Microbes and Infectious Diseases 2021; 2(4): 613-622

Microbes and Infectious Diseases

Journal homepage: https://mid.journals.ekb.eg/

Original article

Role of hemogram-derived ratios and systemic-immune inflammation index in prediction of COVID-19 progression in Egyptian patients

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ARTICLE INFO

Article history:
Received 2 July 2021
Received in revised form 4 August 2021
Accepted 5 August 2021

Keywords:
COVID-19
Inflammation index
Lymphocyte ratio
Mortality
Progression

Abbreviations:
HRCT: high-resolution computed tomography
NLR, neutrophil to lymphocyte ratio
PLR, platelet to lymphocyte ratio
RT-PCR, reverse transcription polymerase chain reaction
SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; SII, systemic immune-inflammation index.

ABSTRACT

Background: Early detection of COVID-19 patients with potentially severe disease is crucial for predicting the disease's course and prioritizing medical resources, lowering overall disease mortality. **Objectives:** To explore the role of baseline hemogram-derived ratios and systemic-immune inflammation index (SII), in addition to C-reactive protein (CRP), in predicting COVID-19 severity and prognosis. **Methods:** In this retrospective study, data were collected from the medical records of 425 COVID-19 patients. The neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and SII, together with the CRP, were investigated and compared. **Results:** NLR, PLR, SII, and CRP increased significantly in severe cases and with ICU admission ($p \leq 0.001$). But, in non-survivors, only NLR and CRP were significantly elevated ($p<0.05$). By interpreting area under the receiver operating characteristic curve (ROC-AUC), CRP and NLR were better predictors of disease severity (AUC: 0.7 for both), the need for ICU admission (AUC: 0.763 and 0.727, respectively), and in-hospital mortality (AUC: 0.812 and 0.75, respectively). SII was significantly associated with the risk of severe disease development (odds ratio (OR): 3.143; 95% confidence interval (CI): 1.101-8.976); CRP (OR: 2.902; CI95%: 1.342-6.273) and NLR (OR: 2.662; CI95%, 1.072-6.611) were significantly associated with ICU admission risk; and only CRP was significantly associated with in-hospital mortality risk (OR: 3.988; CI95%: 1.460-10.892). **Conclusions:** Values of CRP, SII, and NLR at the time of hospital admission could be independent prognostic biomarkers to predict COVID-19 progression.

DOI: 10.21608/MID.2021.84684.1168
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Introduction

Fatal coronavirus, named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has caused novel coronavirus disease (COVID-19) which first broke out in December 2019 in Wuhan, China [1]. Fever, dry cough, and fatigue are the main manifestations of COVID-19. In more severe cases, patients often have dyspnea and/or hypoxemia that can rapidly progress to acute respiratory distress syndrome, septic shock, metabolic acidosis, coagulation dysfunction, and multiple organ failure [2].

Although the majority of COVID-19 patients have been classified as mild cases that can recover shortly after the appropriate clinical intervention, rapid, severe progression of the disease can occur with increasing rates of hospitalization, ICU admission and mortality [3]. Furthermore, not all COVID-19 patients have symptoms in the early stage of the disease, making early tracking of suspected cases very important [4]. Neither the detection capability of viral nucleic acid kits nor the popular rate of pulmonary imaging can support large-scale screening of all populations. In the current novel coronavirus pandemic, if the most routine and inexpensive peripheral blood tests have characteristic changes for infected patients, especially those with severe infections, they will be very helpful for proper early clinical intervention to reduce the mortality of patients. Complete blood count (CBC) is the most widely performed, cost-effective test that can be performed in almost all laboratories, even in those with limited equipment [4].

This study aimed to explore the role of baseline hemogram-derived ratios (namely, NLR and PLR) and SII, in addition to CRP, in predicting COVID-19 severity and prognosis in a cohort of Egyptian patients.

Materials and Methods

Patient selection

This retrospective study was conducted in line with research regulations, including the approval of the Ain-Shams University Faculty of Medicine Research Ethics Committee (REC). Data were acquired anonymously from hospital records and kept private and confidential. They were only used for study purposes.

We aimed to include all adult (age ≥ 18 years) COVID-19 patients (confirmed with reverse transcription-polymerase chain reaction) admitted to Quarantine Hospitals of Ain-Shams University, Cairo, Egypt, between February and April 2021; precisely, El-Obour Ain Shams University Specialized Hospital (with a capacity of 90 beds in the general wards and 25 beds in ICU) and El-demerdash Hospital (with a capacity of 40 beds in the general wards and 18 beds in ICU). The hospital files of only 425 patients who had baseline CBC reports were accessible to us. The study excluded pregnant women and patients with aplastic anemia, lymphoproliferative or myeloproliferative disorders, immune deficiency, and a history of taking drugs that affect blood cell counts such as epinephrine, thyroxin or corticosteroids.

Data collection

Data were collected from the patients' medical records, including age, gender, presence of comorbidities, ICU admission, length of hospital stay, and in-hospital mortality. Also, on admission, laboratory findings were collected and analyzed, including CBC with differential counts and CRP. Blood cell ratios and indexes of systemic inflammation were calculated, including the NLR (neutrophil/lymphocyte ratio), PLR (platelet/lymphocyte ratio), and SII ((neutrophils × platelets)/lymphocytes).

Categorization of patients was done following guidelines of Ain Shams University Hospitals Consensus Statement on Management of Adult COVID-19 Patients. It was as follows: (a) mild cases: asymptomatic with abnormal laboratory findings or high-resolution computed tomography (HRCT) findings of COVID-19 pneumonia /or symptomatic with no HRCT findings of COVID-19 pneumonia; (b) moderate cases: symptomatic with clinical signs of non-severe pneumonia (e.g., fever, cough, dyspnea) and HRCT findings of COVID-19 pneumonia and/or abnormal laboratory test results; (c) severe cases: at rest oxygen saturation of ≤ 93%; dyspnea with a respiratory rate of ≥ 30 breath/min; arterial partial oxygen pressure (PaO2)/fraction of inspired oxygen (FiO2) ≤ 300 mmHg; (d) critical cases: occurrence of respiratory failure requiring mechanical ventilation; presence of shock; sepsis, and other organ failure that requires monitoring and treatment in the ICU [5]. Based on the above classification, we divided all patients into two groups: (1) the mild group, and (2) the moderate to severe group, including moderate, severe and critical types.

Statistical analysis

Categorical variables were analyzed using the Chi-square test and were expressed as a number and percentage. For analysis of the parametric variables, the independent samples t-test was used and they were presented as a mean and standard deviation. Non-parametric variables were analyzed by the Mann–Whitney U test and presented as the median and interquartile range (IQR). The ROC curve analysis was used to assess the predictive performance of the significant parameters. To analyze the association between the COVID-19 severity, need for ICU admission or in-hospital mortality, and related factors, univariate and multivariate analyses were carried out using a logistic regression model. The statistical analysis of the data was performed using SPSS version 20.0 software. A *p*-value of ≤ 0.05 was considered statistically significant.

Results

Characteristics of the entire study cohort

A total of 425 adult patients (227 females and 198 males) with confirmed COVID-19 infection were included in this study. Of them, 188 (44.2%) patients were mild, while 237 (55.8%) were moderate/severe cases. The mean age was 47.90 ± 17.08 years. Hypertension (34.1%) and diabetes (30.4%) were the most common comorbidities. Only 112 (26.4%) patients required ICU admission. Of all studied subjects, 385 (90.6%) patients were discharged alive, whereas the remaining 40 (9.4%) died. The median hospitalization duration was 10 days (IQR: 6 – 17). The baseline characteristics of the included patients are shown in **tables (1a)** and **(2 a)**.

Clinical variables associated with disease severity

Table 1b summarizes the characteristics of the mild (n = 188) and moderate/severe (n = 237) groups. The mean age of the moderate/severe group was significantly higher than that of the mild group (53.47 years ± 16.10 vs. 40.84 years ± 15.65; $p < 0.05$), with no statistically significant difference in gender between both groups ($p>0.05$). Of the moderate/severe group, 108 (45.6%) patients required ICU admission and 40 (16.9%) patients died. In contrast, of the mild group, only 4 (2.1%) patients required ICU admission and no deaths occurred. The moderate/severe group had a statistically significant longer length of hospital stay when compared to the mild group (14 days (IQR: 9 – 20) vs. 7 days (IQR: 5 – 10), $p \leq 0.001$).

Table 2b shows that comorbidities including chronic obstructive pulmonary disease (COPD), diabetes mellitus, hypertension, chronic liver disease, chronic kidney disease and ischemic heart disease were significantly associated with disease severity ($p\leq 0.001$)

The moderate/severe group had statistically significantly lower hemoglobin and lymphocyte count but statistically significant higher total leukocytic count (TLC), PLR, NLR, SII and CRP when compared to the mild group ($p < 0.05$). Platelet and neutrophil counts were not significantly different between groups ($p > 0.05$) **(Table 3b)**.

Clinical variables associated with ICU admission

The mean age of the ICU group (n=112) was significantly higher than that of the non-ICU group (n=313) (56.83 years ± 15.75 vs. 44.70 years ±16.41; $p \leq 0.001$), but no statistically significant difference in gender was found between the groups ($p>0.05$). The ICU group had a statistically significant longer length of hospital stay when compared to the non-ICU group (19 days (IQR: 9 – 22) vs 9 days (IQR: 6 – 13), $p \leq 0.001$). Of the ICU group, 108 (96.4%) patients were moderate/severe and 4 (3.6%) patients were mild. Only 39 (34.8%) patients of the ICU group died **(Table 1 c)**.

All the previously mentioned comorbidities were significantly associated with ICU admission ($p \leq 0.001$) except chronic liver disease ($p > 0.05$) **(Table 2c)** .

Similar to the moderate/severe group, the ICU group had statistically significant lower hemoglobin and lymphocyte count but statistically significant higher TLC, PLR, NLR, SII and CRP when compared to the non-ICU group ($P\leq 0.001$). Platelet and neutrophil counts were not significantly different between groups ($p > 0.05$). **Table 3 (c)**

Clinical variables associated with in-hospital mortality

Table 1d summarizes the characteristics of survivors (n=385) and non-survivors (n=40). Non-survivors were significantly older than survivors (mean age: 60.30 years ± 13.60 vs. 46.61years ± 16.90; $p\leq 0.001$) with no significant gender difference. They had a statistically significant longer length of hospital stay when compared to survivors (18 days (IQR: 7 – 22) vs 10 days (IQR: 6 – 15), $p< 0.05$).

Table 2d shows that chronic liver disease was not significantly associated with in-hospital mortality (*p*

> 0.05) but the other mentioned comorbidities did ($p < 0.05$).

Non-survivors had statistically significantly higher TLC, NLR and CRP when compared to the survivors ($p<0.05$). Hemoglobin, platelet count, lymphocyte count, neutrophil count, PLR and SII were not significantly different between groups ($p > 0.05$) **(Table 3d)**.

Prediction of disease severity, ICU admission and in-hospital mortality

Table 4 shows the independent prediction ability of the studied biomarkers and the optimal cut-off values calculated by the ROC analysis. As regards COVID-19 severity prediction, CRP AUC was 0.707 with a cut off value of 12 mg/L, a sensitivity of 65.66% and a specificity of 69.31%, followed by NLR, SII and PLR with an AUC of 0.700, 0.669 and 0.640, and cut-off values of 4.33, 1012.36 and 185, respectively**.** Regarding ICU admission prediction, CRP AUC was 0.763 with a cut off value of 115 mg/L, a sensitivity of 54.76% and a specificity of 94.30%., followed by NLR, SII and PLR with an AUC of 0.727, 0.717 and 0.580, and cut-off values of 4.5, 668.57 and 300, respectively. For in-hospital mortality prediction, CRP AUC was 0.812 with a cut off value of 141 mg/L, a sensitivity of 70% and a specificity of 95.56%, followed by NLR with an AUC of 0.751 and a cut off value of 4.5 **(Figures 1-3)**.

Association with disease severity, ICU Admission and in-hospital mortality

To identify factors that may affect the disease severity, ICU admission or in-hospital mortality, we obtained the odds ratios (OR) after conducting logistic regression analysis. The multivariate analysis showed that SII (OR, 3.143; 95% CI, 1.101-8.976; p <0.05) was significantly positively associated with the disease severity, CRP (OR, 2.902; 95% CI, 1.342-6.273; p <0.05) and NLR (OR, 2.662; 95% CI, 1.072-6.611; $p < 0.05$) were significantly positively associated with the need for ICU admission, and only CRP (OR, 3.988; 95% CI, 1.460-10.892; $p < 0.05$) was significantly positively associated with in-hospital mortality **(Table 5)**.

Table 1. Comparisons of patients' characteristics according to COVID-19 severity, ICU admission and in-hospital mortality.

Variable		(a) Total (n=425)	(b)Severity			(c)ICU admission			(d) In-hospital mortality		
			Mild (n= 188)	Moderate to severe (n = 237)	*p*-value	Non-ICU (n =313)	ICU (n=112)	*p*-value	Survivors (n=385)	Non-survivors (n= 40)	*p*-value
Age	Mean ± SD	47.90 ± 17.08	40.84± 15.65	53.47± 16.10	**≤ 0.001**	44.70± 16.41	56.83 ± 15.75	**≤ 0.001**	46.61± 16.90	60.30 ± 13.60	**≤ 0.001**
	Range	13 – 94	13 – 94	17 – 92		13 – 94	22 – 91		13 – 94	35 – 85	
Sex	Female	227 (53.4%)	110 (58.5%)	117 (49.4%)	0.061	174 (55.6%)	53 (47.3%)	0.132	205 (53.2%)	22 (55.0%)	0.832
	Male	198 (46.6%)	78 (41.5%)	120 (50.6%)		139 (44.4%)	59 (52.7%)		180 (46.8%)	18 (45.0%)	
Severity	Mild	188 (44.2%)				184 (58.8%)	4 (3.6%)	**≤ 0.001**	188 (48.8%)	0 (0.0%)	**≤ 0.001**
	Moderate to Severe	237 (55.8%)				129 (41.2%)	108 (96.4%)		197 (51.2%)	40 (100.0%)	
Hospital stay (days)	Median (IQR)	10 (6 – 17)	7 (5 – 10)	14 (9 – 20)	**≤ 0.001**	9 (6 – 13)	19 (9 – 22)	**≤ 0.001**	10 (6 – 15)	18 (7 – 22)	**0.018**
	Range	0 – 51	0 – 36	1 – 51		0 – 51	1 – 40		0 – 51	1 – 29	
ICU	Negative	313 (73.6%)	184 (97.9%)	129 (54.4%)	**≤ 0.001**				312 (81.0%)	1 (2.5%)	**≤ 0.001**
	Positive	112 (26.4%)	4 (2.1%)	108 (45.6%)					73 (19.0%)	39 (97.5%)	
Fate	Discharged	385 (90.6%)	188 (100%)	197 (83.1%)	**≤ 0.001**	312 (99.7%)	73 (65.2%)	**≤ 0.001**			
	Death	40 (9.4%)	0 (0.0%)	40 (16.9%)		1 (0.3%)	39 (34.8%)				

ICU, intensive care unit. Statistical significance set at 0.05.

Table 2. Comparisons of patient comorbidities according to COVID-19 severity, ICU admission and in-hospital mortality.

Comorbidity	**(a) Total (n=425)**	**(b)Severity**			**(c)ICU admission**			**(d) In-hospital mortality**		
		Mild (n= 188)	Moderate to severe (n = 237)	*p*-value	Non-ICU (n =313)	ICU (n=112)	*p*-value	Survivors (n=385)	Non-survivors (n= 40)	
COPD	78 (18.4%)	15 (8.0%)	63 (26.6%)	**≤ 0.001**	43 (13.7%)	35 (31.3%)	**≤ 0.001**	65 (16.9%)	13 (32.5%)	**0.015**
DM	129 (30.4%)	22 (11.7%)	107 (45.1%)	**≤ 0.001**	67 (21.4%)	62 (55.4%)	**≤ 0.001**	102 (26.5%)	27 (67.5%)	**≤ 0.001**
HTN	145 (34.1%)	26 (13.8%)	119 (50.2%)	**≤ 0.001**	80 (25.6%)	65 (58.0%)	**≤ 0.001**	119 (30.9%)	26 (65.0%)	**≤ 0.001**
CLD	17 (4.0%)	0 (0.0%)	17 (7.2%)	**≤ 0.001**	11 (3.5%)	6 (5.4%)	0.393	16 (4.2%)	1 (2.5%)	0.611
CKD	27 (6.4%)	2 (1.1%)	25 (10.5%)	**≤ 0.001**	13 (4.2%)	14 (12.5%)	**0.002**	20 (5.2%)	7 (17.5%)	**0.002**
IHD	42 (9.9%)	1 (0.5%)	41 (17.3%)	**≤ 0.001**	16 (5.1%)	26 (23.2%)	**≤ 0.001**	32 (8.3%)	10 (25.0%)	**0.001**

COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HTN, hypertension; CLD, chronic liver disease; CKD, chronic kidney disease; IHD, ischemic heart disease. Statistical significance set at 0.05.

Table 3. Comparisons of patient laboratory findings according to COVID-19 severity, ICU admission and in-hospital mortality**.**

Variable		(a)Total (n=425)	(b)Severity			(c) ICU admission			(d) In-hospital mortality		
			Mild (n= 188)	Moderate to severe (n = 237)	*p*-value	Non-ICU (n =313)	ICU (n=112)	*p*-value	Survivors (n=385)	Non-survivor (n= 40)	*p*-value
HB gm/dl	Mean ± SD	12.01 ± 2.34	12.39 ± 2.19	11.70 ± 2.42	**0.003**	12.25 ± 2.23	11.32 ± 2.51	**≤ 0.001**	12.08 ± 2.32	11.33 ± 2.43	0.055
	Range	2.9 – 17.3	5 – 17.3	2.9 – 16.6		5 – 17.3	2.9 – 16		2.9 – 17.3	6.6 – 16	
PLT ×10³µl	Mean ± SD	248.02 106.49	247.43 ± 90.64	248.49 117.75	0.919	244.57 96.21	257.66 131.06	0.265	247.69 104.01	251.13± 129.51	0.846
	Range	6 – 716	22 – 546	6 – 716		22 – 716	6 – 650		11 – 716	6 – 633	
TLC ×10³µl	Median (IQR)	6.5 (4.5 – 9.8)	5.90 (4.46 – 7.6	7.00 (4.62 – 11.30)	**0.002**	6.00 (4.40 – 8.30)	8.85 (5.05– 13.50)	≤ 0.001	6.20 (4.40 – 9.1	11.50 (5.75 15.90)	**≤ 0.001**
	Range	1.02 – 99.8	2.20 – 28.7	1.02 – 99.80		1.02 – 79.00	1.10 – 99.		1.02 – 79.0	3.30 – 99.	
PNL ×10³µl	Median (IQR)	3.15 (2.2 – 4.9)	3.30 (2.46 – 4.3	3.08 (2.10 – 5.70)	0.698	3.10 (2.20 – 4.40)	3.57 (1.90 – 9.(	0.155	3.10 (2.20 – 4.6	4.04 (2.10 11.50)	0.126
	Range	0.5 – 34.8	0.89 – 9.64	0.50 – 34.80		0.51 – 23.30	0.50 – 34.		0.50 – 24.8	0.90 – 34.	
LYMPH×10³µ	Median (IQR)	1.4 (0.9 – 2.08)	1.80 (1.30 – 2.3(	1.10 (0.70 – 1.60)	**≤ 0.001**	1.50 (1.10 – 2.20)	0.95 (0.70 – 1.4	**≤ 0.001**	1.40 (0.90 – 2.1	1.20 (0.78 – 1.(	0.076
	Range	0.1 – 12.36	0.20 – 12.3	0.10 – 6.60		0.10 – 12.36	0.10 – 5.4		0.10 – 12.3	0.20 – 5.4	
PLR	Median (IQR)	162.5 (110 268.89)	134.67 (100.12– 183.91)	213.75 (125.0 – 344.00)	**≤ 0.001**	148.57 (108.85 232.31)	254.58 (125.30 387.30)	**≤ 0.001**	160.77 (110.00 263.33)	192.26 (115.62 352.08)	0.212
	Range	3.7 – 1351.3	14.67 805.00	3.70 – 1351.3		8.33 – 1025.0	3.70 1351.35		8.33 1351.35	3.70 1055.00	
NLR	Median (IQR)	2.29 (1.5 – 4.17)	1.86 (1.25– 2.77	2.58 (1.75 – 6.92)	**≤ 0.001**	2.17 (1.38 – 3.38)	3.74 (1.75 – 9.7	**≤ 0.001**	2.29 (1.46 – 4.0	2.63 (1.70 11.03)	0.028
	Range	0.24 – 96.8	0.24 – 16.0	0.45 – 96.80		0.24 – 24.80	0.77 – 96.		0.24 – 28.0	0.77 – 96.	
SII	Median (IQR)	549 (308 965.45)	447.68 (280.35- 718.95)	669.67 (348.9 – 1558.25)	**≤ 0.001**	507.50 (287.00 852.62)	737.55 (409.51 2117.54)	**≤ 0.001**	535.07 (304.33 937.44)	682.48 (371.61 2620.45)	0.056
	Range	11.45- 15218.64	43.10- 2576.00	11.45- 15218.64		27.50 5580.00	11.45 15218.64		27.50 9632.00	11.45 15218.64	
CRP mg/L	Median (IQR)	24 (8 – 83)	12 (5 – 25)	64 (18 -129)	**≤ 0.001**	16 (6 – 48)	103 (46 – 152	**≤ 0.001**	20 (7 – 68)	125 (59 – 152	**≤ 0.001**
	Range	1 – 710	2 – 164	1 – 710		1 – 372	1 – 710		1 – 710	1 – 352	

HB, hemoglobin; PLT, platelets; TLC, total leucocytic count; PNL; neutrophils; LYMPH, lymphocytes; PLR, platelet to lymphocyte ratio; NLR, neutrophil to lymphocyte ratio; SII, systemic immune-inflammation index (neutrophil*platelet to lymphocyte ratio); CRP, C-reactive protein. Statistical significance set at 0.05.

Table 4: Recommended cut-off values for the prediction of COVID-19 severity, need for ICU admission and in-hospital mortality.

		AUC	Cut off	Sensitivity %	Specificity %	PPV %	NPV %
Disease severity							
PLR		0.640	>185	51.52	80.20	71.8	62.8
NLR		0.700	>4.33	47.47	95.05	89.1	62.3
SII		0.669	>1012.36	46.46	93.07	86.8	63.9
CRP		0.707	>12	65.66	69.31	67.7	67.3
ICU admission							
PLR		0.580	>300	38.10	89.87	50.0	84.5
NLR		0.727	>4.5	59.52	83.54	49.0	88.6
SII		0.717	>668.57	71.43	63.92	34.5	89.4
CRP		0.763	>115	54.76	94.30	71.9	88.7
In-hospital mortality							
NLR		0.751	>4.5	65.0	78.89	25.5	95.3
CRP		0.812	>141	70.0	95.56	63.6	96.6

PLR, platelet to lymphocyte ratio; NLR, neutrophil to lymphocyte ratio; SII, systemic immune-inflammation index (neutrophil*platelet to lymphocyte ratio); CRP, C-reactive protein; AUC, area under the curve; NPV, negative predictive value; PPV, positive predictive value.

Table 5. Logistic regression analysis for predictors of COVID-19 severity, ICU admission and in-hospital mortality.

	Uni-variate				Multi-variate			
Disease severity	***p*-value**	**Odds ratio (OR)**	**95% C.I. for OR**		***p*-value**	**Odds ratio (OR)**	**95% C.I. for OR**	
			Lower	**Upper**			**Lower**	**Upper**
PLR	**≤ 0.001**	4.407	2.882	6.738	0.452	1.332	0.630	2.817
NLR	**≤ 0.001**	8.095	4.347	15.075	0.616	1.335	0.432	4.124
SII	**≤ 0.001**	7.808	4.191	14.547	0.032	3.143	1.101	8.976
CRP	**≤ 0.001**	6.017	3.893	9.300	0.166	1.533	0.837	2.808
ICU admission								
PLR	**≤ 0.001**	4.757	2.880	7.857	0.069	2.271	0.939	5.491
NLR	**≤ 0.001**	5.111	3.132	8.342	0.035	2.662	1.072	6.611
SII	**≤ 0.001**	2.195	1.416	3.401	0.067	0.414	0.161	1.062
CRP	**≤ 0.001**	7.617	4.465	12.995	0.007	2.902	1.342	6.273
In-hospital mortality								
NLR	**0.001**	3.273	1.673	6.403	0.766	1.149	0.461	2.863
CRP	**≤ 0.001**	10.332	5.024	21.248	0.007	3.988	1.460	10.892

PLR, platelet to lymphocyte ratio; NLR, neutrophil to lymphocyte ratio; SII, systemic immune-inflammation index (neutrophil*platelet to lymphocyte ratio); CRP, C-reactive protein; C.I, confidence interval. Statistical significance set at 0.05.

Figure 1. Receiver-operating characteristic curve for prediction of disease severity.

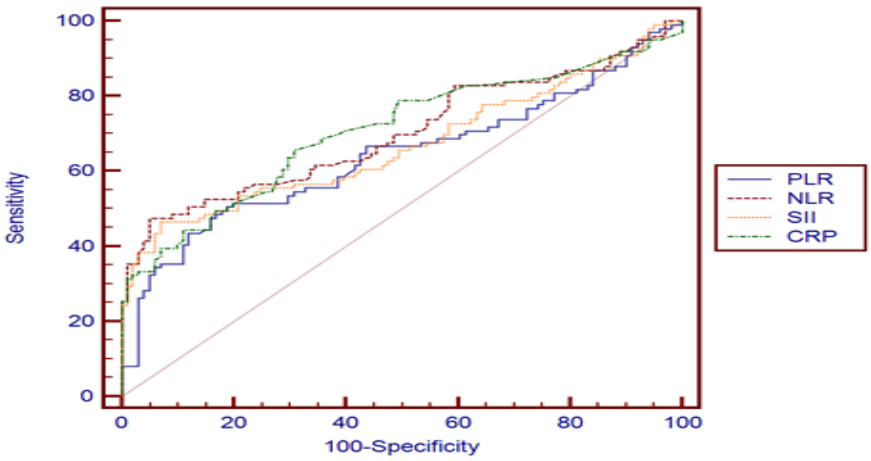


Figure 2. Receiver-operating characteristic curve for prediction of ICU admission.

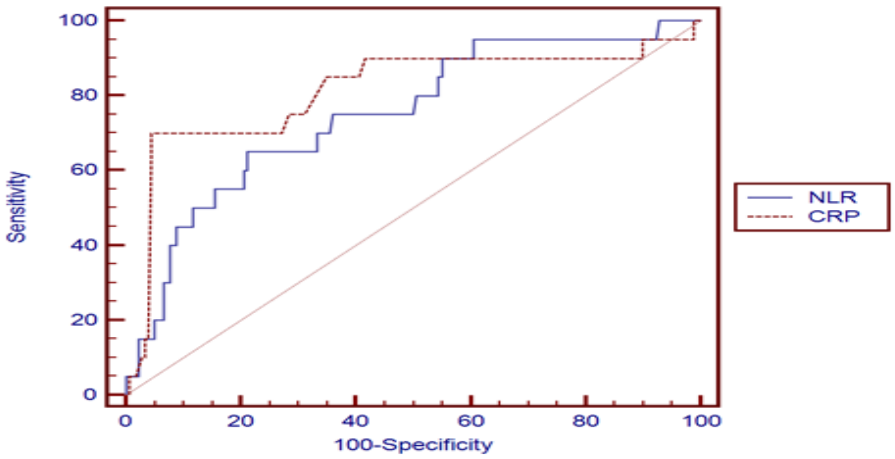
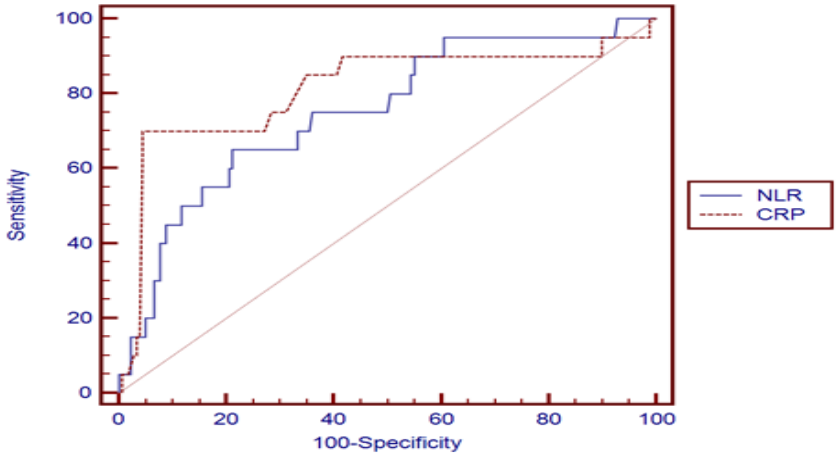


Figure 3. Receiver-operating characteristic curve for prediction of in-hospital mortality.



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Discussion

Since the hyper-inflammatory state has been incriminated in the patho-physiology of COVID-19, information about inflammation and the immune response of patients with different disease severity should be continuously explored for predicting the progression of the disease and improving the outcome of patients [1]. Complete blood counts are the most easily performed tests in a time and cost-effective manner. Included in the CBC are values that can be used as effective inflammatory biomarkers [4].

Neutrophils can be triggered by virus-related inflammatory factors to release large amounts of reactive oxygen species and other cytotoxic mediators, which may dampen the virus. Moreover, neutrophils are able to release neutrophil extracellular traps that help in capturing and damaging different pathogens, including viruses [6].

On the other hand, severe cases of viral infection can result in lymphocyte exhaustion, because viruses can directly attack and damage target cells; also, they can activate immune cells to participate in the anti-viral process, resulting in severe lymphocyte damage and apoptosis. Because systemic inflammation stimulates neutrophil production and accelerates lymphocyte apoptosis, virus-triggered inflammation raises the NLR ratio [6].

Additionally, as platelets have an important role in the regulation of various inflammatory processes, both the NLR and PLR indirectly reflect a patient's inflammatory state [7]. In recent years, NLR and PLR have been validated as prognostic biomarkers in various disorders including cardiac conditions, solid tumors, sepsis, pneumonia, and acute respiratory distress syndrome [8].

A recently proposed score is the SII, which is an index defining the instability in the inflammatory response. SII has been proposed as a prognostic indicator in the follow-up of patients with sepsis and in a number of tumors including small cell lung and hepatocellular carcinomas [7].

The current study is aimed at exploring the role of NLR, PLR, and SII, in addition to the CRP in predicting the severity of the disease, the need for ICU admission and in-hospital mortality in COVID-19 patients.

We found a significant relation between advancing patients' ages and the severity of the disease as well as the rate of ICU admission and in-hospital mortality. However, these could not be linked to a specific gender. Our findings were consistent with the studies of **Yang et al.** and **Fois et al.** [4,9], who reported significantly advanced age and non-significant difference in gender in the more severe cases and the non-survivors, respectively. However, our study was only partially consistent with **Wang and colleagues** [10] who reported non-significant differences in age or gender with the progression of the disease. Similar to the study of **Yang et al.** [4], we found the overall incidence of comorbidities (diabetes, hypertension, kidney dysfunction) to be significantly higher in the more severe cases. However, partially contrary to the study of **Fois et al.** [9], who found only a significant association between heart disease and COVID-19 mortality and a non-significant association between disease mortality and the other comorbidities including smoking, diabetes, and kidney disease, we found that in-hospital disease mortality was significantly higher in patients with diabetes, hypertension, kidney and heart diseases.

Our study also showed a significant increase in NLR, PLR, SII, and CRP in the more severe cases and in those who required ICU admission. However, only NLR and CRP were significantly elevated in patients who died from the disease. This was in accordance with the study of **Yang and colleagues** [4] who reported higher NLR, PLR and CRP in the more severe cases of the disease. However, partially consistent with our study, **Fois and colleagues** [9] reported significant elevation in NLR and SII in the non-survivor group of the disease; they also reported that SII might specifically reflect the pulmonary damage occurring in COVID-19 patients.

Our study revealed that the best cut-off points to predict disease severity and the need for ICU admission were, CRP > 12mg/l & > 115mg/l, NLR > 4.33 & > 4.5, SII > 1012.36 & > 668.57, and PLR > 185 & > 300, respectively. Also, the best cut-off points to predict in-hospital mortality were CRP > 145mg/l and NLR > 4.5. In view of our data, 4 of the 188 included mild cases required ICU admission during their hospital stay. This resulted in lowering the SII cut-off point of the need for ICU admission prediction compared to that used to predict the disease severity. Furthermore, by multivariate regression analysis, the SII was the best independent biomarker associated with disease severity; CRP and NLR were the best independent predictors of the need for ICU admission; and only CRP was

significantly associated with the risk of in-hospital mortality. **Yang and co-workers** [4] found that both NLR and PLR were independent predictors of disease severity and progression in their studied COVID-19 patients. Also, **Fois and colleagues** [9] found in their study that the SII was the only independent biomarker to predict in-hospital mortality of COVID-19 patients.

One limitation in our retrospective study was the limited availability and the incompleteness of data in patients' records. More prospective studies with serial determination of biomarkers' levels at different disease stages are still required for a better definition of the cut off points that could predict the progression of the disease.

Conclusions

Baseline CRP, SII, and NLR values could be used as independent prognostic biomarkers predicting COVID-19 progression.

Funding sources: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgement: None.

Conflicts of interest: The authors declare that there is no conflict of interest regarding the publication of this article.

Consent for publication: Not applicable**.**

Availability of data and materials: All data needed to support the current findings will be available upon request.

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