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Role of hemogram-derived ratios in predicting intensive care unit admission in COVID-19 patients: a multicenter study

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ABSTRACT

Purpose: As hyperinflammation is recognized as a driver of severe COVID-19 disease, checking markers of inflammation is gaining more attention. Our study aimed to evaluate the utility of cost-effective hemogram-derived ratios in predicting intensive care unit (ICU) admission in COVID-19 patients.

Methods: This multicenter retrospective study included hospitalized COVID-19 patients from four dedicated COVID-19 hospitals in Sylhet, Bangladesh. Data on demographics, clinical characteristics, laboratory parameters and survival outcomes were analyzed. Logistic regression analysis was used to identify the significance of each hemogram-derived ratio in predicting ICU admission.

Results: Of 442 included patients, 98 (22.17%) required ICU admission. At the time of admission, patients requiring ICU had a higher neutrophil count and lower lymphocyte and platelet counts than patients not requiring ICU. Peripheral capillary oxygen saturation at admission was significantly lower in those who subsequently required ICU admission. Neutrophil-to-lymphocyte ratio, derived neutrophil-to-lymphocyte ratio, neutrophil-to-platelet ratio, and systemic immune-inflammation index were significant predictors of ICU admission.

Conclusion: Hemogram-derived ratios can be an effective tool in facilitating the early categorization of at-risk patients, enabling timely measures to be taken early in the disease course.

Introduction

The ongoing COVID-19 pandemic poses a major global threat to population health and places a huge strain on the health care delivery system worldwide (Legido-Quigley et al., 2020). Even before the COVID-19 pandemic, health care systems in low-and middle-income countries faced considerable challenges in providing high-quality, affordable and universally accessible care (Agampodi, T. et al., 2015; McGregor, S. et al., 2014). The pandemic has challenged the already weak health systems in these countries (Okereke, M. et al., 2021). Epidemiological studies have shown that the majority of COVID-19 infected patients (>80%) are asymptomatic or have mild symptoms, whereas approximately 14% of infected patients have severe disease and need to be hospitalized (Wu, Z. and McGoogan, J., 2020; Guan, W. et al., 2020). Depending on ethnicity and geographical area, intensive care unit (ICU) admission rates vary between 3.1% and 26%, and the mortality of patients admitted to ICU ranges from 5.8% to 41.6% (Gottlieb, M. et al., 2020; Chang, R. et al., 2021; Zhou, F. et al., 2020; Armstrong, R. et al., 2021; Ali, H. et al., 2021).

While COVID-19 can directly damage epithelial tissues through epithelial cell injury and necrosis, evidence indicates that immune system activation/perturbation is the major cause of organ/tissue damage (Xu, Z. et al., 2020). The activation of multiple complement pathways, dysregulated neutrophil responses, endothelial injury, and hypercoagulability appear to be interlinked with SARS-CoV-2 infection and drive disease severity (Java, A. et al., 2020). It is also clear that hyperinflammation and coagulopathy contribute to disease severity and death (Merad, M. and Martin, J., 2020).

High levels of inflammatory markers, including C-reactive protein (CRP), ferritin and D-dimer and increased levels of inflammatory cytokines and chemokines (Herold, T. et al., 2020; Zhang, X. et al., 2020; Mehta, P. et al., 2020) have been observed in patients with severe COVID-19 diseases. White blood cells, neutrophils, lymphocytes and

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monocytes are directly involved in this systemic inflammatory response, while platelets are the primary mediators of hemostasis. Neutrophils constitute the majority of the leukocytes and are primarily responsible for activating the immune system by migrating from the venous system. Free oxygen radicals that can damage the cell's nuclear material are thereby released (Kral, J. B. et al., 2016; Koupenova, M. et al., 2018). The rapid spread and potential lethality of COVID-19 has generated an urgent need to identify indicators that could be used to predict disease severity and risk associated with infection. Such indicators can help identify patients at high risk of developing severe disease, allowing for better allocation of limited human and technical resources, preventing unnecessary hospitalization and mitigating other impacts.

Biomarkers of inflammation derived from the peripheral blood, such as white blood cell (WBC) count, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and serum CRP levels have been investigated as independent predictors for prognosis of systematic inflammatory diseases (Guthrie, G. et al., 2013; Hu, H. et al., 2016). They have also been widely investigated in several other conditions such as malignancies (including hematological malignancies) and respiratory, gastrointestinal, cardiovascular (including acute coronary syndrome and intracerebral hemorrhage) and systemic diseases. Several studies have tested these biomarkers as a marker of disease severity and prognosis in COVID-19 (Seyit, M. et al., 2021; Liu, J. et al., 2020, Jimeno, S. et al., 2020; Erdogan, A. et al., 2021). As these biomarkers are part of routinely evaluated blood tests and are inexpensive, easily measurable and widely available, they have potential (particularly in low-resource countries) as cost-effective predictors of progression to a severe disease requiring ICU admission. Our study aimed to investigate the role of different hemogram-derived ratios in predicting subsequent ICU admission.

Methods

We conducted a cross-sectional study with patients selected from COVID-19 patients visiting four hospitals in Sylhet City, Bangladesh, from October 2020 to January 2021. COVID-19 diagnosis was carried out by a specialist based on a polymerase chain reaction test, computed tomographic scan or suggestive clinical features. Data on clinical characteristics, results of laboratory tests and clinical outcomes of the enrolled patients were collected from hospital records. The inclusion criteria were as follows: age ≥18 years and a diagnosis of COVID-19 requiring hospitalization. The exclusion criteria were: age <18 years, pregnancy and lack of required data. The final study included 442 patients.

Enrolled patients were assessed at the emergency department, where a blood sample was drawn. Laboratory assessments consisted of complete blood count (including WBC count, leukocyte subtypes, hemoglobin count and platelet count) and biochemical parameters (random blood sugar (RBS), serum ferritin (S. ferritin), D-dimer).

Definitions

WBC count ($\times 10^9$ cells/L), neutrophil ($\times 10^9$ cells/L), lymphocytes ($\times 10^9$ cells/L) and platelets ($\times 10^{11}$ cells/L) were used to define the hemogram-derived ratios. NLR is the ratio between neutrophil and lymphocytes; d-NLR is derived NLR and calculated as d-NLR = ANC/(WBC-ANC), where ANC is the absolute neutrophil count. NPR is the ratio between neutrophil and platelets, PLR is the ratio between platelets and lymphocytes, and finally, systemic immune-inflammation index (SII) is defined as neutrophil multiplied by platelets and divided by lymphocytes.

Study variables

The outcome variable was ICU admission (Yes or No). Clinical data included age; sex; clinical features; presence of comorbidities such as hypertension, chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), diabetes mellitus (DM), ischemic heart disease (IHD) and cerebrovascular accident (CVA); peripheral capillary oxygen saturation (SpO_2) at admission; and length of hospital stay (in days). Laboratory parameters included complete blood count, D-dimer, S. ferritin and RBS. The radiographic findings included chest CT scan reports.

Statistical analysis

We used descriptive statistics to describe the data. Shapiro-Wilk test was used to assess the normality of continuous variables. We presented continuous measurements by mean and SD for data that followed a normal distribution and by the median and interquartile range for data that were skewed. The mean difference between the two groups (ICU vs non-ICU) in a continuous variable was assessed using the two-sample t-test for the normally distributed data and the non-parametric Mann-Whitney U test for the non-normally distributed data. Categorical variables were presented using frequencies and percentages (%). The Chi-Square test (χ^2 test) of independence was used to determine the association (difference) among categorical variables. Differences in the hemogram-derived ratios due to comorbidities were investigated using the multivariate analysis of variance (MANOVA) test.

Multiple logistic regression models were used to identify the predictors of ICU admission. The candidate predictors for the adjusted model were selected based on clinical relevance. Initially, simple logistic regression models were fitted for each candidate predictor. Variables that were highly correlated or associated were excluded from the model due to multicollinearity. Model A included age, DM, CKD and COPD. Models B–D included the previous model and RBS, D-dimer, S. ferritin and admission SpO_2. Each hemogram-derived ratio was added separately to each model and their significance tested. Model findings were presented using odds ratio (OR) and 95% CI. A *P*-value of <0.05 was considered statistically significant. We used the receiver operating characteristic (ROC) curve to detect optimal cut-off values of the hemogram-derived ratios in predicting ICU admission. The effects of comorbidities on the hemogram-derived ratios and ICU admission were determined using the multiple linear regression model and multiple logistic regression model, respectively. Data analysis was performed using R software. The study is reported following the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) (von Elm, E. et al., 2008) statements.

Results

Demographics and baseline characteristics of patients

The final analysis included 442 patients. The clinical characteristics of patients are summarized (overall and by ICU admission status) in Table 1. ICU admission was required in 98 (22.17%) patients. Of the total study patients, 55 (12.44%) died in hospital; 4 (1.2%) were from the non-ICU group . The mean age of study patients was 60.2 ± 13.7 years. The mean age in the ICU group was higher than in the non-ICU group (65.3 ± 14.9 vs 58.8 ± 13.1 years). Men comprised two-thirds of the study sample (65.8% vs 34.2%). Patients requiring ICU had significantly lower SpO_2 at admission than those not requiring ICU (82.7± 11.4 vs 92.0 ± 7.0; *P*=<.001). The length of hospital stay was higher in ICU patients (*P*=<.001).

Laboratory results are shown in Table 2. In those requiring ICU admission, median WBC and neutrophil count were significantly higher (10.45 vs 7.8 × 10^9/L; *P*=<.001 and 8.86 vs 5.7 × 10^9/L; *P*=<.001, respectively), while lymphocyte and platelet count were lower (1.16 vs 1.48 × 10^9/L; *P*=0.006 and 220 vs 230 × 10^9/L; *P*=0.449, respectively). Leukocytosis and lymphocytopenia were more prevalent in ICU patients (52% vs 29.4%; *P*=<.001 and 74.5% vs 48.8%; *P*=<.001, respectively). Compared with patients not requiring ICU, the median values of D-dimer (895 vs 505; *P*=0.005), S. ferritin (466 vs 325; *P*=0.018) and RBS (12 vs 9.2; *P*=0.003) were significantly higher in ICU patients.

The difference in hemogram-derived ratios between the ICU and the non-ICU group is shown in Table 3. The median values of NLR (7.08 vs 3.85; *P*=<.001), d-NLR (5.25 vs 3.16; *P*=<.001), NPR (3.52 vs 2.4;

Table 1
Clinical characteristics of all patients, overall and by survivor status.

					Univariable analysis	
Variables	Total	Non-ICU	ICU	p value	OR (95% CI)	p value
Age	60.2±13.7	58.8 ±13.1	65.3 ±14.9	<.001	1.04 (1.02-1.05)	0.001
Sex		113 (32.8%)	38 (38.8%)	0.332		
Male	291 (65.8%)	231 (67.2%)	60 (61.2%)		0.77(0.48-1.23)	0.276
Female	151 (34.2%)	113 (32.8%)	38 (38.8%)			
Co-morbidities						
Hypertension	311 (70.4%)	241 (70.1%)	70(71.4%)	0.891	1.06(0.66-1.77)	0.793
DM	281 (63.6%)	212 (61.6%)	69(70.4%)	0.14	1.48(0.92-2.43)	0.112
CKD	78 (17.6%)	53 (15.4%)	25(25.5%)	0.03	1.88(1.08-3.20)	0.022
COPD	54 (12.2%)	33 (9.6%)	21(21.4%)	0.003	2.57(1.39-4.66)	0.002
IHD	98 (22.2%)	57 (16.6%)	41(41.8%)	<.001	3.62(2.21-5.92)	0.001
CVA	20 (4.5%)	17 (4.9%)	3 (3.1%)	0.607	0.61(0.14-1.85)	0.434
Admission SpO2	89.9 ±9.0	92.0 ±7.0	82.7±11.4	<.001	0.88 (0.85-0.91)	0.001
LOS	8.7 ± 4.5	7.8 ± 3.2	11.5 ± 6.6	<.001	1.19 (1.13-1.26)	0.001
In-hospital mortality	55(12.44%)	4 (1.2%)	51 (52%)	<.001	NA	NA

Abbreviations: ICU, Intensive Care Unit; DM, Diabetes Mellitus; CKD, Chronic kidney disease; COPD, Chronic obstructive pulmonary disease; IHD, Ischemic heart disease; CVA, Cerebrovascular disease; BP, Blood pressure; SpO2, peripheral capillary oxygen saturation.

Table 2
Lab findings on admission.

					Univariable analysis	
Variables	Total	Non-ICU	ICU	p-value	OR (95% CI)	p-value
TC WBC (× 10^9/L)	4-10	7.8 (6-11)	10.45(6.80-14.38)	<.001	3.13 (1.89-5.18)	0.001
High	152 (34.4%)	101 (29.4%)	51 (52%)	<.001	2.61 (1.65-4.14)	0.001
Normal	279 (63.1%)	233 (67.7%)	46 (46.9%)	<.001	0.42 (0.27-0.66)	0.0002
Low	11 (2.5%)	10 (2.9%)	1 (1%)	0.49	0.34 (0.02-1.83)	0.312
Neutrophil (× 10^9/L)	2.0-7.0	5.7(3.89-8.59)	8.86(5.20-13.43)	<.001	3.10 (2.01-4.76)	0.001
Lymphocyte (× 10^9/L)	0.8–4.5	1.48 (1.08-2.07)	1.16(0.748-1.76)	0.006	0.48 (0.32-0.71)	0.001
Low	241 (54.5%)	168 (48.8%)	73 (74.5%)	<.001	3.06 (1.87-5.12)	0.001
Normal	201 (45.5%)	176 (51.2%)	25 (25.5%)	<.001	0.32 (0.19-0.53)	0.001
High	4 (0.9%)	3 (0.9%)	1 (1%)	1	1.17 (0.05 -9.26)	0.891
Platelet (× 10^9/L)	150-350	230 (180-300)	220(175-285)	0.449	0.72 (0.42 -1.25)	0.248
Low	49(11.1%)	35 (10.2%)	14 (14.3%)	0.336	1.47 (0.73-2.80)	0.255
Normal	320 (72.4%)	252 (73.3%)	68 (69.4%)	0.53	0.83 (0.51-1.36)	0.45
High	73 (16.5%)	57 (16.6%)	16 (16.3%)	1	0.98 (0.52-1.76)	0.954
D-dimer (ng/L)	0-500	505 (278-1100)	895(502-2209)	0.005	1.57 (1.27-1.93)	0.001
S. Ferritin	20-300	325 (164- 695)	466(192-981)	0.018	1.25 (1.02-1.54)	0.02
RBS	4.4-7.2	9.2 (7.4-12.7)	12(8.4- 15.2)	0.003	2.36 (1.35-4.12)	0.002

Abbreviations: TC WBC, total count of white blood cells; RBS, Random blood sugar.

Table 3
Hemogram-derived ratios predicting ICU requirement.

					Univariable analysis	
Variables	Total	Non-ICU	ICU	p-value	0R (95% CI)	p-value
NLR	4.27 (2.55-7.72)	3.85 (2.40-6.55)	7.08 (4.05-15)	<.001	2.66 (1.95-3.62)	0.001
d-NLR	3.34 (2.12-5.66)	3.16 (1.94-4.88)	5.25 (3.35- 10.11)	<.001	3.01 (2.13-4.23)	0.001
NPR	2.59 (1.82-4.07)	2.4 (1.72-3.71)	3.52 (2.42-5.36)	<.001	2.77 (1.76-4.35)	0.001
PLR	1.63 (1.06-2.45)	1.51 (1.02-2.36)	1.98 (1.15- 3.52)	0.04	1.45 (1.06-1.98)	0.019
SII	9.67 (5.33-18.80)	8.90 (4.91-16.22)	14.67 (8.11-35.67)	<.001	1.79 (1.41-2.28)	0.001

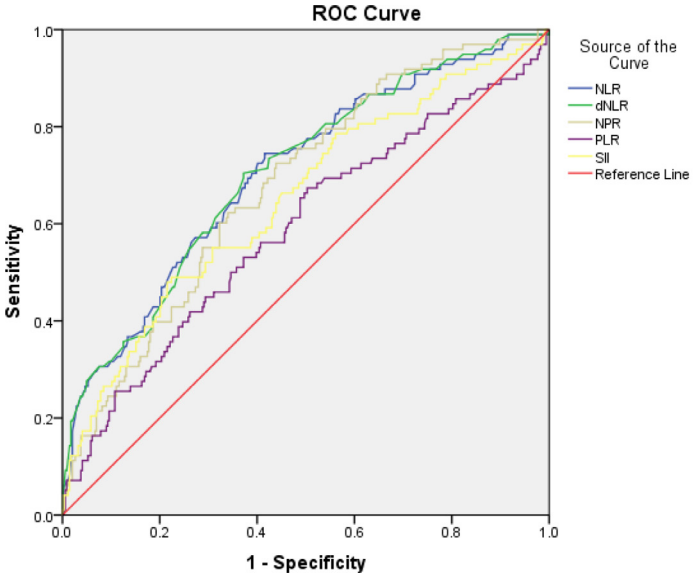
Abbreviations: NLR, neutrophil-to-lymphocyte ratio; d-NLR, derived neutrophil-to-lymphocyte ratio; NPR, neutrophil-to-platelet ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index.

P=<.001), PLR (1.98 vs 1.51; *P*=0.04) and SII (14.67 vs 8.90; *P*=<.001) were significantly higher in ICU patients.

Independent ICU admission prediction ability is shown for each hemogram-derived ratio in Table 4 and ROC curves in Figure 1. The result of multivariable regression models assessing the relationship of different hemogram-derived ratios with ICU admission is shown in Table 4. Model A adjusted the hemogram-derived ratio for age, DM, CKD and COPD. The subsequent models additionally adjusted for RBS, D-dimer, S. ferritin and admission SpO_2. Except for PLR, all ratios remained significant predictors for ICU requirements in all other models.

ROC curve to detect optimal cut-off values of the hemogram-derived ratios

We analyzed the optimal cut-off values of NLR, d-NLR, NPR, PLR and SII, calculated by the ROC analysis and presented in Figure 1. Areas under the curve (AUC) of NLR, d-NLR, NPR, PLR and SII were 0.704, 0.705, 0.679, 0.588 and 0.651, respectively. The optimal cut-off values were NLR 7.29, d-NLR 5.26, NPR 3.69, PLR 2.32 and SII 19.81. SII had the highest specificity (0.78), followed by d-NLR (0.63), then NLR (0.58). The most heightened sensitivity was in favor of NLR (0.74), then NPR (0.72) and d-NLR (0.69) (Table 5).



Variables	Area Under the Curve
NLR	0.704
d-NLR	0.705
NPR	0.679
PLR	0.588
SII	0.651

Figure 1. ROC curve for the different hemogram-derived ratios and their respective area under the curves (AUC).

Table 4
Multivariable adjusted model for ICU requirements.

Model	NLR OR (95% CI) p-value	d-NLR OR (95% CI) p-value	NPR OR (95% CI) p-value	PLR OR (95% CI) p-value	SII OR (95% CI) p-value
Model A	2.38(1.74- 3.27) **0.001**	2.63(1.85-3.74) **0.001**	2.86(1.90 -4.29) **0.001**	1.32(0.95 -1.81) 0.08	1.64(1.28 -2.10) **0.001**
Model B	2.37(1.73-3.24) **0.001**	2.61(1.84-3.71) **0.001**	2.77(1.84 -4.16) **0.001**	1.34(0.97 -1.84) 0.06	1.64(1.28 -2.10) **0.001**
Model C	2.23(1.62-3.08) **0.001**	2.45(1.71-3.50) **0.001**	2.55 (1.68-3.87) **0.001**	1.31(0.96-1.81) 0.08	1.56 (1.22- 2.01) **0.0004**
Model D	2.16 (1.57-2.98) **0.001**	2.36(1.65-3.38) **0.001**	2.45(1.61-3.73) **0.001**	1.30 (0.95-1.79) 0.09	1.55(1.21- 1.99) **0.0005**
Model E	1.80(1.28- 2.53) **0.0007**	1.91(1.30-2.80) **0.0008**	2.09(1.32- 3.31) **0.0016**	1.20(0.86-1.69) 0.273	1.38(1.06-1.80) **0.016**

Model A: Age, DM, CKD, COPD, Model B: Model A + RBS, Model C: Model B + D-dimer, Model D: Model C + Ferritin, Model E: Model D + Admission SpO2.
NLR, neutrophil-to-lymphocyte ratio; d-NLR, derived neutrophil-to-lymphocyte ratio; NPR, neutrophil-to-platelet ratio; PLR, platelet-to-lymphocyte ratio, SII, systemic immune-inflammation index.

Table 5
Cut off value of hemogram-derived ratios in predicting ICU requirement.

Variable	Cut off	Sensitivity	Specificity
NLR	7.29	0.74	0.58
d-NLR	5.26	0.69	0.63
NPR	3.69	0.72	0.56
PLR	2.32	0.67	0.49
SII	19.81	0.49	0.78

Abbreviations: NLR, neutrophil-to-lymphocyte ratio; d-NLR, derived neutrophil-to-lymphocyte ratio; NPR, neutrophil-to-platelet ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index.

Effects of comorbidities on the hemogram-derived ratios and ICU admission

Figure 2 shows the prevalence of comorbidities among all study patients and patients admitted to the ICU. The most prevalent comorbidity was DM (63.3% of all study patients, 70.4% of ICU patients) followed by IHD (22.2% all, 41.8% ICU), CKD (17.6% all, 25.5% ICU) and COPD (12.2% all, 21.4% ICU). The least prevalent comorbidity was CVA (4.5% all, 3.1% ICU). The result of the MANOVA test is presented in **Table A1** in the Appendix. The Pillai's trace test statistic demonstrated that the values of the hemogram-derived ratios significantly varied due to IHD, COPD and CVA.

The effects of comorbidities on the hemogram-derived ratios and ICU admission are presented in Table 6. The results of multiple linear regression models showed that the presence of IHD significantly increased NLR (P=<.001), d-NLR (P=<.001) and SII (P<.001); COPD significantly increased NLR (P=0.02), d-NLR (P=<.001) and NPR (P=<.001); and CVA significantly increased PLR (P=<.001) only. Furthermore, the multiple logistic regression model revealed that IHD and COPD were significantly associated with ICU admission. Patients with IHD and COPD were 3.1 times (P=<.001) and 2.1 times (P=0.03), respectively, more likely to require ICU admission than a patient without these conditions.

DISCUSSION

Statement of principal findings

Our study described the clinical characteristics and laboratory parameters of hospitalized COVID-19 patients and investigated the role of hemogram-derived ratios in predicting ICU admission. Compared with patients who did not require ICU, ICU patients were older with increased comorbidities such as hypertension, CKD, IHD, COPD, DM, and CVA. Patients with IHD and COPD were 3.1 times and 2.1 times, respectively, more likely to require ICU admission than those without these condi-

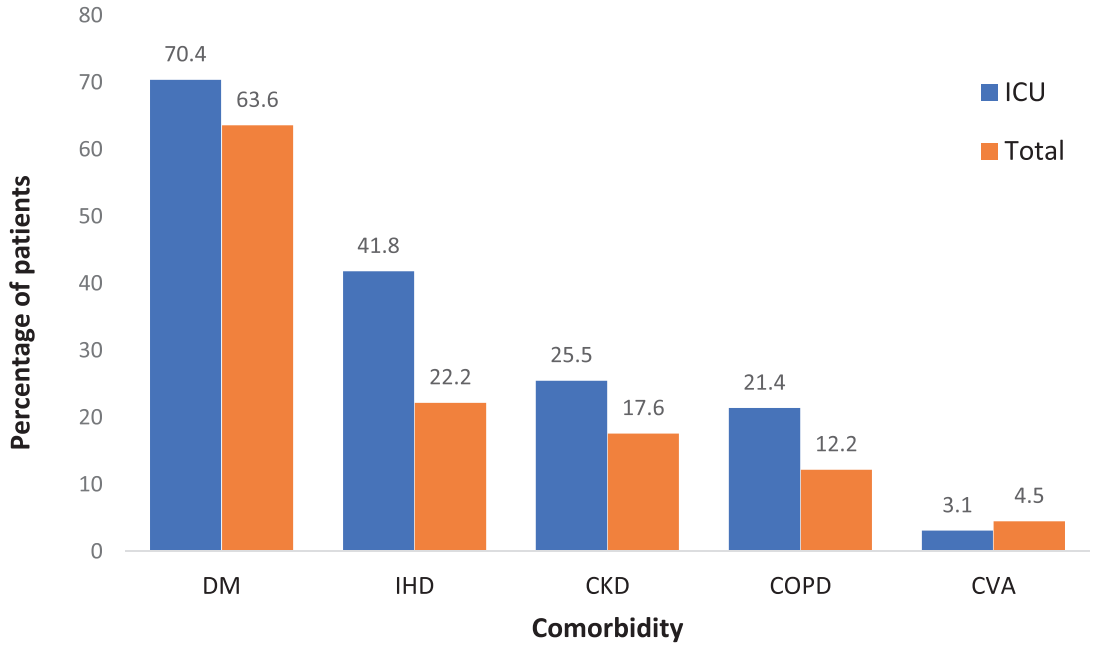


Figure 2. Ranking of comrbidities for total and ICU patients.

Table 6
The effects of comorbidities on the hemogram-derived ratios and ICU admission.*

Comorbidities	NLR		d-NLR		NPR		PLR		SII		ICU admission	
	Coeff.	p-value	Coeff.	p-value	Coeff.	p-value	Coeff.	p-value	Coeff.	p-value	OR	p-value
DM	0.67	0.305	0.63	0.113	0.08	0.779	0.34	0.224	2.88	0.224	1.32	0.307
IHD	3.44	<.001	2.21	<.001	0.17	0.608	0.42	0.198	13.06	<.001	3.12	<.001
CKD	-0.49	0.552	-0.18	0.725	-0.29	0.414	-0.23	0.511	-1.83	0.545	1.21	0.542
COPD	2.21	0.023	2.05	<.001	1.43	<.001	0.34	0.410	6.78	0.053	2.11	0.028
CVA	1.18	0.424	0.64	0.475	-0.04	0.956	2.45	<.001	2.80	0.598	0.53	0.335

* Results from multiple logistic regression for ICU admission and multiple linear regressions for hemogram-derived ratios.

tions. SpO_2 measured at admission was significantly lower in patients who subsequently required ICU admission. The death rate was significantly higher in ICU patients. Adjusted multivariable models revealed that NLR, d-NLR, NPR and SII were significant predictors of ICU admission.

Strengths and limitations

Clinical and pathologic observation has found that hyperinflammation and immunothrombosis are critical pathogenic mechanisms in cell injury in COVID-19; addressing these processes is therefore essential in COVID-19 management. Current studies primarily focus on combating these processes. Early risk stratification of patients can facilitate effective intervention at the outset, which may substantially improve outcomes. The present study contributes tools for risk stratification that are within reach of all hospitals, even peripheral centers.

However, our study has some limitations. We did not consider the effect of other inflammatory markers such as CRP, lactate dehydrogenase, procalcitonin, troponin and interleukin-6 because ours is a retrospective study and these measures were not available in the dataset. We used only admission laboratory parameters and did not evaluate the dynamic change of these biomarkers. As a result, their effects on disease course may be underestimated here.

Interpretation in the context of the wider literature

The COVID-19 pandemic has threatened the global health system. Even developed countries such as the USA, with their very organized health care system, have seen a huge death toll (Bilinski, A and Emanuel, E. J., 2020). On the other hand, some developing countries such as Vietnam, India's Kerala state and South Korea have tackled the pandemic far more effectively with limited resources, at low cost and with impressive results (Tran, T. P. T. et al., 2020; Chathukulam, J., and Tharamangalam, J., 2021; You, J., 2020). Identifying at-risk patients at the earliest opportunity and prioritizing available resources to them can be a very effective strategy to manage the unprecedented challenge of COVID-19, particularly for developing countries. Allocating scarce resources to those with the highest probability of getting benefits from them will save more lives; this is particularly important in critical care services, given the unprecedented need for ICU beds during this COVID-19 pandemic.

The rates of ICU admission and death in our study participants were 22.17% and 12.44%, respectively. These figures are similar to findings in other studies (Chang, R. et al., 2021; Covino, M. et al., 2020). The presence of comorbidity has been found to increase the risk of becoming infected with COVID-19 (Yang, J. et al., 2020; Guan, W. et al., 2020) and be predictive of severe disease with resultant increased ICU admission and higher mortality (Jain, V. and Yuan, J., 2020; Thakur, B. et al., 2021; Honardoost, M. et al., 2021; Liu, B. et al., 2021). Our study aligns with these findings.

Various immune-inflammatory parameters have been studied to understand their role as predictors of disease severity and mortality (Lipworth, B. et al., 2020; Del Valle, D. et al., 2020; Satış, H. et al., 2021; Prasetya, I. et al., 2021). However, inflammatory biomarkers such as interleukin, lymphocyte subset, CRP, Ferritin and D-dimer are costly and not widely available in all health care facilities, particularly in rural areas. Therefore, there is an urgent need to identify predictors of ad-

verse outcomes that are readily available and cost-effective. The present study was designed to evaluate the role of different hemogram-derived ratios in predicting ICU admission of COVID-19 patients. These ratios are available from routine laboratory tests.

Neutrophil is a major component of the leukocyte population that activates and migrates from the venous system to the immune organ or system (Rosales, C., 2018). On the other hand, human immune response triggered by viral infection mainly relies on lymphocytes (Rabinowich, H. et al., 1987), whereas systematic inflammation significantly depresses cellular immunity, which significantly decreases CD4+ T lymphocytes and increases CD8+ suppressor T lymphocyte (Menges, T. et al., 1999). Thus, virus-triggered inflammation leads to an increased NLR. The role of NLR has been extensively studied and shown to be associated with poor outcomes in infectious diseases, stroke, cancer and cardiovascular diseases (Furman, D. et al., 2019; Liu, Y. et al., 2020; Park, J. et al., 2018; Wei, Y. and Qian, W., 2014; Duan, J. et al., 2018). Current evidence suggests that high NLR and d-NLR are associated with disease progression and ICU admission in COVID-19 (Yang, A. et al., 2020; Núñez, I. et al., 2021; Liu, Y. et al., 2020; Alkhatip, A. et al., 2021). Our study also found NLR and d-NLR as significant predictors of ICU admission.

Activated platelets enhance lymphocyte adhesion to the endothelium, promoting lymphocyte homing in endothelial veins and migration to inflammatory sites (von Hundelshausen, P. and Weber, C., 2007). PLR as a marker of inflammation reflects both aggregation and inflammatory pathways and may be more valuable in predicting various inflammations than platelet or lymphocyte counts alone (Qu, R. et al., 2020). A systematic review and meta-analysis concluded that elevated PLR levels on admission could be utilized as a prognostic indicator of severity in COVID-19 patients, especially in resource-limited settings where there is an urgent need to effectively allocate medical resources and divert attention to patients with poorer prognosis (Simadibrata, D. et al., 2020). A few retrospective studies found that NLR was a dependent predictor associated with mortality while PLR was not (Açıksarı, G. et al., 2021; Wang, X. et al., 2020; Dávila-Collado, R. et al., 2021). Our study did not find any significant association of PLR with ICU admission.

Platelets and neutrophils interact during infection, inflammation and thrombosis and modulate each other's functions (Lisman, T., 2017). Ratios of these cells (NPR) have been investigated in COVID-19 and found to be a prognostic factor of disease severity and mortality (López-Escobar, A. et al., 2021; Zhang, N. et al., 2021; López-Escobar, A. et al., 2021). Consistent with these findings, our study found NPR as a significant predictor of ICU admission.

The SII index uses measures of platelets, inflammatory activators (neutrophils/monocytes), and regulators (lymphocytes), which are accepted as potential prognostic markers and sometimes a more powerful tool than NLR and PLR for predicting survival outcomes in different types of cancer (Liu, J. et al., 2019; Yang, R. et al., 2018; Chen, J. et al., 2017). Evidence suggests that higher SII is found in COVID-19 ICU patients compared with non-ICU patients and that SII is a potent marker for predicting the requirement for invasive ventilator support, disease severity and poor prognosis in COVID-19 patients (Muhammad, S. et al., 2021; Nalbant, A. et al., 2021; Fois, A. et al., 2020), all of which is consistent with our study.

Implications for policy, practice and future research

With the unforeseen and unprecedented challenges to the global health system imposed by COVID-19, there has been an urgent need to find strategies to mitigate the loss of human life within existing health care resources. Research directed at identifying at-risk patients at hospital admission using readily available, low-cost parameters is paramount. We focused on cost-effective and straightforward investigations studying several hemogram-derived parameters and analyzing their ability to predict ICU admission. Our findings can guide policymakers and clinicians to risk-stratify patients at admission. We suggest multinational studies be carried out to validate these predictors in different ethnic groups and geographic areas. Future studies should also investigate the dynamic changes of these markers in the clinical course of the disease. Our findings can help policymakers adopt appropriate strategies that are likely to better target at-risk patients and substantially decrease health expenditure.

Conclusion

Our study investigated the efficacy of inflammatory markers in predicting ICU admission in COVID-19 patients. These markers are easily measurable, widely available at low cost and can be calculated from routine blood tests. We found that higher NLR, d-NLR, NPR and SII at hospital admission are significant predictors of subsequent ICU admission for COVID-19 patients. Therefore, we recommend using these markers on admission for triaging patients at high risk of developing severe disease and requiring ICU admission and ensuring appropriate resources are allocated to them.

Declarations

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Availability of data and materials

The datasets analyzed during the current study are not publicly available because of having no permission from the hospitals from where data were collected.

Authors' contributions

MA contributed to data acquisition, conception and design of the study, data analysis, data interpretation and manuscript writing. MRB contributed to all the stages of development of the manuscript, including data analysis and report writing. ZJB, NA and TF contributed to the acquisition of data, conception and design of the study and revising the manuscript. All authors have approved the submitted version of the manuscript.

Ethics approval and consent to participate

We obtained ethical approval from the ethical committee of Sylhet Women's Medical College, Sylhet, Bangladesh, and the committee waived the need for consent. The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijregi.2022.04.011.

References

Açıksarı G, Koçak M, Çağ Y, Altunal L, Atıcı A, Çelik F, et al. Prognostic Value of Inflammatory Biomarkers in Patients with Severe COVID-19: A Single-Center Retrospective Study. Biomarker Insights 2021;16. doi:10.1177/11772719211027022.

Agampodi T, Agampodi S, Glozier N, Siribaddana S. Measurement of social capital in relation to health in low and middle income countries (LMIC): A systematic review. Social Science & Medicine 2015;128:95–104. doi:10.1016/j.socscimed.2015.01.005.

Ali H, Alshukry A, Marafie S, AlRukhayes M, Ali Y, Abbas M, et al. Outcomes of COVID-19: Disparities by ethnicity. Infection, Genetics And Evolution, 2021;87. doi:10.1016/j.meegid.2020.104639.

Alkhatip A, Kamel M, Hamza M, Farag E, Yassin H, Elayashy M, et al. The diagnostic and prognostic role of neutrophil-to-lymphocyte ratio in COVID-19: a systematic review and meta-analysis. Expert Review Of Molecular Diagnostics 2021;21(5):505–14. doi:10.1080/14737159.2021.1915773.

Armstrong R, Kane A, Kursumovic E, Oglesby F, Cook T. Mortality in patients admitted to intensive care with COVID-19: an updated systematic review and meta-analysis of observational studies. Anaesthesia 2021;76(4):537–48. doi:10.1111/anae.15425.

Bilinski A, Emanuel EJ. COVID-19 and excess all-cause mortality in the US and 18 comparison countries. JAMA: The Journal of the American Medical Association 2020;324(20):2100–2. doi:10.1001/jama.2020.20717.

Chang R, Elhusseiny K, Yeh Y, Sun W. COVID-19 ICU and mechanical ventilation patient characteristics and outcomes—A systematic review and meta-analysis. PLOS ONE 2021;16(2). doi:10.1371/journal.pone.0246318.

Chang R, Elhusseiny K, Yeh Y, Sun W. COVID-19 ICU and mechanical ventilation patient characteristics and outcomes—A systematic review and meta-analysis. PLOS ONE 2021;16(2). doi:10.1371/journal.pone.0246318.

Chathukulam J, Tharamangalam J. The Kerala model in the time of COVID19: Rethinking state, society and democracy. World Development 2021;137(105207). doi:10.1016/j.worlddev.2020.105207.

Chen J, Zhai E, Yuan Y, Wu K, Xu J, Peng J, et al. Systemic immune-inflammation index for predicting prognosis of colorectal cancer. World Journal Of Gastroenterology 2017;23(34):6261. doi:10.3748/wjg.v23.i34.6261.

Covino M, Sandroni C, Santoro M, Sabia L, Simeoni B, Bocci M, et al. Predicting intensive care unit admission and death for COVID-19 patients in the emergency department using early warning scores. Resuscitation 2020;156:84–91. doi:10.1016/j.resuscitation.2020.08.124.

Dávila-Collado R, Jarquín-Durán O, Solís-Vallejo A, Nguyen M, Espinoza J. Elevated Monocyte to Lymphocyte Ratio and Increased Mortality among Patients with Chronic Kidney Disease Hospitalized for COVID-19. Journal Of Personalized Medicine 2021;11(3):224. doi:10.3390/jpm11030224.

Del Valle D, Kim-Schulze S, Huang H, Beckmann N, Nirenberg S, Wang B, et al. An inflammatory cytokine signature predicts COVID-19 severity and survival. Nature Medicine 2020;26(10):1636–43. doi:10.1038/s41591-020-1051-9.

Duan J, Pan L, Yang M. Preoperative elevated neutrophil-to-lymphocyte ratio (NLR) and derived NLR are associated with poor prognosis in patients with breast cancer. Medicine 2018;97(49):e13340. doi:10.1097/md.0000000000013340.

Erdogan A, Can F, Gönüllü H. Evaluation of the prognostic role of NLR, LMR, PLR, and LCR ratio in COVID-19 patients. Journal Of Medical Virology 2021;93(9):5555–9. doi:10.1002/jmv.27097.

Fois A, Paliogiannis P, Scano V, Cau S, Babudieri S, Perra R, et al. The Systemic Inflammation Index on Admission Predicts In-Hospital Mortality in COVID-19 Patients. Molecules 2020;25(23):5725. doi:10.3390/molecules25235725.

Furman D, Campisi J, Verdin E, Carrera-Bastos P, Targ S, Franceschi C, et al. Chronic inflammation in the etiology of disease across the life span. Nature Medicine 2019;25(12):1822–32. doi:10.1038/s41591-019-0675-0.

Gottlieb M, Sansom S, Frankenberger C, Ward E, Hota B. Clinical Course and Factors Associated With Hospitalization and Critical Illness Among COVID-19 Patients in Chicago, Illinois. Academic Emergency Medicine 2020;27(10):963–73. doi:10.1111/acem.14104.

Guan W, Liang W, Zhao Y, Liang H, Chen Z, Li Y, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. European Respiratory Journal 2020;55(5). doi:10.1183/13993003.00547-2020.

Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. New England Journal Of Medicine 2020;382(18):1708–20. doi:10.1056/nejmoa2002032.

Guthrie G, Charles K, Roxburgh C, Horgan P, McMillan D, Clarke S. The systemic inflammation-based neutrophil–lymphocyte ratio: Experience in patients with cancer. Critical Reviews In Oncology/Hematology 2013;88(1):218–30. doi:10.1016/j.critrevonc.2013.03.010.

Herold T, Jurinovic V, Arnreich C, Lipworth B, Hellmuth J, von Bergwelt-Baildon M, et al. Elevated levels of IL-6 and CRP predict the need for mechanical ventilation in COVID-19. Journal Of Allergy And Clinical Immunology 2020;146(1):128–36 .e4. doi:10.1016/j.jaci.2020.05.008.

Honardoost M, Janani L, Aghili R, Emami Z, Khamseh M. The Association between Presence of Comorbidities and COVID-19 Severity: A Systematic Review and Meta-Analysis. Cerebrovascular Diseases 2021;50(2):132–40. doi:10.1159/000513288.

Hu H, Yao X, Xie X, Wu X, Zheng C, Xia W, Ma S. Prognostic value of preoperative NLR, dNLR, PLR and CRP in surgical renal cell carcinoma patients. World Journal Of Urology 2016;35(2):261–70. doi:10.1007/s00345-016-1864-9.

Jain V, Yuan J. Predictive symptoms and comorbidities for severe COVID-19 and intensive care unit admission: a systematic review and meta-analysis. International Journal Of Public Health 2020;65(5):533–46. doi:10.1007/s00038-020-01390-7.

Java A, Apicelli A, Liszewski M, Coler-Reilly A, Atkinson J, Kim A, Kulkarni H. The complement system in COVID-19: friend and foe? JCI Insight 2020;5(15). doi:10.1172/jci.insight.140711.

Jimeno S, Ventura P, Castellano J, García-Adasme S, Miranda M, Touza P, et al. Prognostic implications of neutrophil-lymphocyte ratio in COVID-19. European Journal Of Clinical Investigation 2020;51(1). doi:10.1111/eci.13404.

Kral JB, Schrottmaier WC, Salzmann M, Assinger A. Platelet interaction with innate immune cells. Transfusion Medicine and Hemotherapy 2016;43(2):78–88. doi:10.1159/000444807.

Koupenova M, Clancy L, Corkrey HA, Freedman JE. Circulating platelets as mediators of immunity, inflammation, and thrombosis. Circulation Research 2018;122(2):337–51. doi:10.1161/CIRCRESAHA.117.310795.

Legido-Quigley H, Asgari N, Teo Y, Leung G, Oshitani H, Fukuda K, et al. Are high-performing health systems resilient against the COVID-19 epidemic? The Lancet 2020;395(10227):848–50. doi:10.1016/s0140-6736(20)30551-1.

Lipworth B, Chan R, Kuo C. Predicting Severe Outcomes in COVID-19. The Journal Of Allergy And Clinical Immunology: In Practice 2020;8(8):2582–4. doi:10.1016/j.jaip.2020.06.039.

Lisman T. Platelet–neutrophil interactions as drivers of inflammatory and thrombotic disease. Cell And Tissue Research 2017;371(3):567–76. doi:10.1007/s00441-017-2727-4.

Liu B, Spokes P, He W, Kaldor J. High risk groups for severe COVID-19 in a whole of population cohort in Australia. BMC Infectious Diseases 2021;21(1). doi:10.1186/s12879-021-06378-z.

Liu J, Li S, Zhang S, Liu Y, Ma L, Zhu J, et al. Systemic immune-inflammation index, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio can predict clinical outcomes in patients with metastatic non-small-cell lung cancer treated with nivolumab. Journal Of Clinical Laboratory Analysis 2019;33(8). doi:10.1002/jcla.22964.

Liu J, Liu Y, Xiang P, Pu L, Xiong H, Li C, et al. Neutrophil-to-lymphocyte ratio predicts critical illness patients with 2019 coronavirus disease in the early stage. Journal Of Translational Medicine 2020;18(1). doi:10.1186/s12967-020-02374-0.

Liu Y, Du X, Chen J, Jin Y, Peng L, Wang H, et al. Neutrophil-to-lymphocyte ratio as an independent risk factor for mortality in hospitalized patients with COVID-19. Journal Of Infection 2020;81(1):e6–e12. doi:10.1016/j.jinf.2020.04.002.

Liu Y, Lu J, Yin H, Xia P, Qiu D, Liang M, et al. High Neutrophil-to-Lymphocyte Ratio Predicts Hemorrhagic Transformation in Acute Ischemic Stroke Patients Treated with Intravenous Thrombolysis. International Journal Of Hypertension 2020;2020:1–6. doi:10.1155/2020/5980261.

López-Escobar A, Madurga R, Castellano J, Ruiz de Aguiar S, Velázquez S, Bucar M, et al. Hemogram as marker of in-hospital mortality in COVID-19. Journal Of Investigative Medicine 2021;69(5):962–9. doi:10.1136/jim-2021-001810.

López-Escobar A, Madurga R, Castellano J, Velázquez S, Suárez del Villar R, Menéndez J, et al. Risk Score for Predicting In-Hospital Mortality in COVID-19 (RIM Score). Diagnostics 2021;11(4):596. doi:10.3390/diagnostics11040596.

McGregor S, Henderson K, Kaldor J. How Are Health Research Priorities Set in Low and Middle Income Countries? A Systematic Review of Published Reports. Plos ONE 2014;9(10). doi:10.1371/journal.pone.0108787.

Mehta P, McAuley D, Brown M, Sanchez E, Tattersall R, Manson J. COVID-19: consider cytokine storm syndromes and immunosuppression. The Lancet 2020;395(10229):1033–4. doi:10.1016/s0140-6736(20)30628-0.

Menges T, Engel J, Welters I, Wagner R, Little S, Ruwoldt R, et al. Changes in blood lymphocyte populations after multiple trauma. Critical Care Medicine 1999;27(4):733–40. doi:10.1097/00003246-199904000-00026.

Merad M, Martin J. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. Nature Reviews Immunology 2020;20(6):355–62. doi:10.1038/s41577-020-0331-4.

Muhammad S, Fischer I, Naderi S, Faghih Jouibari M, Abdolreza S, Karimialavijeh E, et al. Systemic Inflammatory Index Is a Novel Predictor of Intubation Requirement and Mortality after SARS-CoV-2 Infection. Pathogens 2021;10(1):58. doi:10.3390/pathogens10010058.

Nalbant A, Demirci T, Kaya T, Aydın A, Altındiş M, Güçlü E. Can prognostic nutritional index and systemic immune-inflammatory index predict disease severity in COVID-19? International Journal Of Clinical Practice 2021. doi:10.1111/ijcp.14544.

Núñez I, Priego-Ranero Á, García-González H, Jiménez-Franco B, Bonilla-Hernández R, Domínguez-Cherit G, et al. Common hematological values predict unfavorable outcomes in hospitalized COVID-19 patients. Clinical Immunology 2021;225. doi:10.1016/j.clim.2021.108682.

Okereke M, Ukor NA, Adebisi YA, Ogunkola IO, Favour Iyagbaye E, Adiela Owhor G, Lucero-Prisno 3rd DE. Impact of COVID-19 on access to healthcare in low- and middle-income countries: Current evidence and future recommendations. The International Journal of Health Planning and Management 2021;36(1):13–17. doi:10.1002/hpm.3067.

Park J, Seo K, Choi B, Choi S, Yoon M, Hwang G, et al. Importance of prognostic value of neutrophil to lymphocyte ratio in patients with ST-elevation myocardial infarction. Medicine 2018;97(48):e13471. doi:10.1097/md.0000000000013471.

Prasetya I, Cucunawangsih, Lorens J, Sungono V, El-Khobar K, Wijaya R. Prognostic value of inflammatory markers in patients with COVID-19 in Indonesia. Clinical Epidemiology And Global Health 2021;11. doi:10.1016/j.cegh.2021.100803.

Qu R, Ling Y, Zhang Y, Wei L, Chen X, Li X, et al. Platelet-to-lymphocyte ratio is associated with prognosis in patients with coronavirus disease-19. Journal Of Medical Virology 2020;92(9):1533–41. doi:10.1002/jmv.25767.

Rabinowich H, Cohen R, Bruderman I, Steiner Z, Klajman A. Functional analysis of mononuclear cells infiltrating into tumors: lysis of autologous human tumor cells by cultured infiltrating lymphocytes. Cancer research 1987;47(1):173–7.

Rosales C. Neutrophil: A cell with many roles in inflammation or several cell types? Frontiers in Physiology 2018:9. doi:10.3389/fphys.2018.00113.

Satış H, Özger H, Aysert Yıldız P, Hızel K, Gulbahar Ö, Erbaş G, et al. Prognostic value of interleukin-18 and its association with other inflammatory markers and disease severity in COVID-19. Cytokine 2021;137. doi:10.1016/j.cyto.2020.155302.

Seyit M, Avci E, Nar R, Senol H, Yilmaz A, Ozen M, et al. Neutrophil to lymphocyte ratio, lymphocyte to monocyte ratio and platelet to lymphocyte ratio to predict the severity of COVID-19. The American Journal Of Emergency Medicine 2021;40:110–14. doi:10.1016/j.ajem.2020.11.058.

Simadibrata D, Pandhita B, Ananta M, Tango T. Platelet-to-lymphocyte ratio, a novel biomarker to predict the severity of COVID-19 patients: A systematic review and meta-analysis. Journal Of The Intensive Care Society 2020. doi:10.1177/1751143720969587.

Thakur B, Dubey P, Benitez J, Torres J, Reddy S, Shokar N, et al. A systematic review and meta-analysis of geographic differences in comorbidities and associated severity and mortality among individuals with COVID-19. Scientific Reports 2021;11(1). doi:10.1038/s41598-021-88130-w.

Tran TPT, Tran TPT, Le TH, Nguyen TNP, Hoang VM. Rapid response to the COVID-19 pandemic: Vietnam government's experience and preliminary success. Journal of Global Health 2020;10(2). doi:10.7189/jogh.10.020502.

von Elm E, Altman D, Egger M, Pocock S, Gøtzsche P, &Vandenbroucke J. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Journal Of Clinical Epidemiology 2008;61(4):344–9. doi:10.1016/j.jclinepi.2007.11.008.

von Hundelshausen P, Weber C. Platelets as immune cells: bridging inflammation and cardiovascular disease: Bridging inflammation and cardiovascular disease. Circulation Research 2007;100(1):27–40. doi:10.1161/01.RES.0000252802.25497.b7.

Wang X, Li X, Shang Y, Wang J, Zhang X, Su D, et al. Ratios of neutrophil-to-lymphocyte and platelet-to-lymphocyte predict all-cause mortality in inpatients with coronavirus disease 2019 (COVID-19): a retrospective cohort study in a single medical centre. Epidemiology And Infection 2020;148. doi:10.1017/s0950268820002071.

Wei Y, Jiang Y, Qian W. Prognostic Role of NLR in Urinary Cancers: A Meta-Analysis. Plos ONE 2014;9(3):e92079. doi:10.1371/journal.pone.0092079.

Wu Z, McGoogan J. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China. JAMA 2020;323(13):1239. doi:10.1001/jama.2020.2648.

Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. The Lancet Respiratory Medicine 2020;8(4):420–2. doi:10.1016/s2213-2600(20)30076-x.

Yang A, Liu J, Tao W, Li H. The diagnostic and predictive role of NLR, d-NLR and PLR in COVID-19 patients. International Immunopharmacology 2020;84. doi:10.1016/j.intimp.2020.106504.

Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, et al. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. International Journal Of Infectious Diseases 2020;94:91–5. doi:10.1016/j.ijid.2020.03.017.

Yang R, Chang Q, Meng X, Gao N, Wang W. Prognostic value of Systemic immune-inflammation index in cancer: A meta-analysis. Journal Of Cancer 2018;9(18):3295–302. doi:10.7150/jca.25691.

You J. Lessons from South Korea's Covid-19 policy response. American Review of Public Administration 2020;50(6–7):801–8. doi:10.1177/0275074020943708.

Zhang N, Zhang H, Tang Y, Zhang H, Ma A, Xu F, et al. Risk factors for illness severity in patients with COVID-19 pneumonia: a prospective cohort study. International Journal Of Medical Sciences 2021;18(4):921–8. doi:10.7150/ijms.51205.

Zhang X, Tan Y, Ling Y, Lu G, Liu F, Yi Z, et al. Viral and host factors related to the clinical outcome of COVID-19. Nature 2020;583(7816):437–40. doi:10.1038/s41586-020-2355-0.

Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The Lancet 2020;395(10229):1054–62. doi:10.1016/s0140-6736(20)30566-3.