicted a significant negative correlation ($P < 0.001$). Renal and hepatic biomarkers also showed an inverse relationship with SpO_2. On the contrary, total protein, albumin, and AGR correlated

Table 4: Relationship between the laboratory parameters with the inflammatory markers in study population (*n*=1233)

Variables (Units)	SBII (B)	*P*	SII (B)	*P*	SpO_2 (B)	*P*
Age (years)	0.094	0.001*	0.128	<0.001*	−0.165	<0.001*
Comorbidity score	0.076	0.008	0.054	0.059	−0.091	0.001*
TCS	0.144	<0.001*	0.111	<0.001*	−0.176	<0.001*
hs-CRP (mg/L)	0.563	<0.001*	0.295	<0.001*	−0.418	<0.001*
LDH (U/L)	0.797	<0.001*	0.252	<0.001*	−0.416	<0.001*
Ferritin (ng/mL)	0.923	<0.001*	0.285	<0.001*	−0.468	<0.001*
Urea (mg/dL)	0.416	<0.001*	0.346	<0.001*	−0.366	<0.001*
Creatinine (mg/dL)	0.206	<0.001*	0.106	<0.001*	−0.085	0.003*
Uric Acid (mg/dL)	0.053	0.062	0.102	<0.001*	−0.052	0.067
Na^+(mmol/L)	0.082	0.004*	0.118	<0.001*	−0.145	<0.001*
K^+ (mmol/L)	0.2	<0.001*	0.191	<0.001*	−0.238	<0.001*
Cl^- (mmol/L)	−0.105	<0.001*	0.024	0.391	−0.001	0.98
TBil (mg/dL)	0.225	<0.001*	0.068	0.016*	−0.101	<0.001*
DBil (mg/dL)	0.211	<0.001*	0.086	0.002*	−0.111	<0.001*
SGOT (U/L)	0.27	<0.001*	0.062	0.029*	−0.177	<0.001*
SGPT (U/L)	0.269	<0.001*	0.083	0.003*	−0.217	<0.001*
SGOT/SGPT	−0.011	0.697	−0.067	0.019*	0.069	0.016*
ALP (U/L)	0.224	<0.001*	0.073	0.011*	−0.102	<0.001*
GGT (U/L)	0.27	<0.001*	0.089	0.002*	−0.174	<0.001*
Total Protein (gm/dL)	−0.282	<0.001*	−0.230	<0.001*	0.287	<0.001*
Albumin (gm/dL)	−0.444	<0.001*	−0.368	<0.001*	0.436	<0.001*
Globulin (gm/dL)	0.06	0.036*	0.054	0.056	−0.044	0.12
AGR	−0.359	<0.001*	−0.296	<0.001*	0.341	<0.001*
CAR	0.576	<0.001*	0.324	<0.001*	−0.447	<0.001*
Hb (gm/dL)	−0.036	0.206	−0.023	0.417	0.011	0.89
Hct(%)	−0.052	0.067	−0.012	0.675	−0.033	0.246
RBC (×10^6/L)	−0.113	<0.001*	0.006	0.84	−0.023	0.427
MCV (FL)	0.127	<0.001*	−0.03	0.289	−0.008	0.768
MCH (pg)	0.121	<0.001*	−0.044	0.119	0.03	0.285
MCHC (gm/dL)	0.064	0.025*	−0.048	0.093	0.091	0.001*
RDW (%)	0.102	<0.001*	0.099	0.001*	−0.129	<0.001*
RDW/Hct	0.137	<0.001*	0.048	0.09	−0.097	0.001*
Hb/RDW	−0.072	0.011*	−0.078	0.006*	0.068	0.017*
TLC (×10^3/L)	0.392	<0.001*	0.611	<0.001*	−0.484	<0.001*
NC (%)	0.45	<0.001*	0.603	<0.001*	−0.479	<0.001*
LC (%)	−0.447	<0.001*	−0.579	<0.001*	0.455	<0.001*
MC (%)	−0.198	<0.001*	−0.316	<0.001*	0.256	<0.001*
NLR	0.363	<0.001*	0.848	<0.001*	−0.499	<0.001*
LMR	−0.223	<0.001*	−0.342	<0.001*	0.238	<0.001*
EC (%)	−0.196	<0.001*	−0.296	<0.001*	0.25	<0.001*
PC (×10^3/L)	0.052	0.69	0.341	<0.001*	0.053	0.065
PLR	0.32	<0.001*	0.997	<0.001*	−0.44	<0.001*
ESR (mm/hr)	0.148	<0.001*	0.096	0.001*	−0.077	0.007*
PT (seconds)	0.247	<0.001*	0.13	<0.001*	−0.166	<0.001*
INR	0.235	<0.001*	0.139	<0.001*	−0.163	<0.001*
APTT (seconds)	0.144	<0.001*	0.055	0.053	−0.082	0.004*

*Denotes significance at *P*<0.05; B denotes the coefficient for a variable when all other variables taken together; shaded area denotes significant for multivariate regression analysis; all other full names are mentioned in the abbreviation section

positively ($P < 0.001$). However, CAR depicted a significant inverse relationship with SpO_2.

SpO_2 correlated negatively with RDW% and RDW/Hct ($P < 0.01$), but positively with Hb/RDW ($P = 0.017$). An increase in TLC, NC, NLR, PLR, ESR, PT, INR, and APTT tend to lower SpO_2, whereas LC, MC, LMR, and EC showed a linear effect.

Predictors of severity in COVID-19 cases by sequential multiple regression model

The sequential multiple regression model in [Table 5] depicted that SpO_2 values at the time of admission were highly influenced by variables like gender, TCS score, serum inflammatory markers, urea, creatinine, potassium levels, liver enzymes such as ALP and GGT, hematological indices like RDW/Hct, MC, EC, and INR (model-6).

Table 5: Sequential multiple regression model to explore influence of predictor biomarkers on SpO_2

SpO_2	*R*	R^2	R^2 change	B coefficient	Beta coefficient	*P*
Model 1						
Gender	0.236	0.056	0.056	1.066	0.055	0.05
Age				−0.089	−0.156	<0.001*
Comorbidity score				0.921	0.093	0.014*
TCS score				−1.136	−0.194	<0.001*
Model 2						
Gender	0.562	0.316	0.26	−1.328	−.068	0.006*
Age				−.053	−.094	<.001*
Comorbidity score				0.655	0.066	0.041*
TCS				−.684	−.117	<.001*
hs-CRP				−.029	−.190	<.001*
LDH				−.006	−.183	<.001*
Ferritin				−.005	−.289	<.001*
Model 3						
Gender	0.613	0.375	0.06	−1.139	−.059	0.014*
Age				−.035	−.062	0.013*
Comorbidity score				0.709	0.072	0.024*
TCS Score				−.627	−.107	<.001*
hs-CRP				−.022	−.148	<.001*
LDH				−.004	−.145	<.001*
Ferritin				−.005	−.241	<.001*
Urea				−.067	−.328	<.001*
Creatinine				1.429	0.261	<.001*
Na^+				−.082	−.055	0.028*
K^+				−.904	−.069	0.006*
Model 4						
Gender	0.639	0.408	0.033	−1.205	−.062	0.011*
Age				−.023	−.041	0.111
Comorbidity score				0.687	0.069	0.026*
TCS Score				−.593	−.101	0.001*
hs-CRP				−.018	−.122	0.262
LDH				−.003	−.109	<.001*
Ferritin				−.004	−.209	<.001*
Urea				−.054	−.267	<.001*
Creatinine				1.169	0.214	<.001*
Na^+				−.098	−.065	0.009*
K^+				−.982	−.075	0.003*
SGOT				0.005	0.057	0.250
SGPT				−.011	−.104	0.033*
SGOT/SGPT				0.624	0.051	0.072
ALP				0.007	0.047	0.100
GGT				−.007	−.056	0.032*
Total protein				2.240	0.155	0.010*
Albumin				0.633	0.044	0.410
AGR				1.174	0.038	0.625
CAR				0.052	0.012	0.918
Model 5						
Gender	0.643	0.414	0.006	−.965	−.050	0.046*
Age				−.022	−.038	0.132
Comorbidity score				0.693	0.070	0.025*
TCS Score				−.608	−.104	0.001*
hs-CRP				−.019	−.129	0.235
LDH				−.003	−.102	<.001*
Ferritin				−.004	−.225	<.001*
Urea				−.056	−.276	<.001*
Creatinine				1.187	0.217	<.001*

Contd...

Table 5: Contd...

SpO_2	*R*	R^2	R^2 change	B coefficient	Beta coefficient	*P*
Na^+				−.074	−.049	0.053
K^+				−.844	−.065	0.011*
SGOT				0.004	0.041	0.408
SGPT				−.010	−.089	0.070
SGOT/SGPT				0.728	0.059	0.037*
ALP				0.006	0.044	0.123
GGT				−.007	−.056	0.033*
Total protein				2.120	0.147	0.015*
Albumin				0.802	0.056	0.299
AGR				1.419	0.045	0.555
CAR				0.119	0.027	0.816
Globulin				0.450	0.081	0.003*
MCHC				−.032	−.009	0.811
RDW				1.263	0.022	0.537
RDW/Hct				−.965	−.050	0.046*
Hb/RDW				−.022	−.038	0.132
Model 6						
Gender	0.688	0.473	0.06	−.959	−.049	0.041*
Age				−.024	−.041	0.094
Comorbidity score				0.542	0.055	0.068
TCS Score				−.537	−.092	0.002*
hs-CRP				−.017	−.114	0.286
LDH				−.002	−.079	0.004*
Ferritin				−.004	−.200	<.001*
Urea				−.027	−.133	0.003*
Creatinine				0.771	0.141	<.001*
Na^+				−.058	−.038	0.115
K^+				−.785	−.060	0.014*
SGOT				0.002	0.020	0.679
SGPT				−.006	−.054	0.254
SGOT/SGPT				0.548	0.044	0.106
ALP				0.010	0.067	0.016*
GGT				−.008	−.064	0.010*
Total protein				1.296	0.090	0.126
Albumin				0.494	0.034	0.504
AGR				1.012	0.032	0.662
CAR				−.011	−.003	0.982
Globulin				0.462	0.083	0.001*
MCHC				0.142	0.039	0.278
RDW				−2.585	−.045	0.203
RDW/Hct				−.236	−.139	<.001*
Hb/RDW				−.056	−.099	0.498
TLC				−.079	−.118	0.362
NC				0.074	0.031	0.499
LC				0.068	0.017	0.575
MC				−.167	−.177	<.001*
NLR				0.200	0.060	0.117
LMR				0.008	0.023	0.561
EC				0.013	0.073	0.002*
PLR				−.038	−.009	0.914
ESR				1.541	0.037	0.647
PT				−.004	−.004	0.840
INR				−.959	−.049	0.041*
APTT				−.024	−.041	0.094

*Denotes significance at $P<0.05$, B denotes the unstandardized coefficient for a variable, Beta denotes the standardized coefficient for a variable; all the full names are mentioned in the abbreviation section

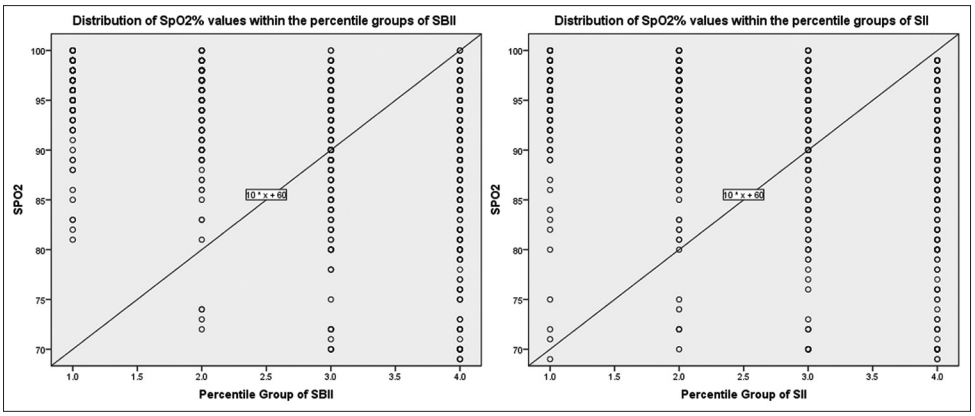

Figure 4: Distribution of SpO_2% values within the percentile groups of the two inflammatory indices

As showed in [Table 6], the predictor markers that reflected a significant impact on SBII were gender, comorbidity score, TCS score, renal parameters like urea, sodium, and chloride, serum GGT, CAR values, total RBC count, RDW, RDW/Hct, TLC, PT, and INR values (model-6).

The independent predictor variables for SII, as depicted in [Table 7], were serum urea, creatinine, SGOT/SGPT ratio, MC, and EC (model-6).

The negative regression of gender with SpO_2 indicated that male individuals had more chances for severity (OR: 95% CI = 1.603: 1.185–2.186; P = 0.001). TCS score, serum urea, serum GGT, RDW/Hct, MC, and EC significantly influenced the severity and inflammatory index of the COVID-19 admitted cases.

Receiver operating characteristic and cut-off values for laboratory variables for predicting severity in COVID-19 cases

The curves and cut-off values of ROC have been delineated in [Table 8] and [Figure 5]. The sensitivity and specificity of hs-CRP at 51.5 mg/L were, respectively, 70.5% and 70.3% for severity. Serum values of LDH at 560 U/L showed a sensitivity of 70.2% and specificity of 65.6%. A serum ferritin level of 359.5 ng/mL depicted the highest sensitivity of 80%. A value greater than 34.5 mg/dL of serum urea depicted 74% sensitivity for severe grade COVID-19. Serum potassium's sensitivity and specificity at 4.07 mmol/L and GGT at 70.9 U/L were 70.5% and 70.9%, respectively. MC% of 7.85% and EC% of 2.05% recorded a sensitivity of 70.2% and 72.3% and specificity of 53.6% and 55.5%, respectively. The AUC for SBII was 0.834, and the sensitivity and specificity for severity at 343.67 were 81.4% and 70.1%, respectively. SII exhibited 77.2% sensitivity and 70.8% specificity at 998.72, and the AUC was 0.793.

Discussion

The relationship of various basic parameters with inflammatory indices and their role as predictors for severity status was explored in this study. Among the study population, 23.1% were admitted as severe grade COVID-19 cases and 31.9% died against a death toll of 3.8% in non-severe cases. Almost 50% of the individuals admitted under severe grade were of age group 41 to 60 years. The coexistence of diabetes with hypertension was most common in this study [Table 1]. With increasing age, the presence of comorbid conditions like diabetes mellitus and hypertension would increase the probability of having a severe grade of COVID-19.[17–19] Various studies have shown a strong association of severe SARS-CoV-2 infection with age. The reason resides that the immune mechanism for defense is supposed to be weakened with the aging process. Moreover, the coexistence of morbidities like diabetes mellitus, hypertension, cardiovascular diseases, endocrine disorders, and other comorbid conditions further makes them vulnerable to severe illness.[17,20,21] A meta-analysis study by Sanyaolu *et al.*[22] documented the most common comorbid condition associated with COVID-19 patients were hypertension (15.8%), followed by cardiac and cerebrovascular disease (11.7%) and diabetes mellitus in 9.4%. Similarly, Huang *et al.*'s[23] study also observed diabetes in 20%, hypertension in 15%, and cardiovascular in 15% of patients. Although cardiac and cerebrovascular cases were very few, the frequency percentage of hypertension (14.2%) and diabetes mellitus (12.7%) were quite similar to Sanyaolu *et al.* [Table 1].

TCS score was significantly higher in moderate and severe cases than in mild grade disease individuals [Table 2]. The clinical manifestations of the individual were also associated with age and the comorbid condition associated that explained the linear association of TCS score with disease severity and inflammatory indices [Table 4].[15,24] The TCS score was found to be associated with the disease severity [Figure 1]. Symptoms are usually very mild, like fever, cough, muscle aches, sore throat, loss of smell, diarrhea, and headache, to start. But it worsens within 5 to 7 days, especially in the presence of more than one comorbidity and multiple clinical presentations at the time of admission.[22] Such patients usually do not respond to standard treatment protocol and succumb to death with a week of admission. Similar studies conducted in various institutes also indicated a delayed recovery in patients with multiple clinical features and comorbidities.[17,22,24]

Nearly 76.5% of severe cases were males as against 23.5% females [Figure 2]. The probability of severe grade disease in

Table 6: Sequential multiple regression model to explore influence of predictor biomarkers on SBI index

SBII	*R*	R^2	R^2 change	B coefficient	Beta coefficient	*P*
Model 1						
Gender	0.285	0.081	0.081	−121.443	−.236	<.001*
Age				1.236	0.082	0.005*
Comorbidity score				−11.689	−.045	0.234
TCS score				18.893	0.122	0.001*
Model 2						
Gender	0.536	0.287	0.206	−88.694	−.172	<.001*
Age				0.087	0.006	0.828
Comorbidity score				−27.046	−.103	0.002*
TCS Score				14.646	0.094	0.003*
Urea				3.004	0.555	<.001*
Creatinine				−34.478	−.238	<.001*
Na+				7.402	0.185	<.001*
K+				17.129	0.050	0.072
Cl−				−12.583	−.291	<.001*
Model 3						
Gender	0.705	0.497	0.21	−77.237	−.150	<.001*
Age				−.570	−.038	0.105
Comorbidity score				−18.492	−.070	0.014*
TCS Score				10.173	0.065	0.018*
Urea				1.303	0.241	<.001*
Creatinine				−9.123	−.063	0.060
Na+				6.901	0.173	<.001*
K+				4.410	0.013	0.590
Cl−				−9.102	−.211	<.001*
SGOT				0.140	0.058	0.143
SGPT				0.192	0.067	0.078
ALP				0.313	0.082	0.002*
GGT				0.298	0.092	<.001*
Total protein				−33.833	−.121	0.071
Albumin				12.654	0.033	0.731
AGR				−106.637	−.129	0.069
CAR				38.760	0.330	<.001*
Model 4						
Gender	0.721	0.52	0.023	−58.702	−.114	<.001*
Age				−.458	−.030	0.188
Comorbidity score				−17.044	−.065	0.022*
TCS Score				9.251	0.060	0.028*
Urea				1.152	0.213	<.001*
Creatinine				−7.645	−.053	0.125
Na+				7.684	0.193	<.001*
K+				6.919	0.020	0.396
Cl−				−9.951	−.230	<.001*
SGOT				0.099	0.041	0.296
SGPT				0.229	0.080	0.033*
ALP				0.240	0.063	0.016*
GGT				0.296	0.091	<.001*
Total protein				−34.648	−.123	0.062
Albumin				11.174	0.029	0.762
AGR				−111.778	−.135	0.053
CAR				40.083	0.342	<.001*
RBC				68.271	0.233	0.002*
MCV				12.887	0.466	0.058
MCH				−23.853	−.355	0.232
MCHC				33.198	0.224	0.063
RDW				−18.563	−.193	0.001*

Contd...

Table 6: Contd...

SBII	*R*	R^2	R^2 change	B coefficient	Beta coefficient	*P*
RDW/Hct				420.137	0.276	<.001*
Hb/RDW				−117.579	−.105	0.186
Model 5						
Gender	0.732	0.535	0.016	−53.453	−.104	<.001*
Age				−.408	−.027	0.243
Comorbidity score				−15.773	−.060	0.034*
TCS Score				8.926	0.057	0.035*
Urea				0.802	0.148	<.001*
Creatinine				−3.221	−.022	0.525
Na+				7.289	0.183	<.001*
K+				5.151	0.015	0.528
Cl−				−9.295	−.215	<.001*
SGOT				0.122	0.050	0.196
SGPT				0.175	0.061	0.104
ALP				0.190	0.049	0.055
GGT				0.296	0.091	<.001*
Total protein				−28.260	−.101	0.126
Albumin				19.208	0.050	0.601
AGR				−98.033	−.118	0.090
CAR				39.097	0.333	<.001*
RBC				57.386	0.196	0.008*
MCV				10.066	0.364	0.136
MCH				−16.622	−.247	0.401
MCHC				26.611	0.180	0.133
RDW				−19.137	−.199	<.001*
RDW/Hct				440.888	0.290	<.001*
Hb/RDW				−91.199	−.081	0.303
TLC				3.236	0.072	0.014*
NC				0.087	0.006	0.966
LC				−1.985	−.112	0.360
MC				1.231	0.020	0.650
NLR				0.402	0.016	0.690
LMR				3.705	0.042	0.245
EC				0.192	0.002	0.949
PLR				−.181	−.020	0.587
ESR				−.173	−.037	0.100
PT				22.578	0.194	0.012*
INR				−172.749	−.158	0.041*
APTT				0.206	0.008	0.685

*Denotes significance at $P<0.05$, B denotes the unstandardized coefficient for a variable, Beta denotes the standardized coefficient for a variable; all the full names are mentioned in the abbreviation section

males was 1.6 times that the female. A few other studies also documented gender proneness for COVID-19 infection and the severity of the disease.[17,19,25] Li *et al.*'s[26] study depicted that 56% of the COVID-19 patients were male, and the median age was 59. Similarly, the Guan *et al.*'s[27] study published a frequency percentage of 52.1% male and the median age of the study population was 47 years.

Highly elevated serum inflammatory markers like hs-CRP, LDH, and ferritin, reflect a greater degree of inflammation and greater probability for adverse outcomes. The SBII calculated using these biomarkers could aid in the early prediction of the progress of disease severity. Both SBII ($r = -0.582$, $P < 0.001$) and SII ($r = -0.52$, $P < 0.001$) strongly correlated inversely with SpO_2 values [Figures 3a and 3b]. More than 80% of individuals admitted with severe grade COVID-19 had a value of more than 50th percentile of SBII and SII [Table 3 and Figure 4]. An SBII value beyond 343 would increase the probability of the progress of disease inflammation with a sensitivity of 81.4% and specificity of 70.1% [Table 8 and Figure 5]. Besides, serum inflammatory markers, serum renal parameters like raised urea, creatinine, and potassium values also proved their impact on low SpO_2 percentage at admission. Hachim *et al.*'s[28] study reported raised urea and creatinine in ICU patients admitted with severe grade infection. The frequency of uremia and dyselectrolemia in this study was significantly higher in moderate to severe cases. The RFT parameters significantly influenced the inflammatory indices [Tables 6 and 7]. Although electrolyte imbalance was evidenced in nearly 17% to 50% of the study population, dyselectrolemia in the form

Table 7: Sequential multiple regression model to explore influence of predictor biomarkers on SII

SII	*R*	R^2	R^2 change	B coefficient	Beta coefficient	*P*
Model 1						
Gender	0.169	0.029	0.029	−389.892	−.072	0.012*
Age				17.685	0.111	<.001*
TCS score				126.369	0.077	0.008*
Model 2						
Gender	0.36	0.129	0.101	15.243	0.003	0.920
Age				11.259	0.071	0.011*
TCS				59.484	0.036	0.195
hs-CRP				7.039	0.167	<.001*
LDH				0.824	0.098	0.002*
Ferritin				0.789	0.150	<.001*
Model 3						
Gender	0.46	0.212	0.082	−45.471	−.008	0.755
Age				2.920	0.018	0.500
TCS Score				26.870	0.016	0.545
hs-CRP				4.690	0.111	<.001*
LDH				0.339	0.040	0.204
Ferritin				0.374	0.071	0.032*
Urea				28.611	0.499	<.001*
Creatinine				−420.598	−.274	<.001*
Uric acid				−106.763	−.094	0.003*
Na^+				13.183	0.031	0.267
K^+				114.662	0.031	0.272
Model 4						
Gender	0.493	0.243	0.032	−90.880	−.017	0.545
Age				−.476	−.003	0.914
TCS Score				23.308	0.014	0.600
hs-CRP				6.891	0.163	0.183
LDH				0.141	0.017	0.602
Ferritin				0.265	0.050	0.134
Urea				22.803	0.398	<.001*
Creatinine				−337.838	−.220	<.001*
Uric acid				−54.833	−.048	0.138
Na^+				19.384	0.046	0.103
K^+				100.852	0.028	0.337
SGOT				−.462	−.018	0.751
SGPT				−.627	−.021	0.708
SGOT/SGPT				−307.144	−.089	0.005*
ALP				0.295	0.007	0.821
GGT				0.433	0.013	0.669
Total protein				−81.057	−.027	0.740
Albumin				−685.915	−.169	0.158
AGR				−369.942	−.042	0.628
CAR				−122.061	−.098	0.451
Model 5						
Gender	0.495	0.245	0.002	−22.868	−.004	0.884
Age				0.080	0.000	0.986
TCS Score				24.774	0.015	0.578
hs-CRP				7.705	0.183	0.138
LDH				0.108	0.013	0.689
Ferritin				0.261	0.050	0.140
Urea				22.358	0.390	<.001*
Creatinine				−311.546	−.203	<.001*
Uric acid				−53.042	−.047	0.154
Na^+				18.399	0.044	0.122
K^+				92.671	0.025	0.380

Contd...

Table 7: Contd...

SII	*R*	R^2	R^2 change	B coefficient	Beta coefficient	*P*
SGOT				−.278	−.011	0.849
SGPT				−.840	−.028	0.618
SGOT/SGPT				−314.487	−.091	0.005*
ALP				0.291	0.007	0.825
GGT				0.381	0.011	0.707
Total protein				−53.584	−.018	0.827
Albumin				−795.663	−.196	0.107
AGR				−279.805	−.032	0.715
CAR				−144.093	−.116	0.375
RDW				54.917	0.054	0.161
Hb/RDW				792.197	0.067	0.119
Model 6						
Gender	0.545	0.297	0.052	−144.894	−.027	0.344
Age				4.255	0.027	0.325
TCS Score				−24.390	−.015	0.576
hs-CRP				4.797	0.114	0.344
LDH				0.112	0.013	0.672
Ferritin				0.238	0.045	0.165
Urea				18.749	0.327	<.001*
Creatinine				−253.942	−.165	<.001*
Uric acid				−38.328	−.034	0.289
Na^+				14.957	0.035	0.195
K^+				53.722	0.015	0.599
SGOT				−.070	−.003	0.960
SGPT				−.920	−.030	0.573
SGOT/SGPT				−269.492	−.078	0.013*
ALP				−.102	−.002	0.937
GGT				0.484	0.014	0.623
Total protein				32.293	0.011	0.892
Albumin				−776.030	−.191	0.106
AGR				10.998	0.001	0.988
CAR				−82.373	−.066	0.601
RDW				48.340	0.048	0.209
Hb/RDW				519.666	0.044	0.300
MC				−109.671	−.165	<.001*
EC				−165.413	−.150	<.001*
ESR				−1.081	−.022	0.421
PT				−199.863	−.162	0.085
INR				1628.945	0.141	0.135

*Denotes significance at $P<0.05$, B denotes the unstandardized coefficient for a variable, Beta denotes the standardized coefficient for a variable; all the full names are mentioned in the abbreviation section

of hypernatremia and hyperkalemia exhibited a significant relationship with SpO_2% and SBII [Tables 4 and 5, model-6]. Fluid loss, renal impairment, and drug interaction could be responsible for such electrolyte derangements. Decreased activity of angiotensin-converting enzyme 2, the receptor for the SARS-CoV-2 virus, could be the possible explanation that leads to impaired water and salt homeostasis. There are few published data that both raised and reduced electrolytes associated with mortality.[2,11,29]

In addition, serum GGT above 70U/L exhibited a considerable influence on inflammatory serum markers [Table 5, model 6] and disease severity [Table 4 and model-6 of Table 5]. Ali *et al.*'s[30] study documented elevated serum GGT levels in severe grade COVID-19 cases.

The pathogenesis of the SARS-CoV-2 virus on various systems is still under research, and no specific mechanism has yet been established. The virus might directly target the renal or hepatic system or indirectly through the inflammatory cytokine storm that resulted in altered renal and liver serum profiles.[1,4,31] However, serum globulin recorded a significant positive association with SpO_2 that might explain that raised immunoglobulin production as an immune response to defend the virus that would prevent the disease progression toward severity.

After adjusting for covariates, low MC (<7.85%) and EC (<2.05%) were found to influence the SII and the disease severity to a great extent [Tables 4, 5 and 7]. Mao *et al.*'s[32] study observed monocytosis in nearly 52% of cases and monocytopenia in only 2 patients of 127 study population. Eosinopenia was found in

Table 8: Receiver operating characteristics and cut-off values for laboratory variables for severity

Lab variables (Units)	AUC	SE	*P*	Cut-off value	Sensitivity	1-Sensitivity
hs-CRP (mg/L)	0.76	0.016	<0.001*	51.5	70.5	29.7
LDH (U/L)	0.759	0.016	<0.001*	560	70.2	34.4
Ferritin (ng/mL)	0.81	0.015	<0.001*	359.5	80	30
Urea (mg/dL)	0.779	0.015	<0.001*	34.5	74	30.1
K^+ (mmol/L)	0.646	0.02	<0.001*	4.07	70.5	48.7
GGT (U/L)	0.701	0.017	<0.001*	37.5	70.9	41.9
RDW/Hct	0.48	0.02	0.317	6.6	66.9	32
MC (%)	0.661	0.019	<0.001*	7.85	70.2	46.4
EC (%)	0.669	0.018	<0.001*	2.05	72.3	44.5
SBII	0.834	0.013	<0.001*	343.67	81.4	29.9
				280.34	90.2	40.5
SII	0.793	0.015	<0.001*	998.72	77.2	29.2

*Denotes significance at *P* of 0.05; AUC: area under curve; SE: standard error; all other full names are mentioned in the abbreviation section

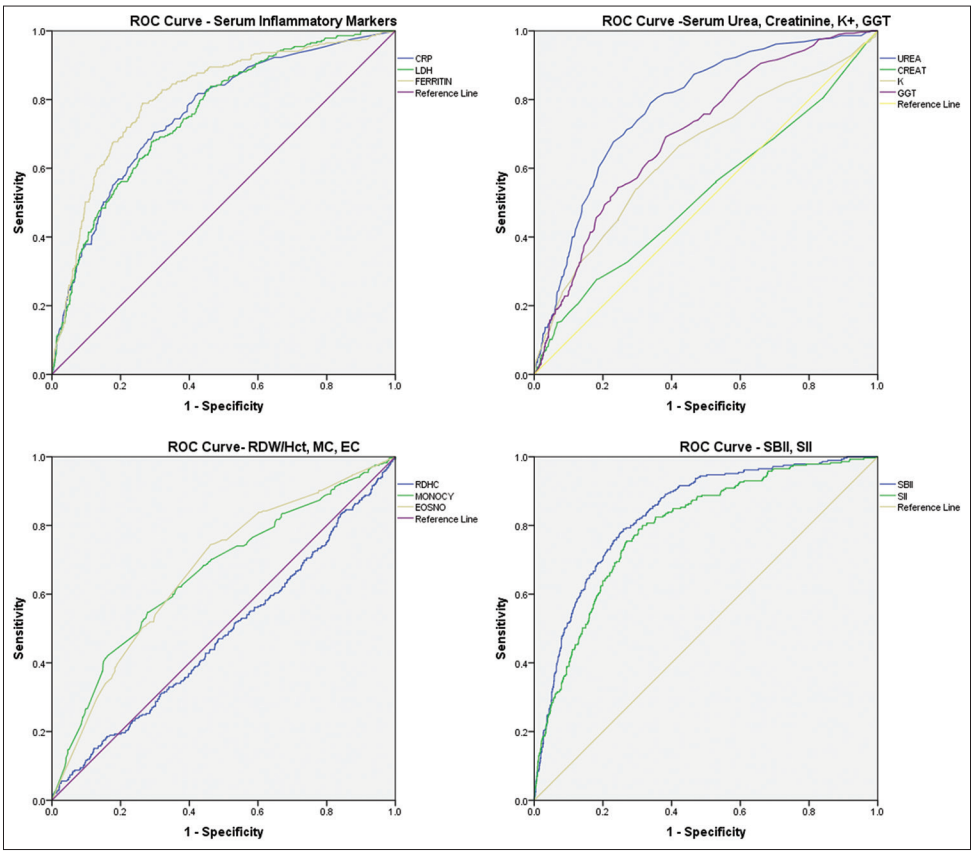

Figure 5: Receiver operating characteristics curves for laboratory variables to predict survival outcome

37.8% of patients. Outh *et al.*'s[33] study noted a sensitivity of 89.5% and specificity of 78.1% for eosinopenia (<0.03 G/L) as a marker of COVID-19 infection. Alzaid *et al.*[34] explained monocytopenia and altered morphology of monocytes as a marker for COVID-19 severity in type-2 diabetes mellitus.

Similarly, low RDW/Hct, leucocytosis, raised NLR, and ESR exhibited a substantial relationship with low SpO_2 values and documented increased probability for the severity of the disease. Anemia, leucocytosis, and other hematocrit derangements refer to systemic inflammation and stress index.[6,7,35] However, multivariate analysis depicted a significant influence of leucocytosis and raised NLR with SpO_2 and inflammatory indices in the study population. Studies have published leucocytosis and NLR as critical predictors for mortality.[7,8]

Although absolute NC, LC, and PC failed to show any detrimental effect on the inflammatory status and severity of the disease, the ratios derived from these laboratory biomarkers like NLR and PLR showed a significant linear effect on SBII and SII in the study population after adjusting the covariates [Table 4]. SII is a newly proposed prognostic marker that reflects an altered inflammatory

response in sepsis patients that relies on platelets, neutrophils, and lymphocyte populations.[36,37] Usul *et al.*'s[37] study calculated a cut-off value of ≤479.1 with AUC = 0.76 and sensitivity of 74.9%, and specificity of 68.9% for COVID-19 patients. The study demonstrated low neutrophils, NLR, platelets, and SII values, whereas this study denoted raised values of the parameters. An increase of SII beyond 998 would be an alarming sign for severity progression with a sensitivity of 77.2% and specificity of 70.8% [Table 8, Figure 5].

Close monitoring of raised inflammatory biomarkers, along with any of the following progressive changes like uremia, dyselectrolemia, deranged RDW, low MC, low EC, high NLR, or PLR would thus aid in depicting the disease severity and course for adverse outcome.

The strength of the study is that the blood parameters included in this study can be estimated in the primary health care centers as well and thus would enable the physicians to predict the severity status at an earliest. Thus, the overall mortality would be reduced.

A major limitation of the study is the retrospective observational study design. However, the large sample size and assessment of a broad group of laboratory biomarkers are the main strength that allows a more precise statistical analysis estimate.

Conclusion

This study assessed a broad group of lab parameters that can be evaluated in primary health care centers with limited infrastructure. Serum SBII above 343 and SII above 998 showed a significant effect on the severity in COVID-19 patients. Serial monitoring of other markers, especially urea, electrolytes, GGT, MC, or EC, could also predict severity progression in COVID-19 cases. Therefore, monitoring of the routinely available biomarkers would provide considerable input regarding disease prognosis and adverse outcomes.

Summary

- This study assessed the effect of various laboratory variables with inflammatory status and severity of COVID-19.
- Monitoring the inflammatory biomarkers, serum urea, and electrolytes aid in assessing the disease progression.
- Deranged RDW, low MC, low EC, high NLR, or PLR enable physicians in predicting the adverse outcome.
- An increase of SII beyond 998 would be an alarming sign for severity progression.

Abbreviations

- 95% CI: 95% Confidence interval
- ALP: Alkaline phosphatase
- AGR: Albumin-to-Globulin ratio
- APTT: Activated plasma thromboplastin time
- AUC: Area under curve
- CAD: coronary artery disease
- CAR: CRP-to-Albumin ratio
- CBC: Complete blood count
- CKD: Chronic kidney disease
- Cl^-: chloride ion
- COPD: Chronic obstructive pulmonary disease
- COVID-19: Coronavirus disease of 2019
- CVA: Cerebrovascular accident
- DBil: Direct bilirubin
- DM: Diabetes mellitus
- EC: Eosinophil count
- ESR: Erythrocyte sedimentation rate
- GGT: Gamma glutamyltransferase
- Hb: Hemoglobin
- Hct: hematocrit
- hs-CRP: high-sensitivity C-reactive protein
- DOH: Duration of Hospitalization
- INR: International normalized ratio
- K^+: Potassium ion
- LC: Lymphocyte count
- LDH: Lactate dehydrogenase
- LFT: Liver function test
- LMR: Lymphocyte-to-monocyte ratio
- MC: Monocyte count
- MCH: Mean corpuscular hemoglobin
- MCHC: Mean corpuscular hemoglobin concentration
- MCV: Mean corpuscular volume
- Na^+: Sodium ion
- NC: Neutrophil count
- NLR: Neutrophil-to-lymphocyte ratio
- OR: Odds ratio
- PC: Platelet count
- PT: Prothrombin time
- RBC: Red blood cell count
- RDW: Red cell distribution width
- RFT: Renal function test
- ROC: Receiver operating characteristics
- RT-PCR: Reverse transcriptase polymerase chain reaction
- SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2
- SBII: Serum bio-inflammatory index
- SCD: Sickle cell disease
- SD: Standard deviation
- SE: Standard error
- SGOT: Serum Glutamate Oxaloacetate transaminase
- SGPT: Serum Glutamate Pyruvate transaminase
- SGOT/SGPT: Ratio of SGOT-to-SGPT
- SII: Systemic inflammatory index
- TB: Tuberculosis
- TBil: Total bilirubin
- TCS: Total Clinical Score
- TLC: Total leucocyte count

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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