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Significance of hemogram-derived ratios for predicting in-hospital mortality in COVID-19: A multicenter study

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Abstract

Background: To address the problem of resource limitation, biomarkers having a potential for mortality prediction are urgently required. This study was designed to evaluate whether hemogram-derived ratios could predict in-hospital deaths in COVID-19 patients.

Materials and Methods: This multicenter retrospective study included hospitalized COVID-19 patients from four COVID-19 dedicated hospitals in Sylhet, Bangladesh. Data on clinical characteristics, laboratory parameters, and survival outcomes were analyzed. Logistic regression models were fitted to identify the predictors of in-hospital death.

Results: Out of 442 patients, 55 (12.44%) suffered in-hospital death. The proportion of male was higher in nonsurvivor group (61.8%). The mean age was higher in nonsurvivors (69 ± 13 vs. 59 ± 14 years, $p < 0.001$). Compared to survivors, nonsurvivors exhibited higher frequency of comorbidities, such as chronic kidney disease (34.5% vs. 15.2%, $p \leq 0.001$), chronic obstructive pulmonary disease (23.6% vs. 10.6%, $p = 0.011$), ischemic heart disease (41.8% vs. 19.4%, $p < 0.001$), and diabetes mellitus (76.4% vs. 61.8%, $p = 0.05$). Leukocytosis and lymphocytopenia were more prevalent in nonsurvivors ($p < 0.05$). Neutrophil-to-lymphocyte ratio (NLR), derived NLR (d-NLR), and neutrophil-to-platelet ratio (NPR) were significantly higher in nonsurvivors ($p < 0.05$). After adjusting for potential covariates, NLR (odds ratio [OR] 1.05; 95% confidence interval [CI] 1.009-1.08), d-NLR (OR 1.08; 95% CI 1.006-1.14), and NPR (OR 1.20; 95% CI 1.09-1.32) have been found to be significant predictors of mortality in hospitalized COVID-19 patients. The optimal cut-off points for NLR, d-NLR, and NPR for prediction of in-hospital mortality for COVID-19 patients were 7.57, 5.52 and 3.87, respectively.

Conclusion: Initial assessment of NLR, d-NLR, and NPR values at hospital admission is of good prognostic value for predicting mortality of patients with COVID-19.

KEYWORDS

COVID-19, mortality, predictors

1 | INTRODUCTION

The ongoing COVID-19 pandemic is threatening the global health system. Countries around the world reported 6.07 million deaths from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) until mid-March 2022.[1] However, preliminary estimates suggest an excess death of 1.2 million than officially reported in 2020. The underlying reason behind this discrepancy may be the lack of a proper national vital statistics system and lack of uniformity in test strategy as well as in defining COVID-19 death.[2]

Case fatality rate (CFR) is an important indicator to understand the severity and epidemiological features of infectious diseases. Reported CFR for COVID-19 varies depending on geographic areas. For example, Central Europe and North America had a higher fatality than East Asia due to COVID-19.[3,4] Among the SAARC countries, the reported CFR is highest in Afghanistan, followed by Pakistan, India, and then Bangladesh. The crude CFR in Bangladesh is about 1.458%.[5]

For better utilization of the existing healthcare resources during the ongoing COVID-19 pandemic, identification of the prognostic markers is of paramount importance. Several systematic reviews and meta-analyses found higher age, pre-existing comorbidities like diabetes, chronic obstructive pulmonary disease (COPD), hypertension, renal disease, or cardiovascular disease are important predictors of mortality.[6–8] Among the hematological parameters, higher baseline total white blood cell count (WBC), thrombocytopenia, C-reactive protein (CRP), lactate-dehydrogenase (LDH), creatine kinase (CK), ᴅd-dimer, and lower absolute lymphocyte count (ALC) were all associated with higher mortality rate.[7,9] However, prognostic parameters like procalcitonin, hs-CRP, interleukin (IL)-6, and LDH are costly and not widely available, particularly in low and middle-income countries. To mitigate this economic and logistic constraint, we need to focus more on exploring rapid, inexpensive, and readily available prognostic tools. Hemogram-derived ratios can play a very effective role in this regard. Hemogram-derived ratios like neutrophil (NEU)-to-lymphocyte (LYM) ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have been found to have significant prognostic value in predicting severe disease as well as mortality in COVID-19.[10,11] In this study, we evaluated whether parameters derived from a routine blood test, at the time of hospital admission, can be valuable predictors of mortality in hospitalized COVID-19 patients.

2 | MATERIALS AND METHODS

2.1 | Data collection

Data were extracted from the hospital record of patients who had been admitted with a diagnosis of COVID-19 in four hospitals of Sylhet, Bangladesh (a major city in north-eastern Bangladesh) during the COVID-19 pandemic, between October 2020 and January 2021. Clinical, demographic, and laboratory data from all adult patients were recorded at the time of hospital admission. The blood samples were sent soon after hospital admission, preferably within 1 h. Cell count was done by fully automated analyzer SYSMEX-XT2000i (Made in Japan).

Inclusion criteria: Patients above the age of 18 years, patients who were polymerase chain reaction (PCR) positive for SARS-CoV-2, and PCR negative patients who had typical clinical and radiographic findings of COVID-19.

Exclusion criteria: Patients below the age of 18 years and patients without typical symptoms or absence of radiographic findings compatible with COVID-19 pneumonia.

2.2 | Definition

In-hospital death refers to those patients who died at least 24 h after hospital admission due to COVID-19.

COVID-19 death was defined as certified by WHO, which states "A death due to COVID-19 is defined as a death resulting from a clinically compatible illness, in a probable or confirmed COVID-19 case, unless there is a clear alternative cause of death that cannot be related to COVID disease."

Count of white blood cells ($\times 10^9$ cells/L), neutrophil ($\times 10^9$ cells/L), lymphocytes ($\times 10^9$ cells/L), and platelets ($\times 10^{11}$ cells/L) were used to calculate the hemogram-derived ratios. NLR is the ratio between neutrophils and lymphocytes, d-NLR is derived NLR and calculated as d-NLR = ANC/(WBC − ANC), NPR is the ratio between neutrophils and platelets, PLR is the ratio between platelets and lymphocytes, and systemic immune-inflammation index (SII) is determined by multiplying the neutrophil and platelet counts and then divided by the lymphocyte count.

2.3 | Study variables

The outcome variable was in-hospital death (nonsurvivors and survivors); a binary variable. Clinical data included were age, sex, clinical features, presence of comorbidities like hypertension, chronic kidney disease (CKD), 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 (CBC), D-dimer, S. Ferritin, and random blood sugar (RBS).

2.4 | 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 the mean and standard deviation (SD) for data that followed a normal distribution, and by the median and interquartile range (IQR) for data that were skewed. The mean difference between two groups (survivor vs. nonsurvivor) in a continuous variable was assessed using two independent sample mean tests (*t*-test) for the normally distributed data and using nonparametric Mann–Whitney *U* test for the non-normally distributed data. Categorical variables were presented using frequencies

TABLE 1 Clinical characteristics of patients, overall and by survivor status

Variables	Total	Nonsurvivor (*n*= 55)	Survivor (n= 387)	*p* value	Univariable analysis OR (95% CI)	*p* value
Age, mean (±SD)	60 ± 14	69 ± 13	59 ± 14	<0.001	1.06 (1.03–1.08)	0.001
Male	291 (65.84%)	34 (61.8%)	257 (66.4%)	0.63	0.81 (0.46–1.48)	0.502
Female	151 (34.16%)	21 (38.2%)	130 (33.6%)	0.603		
Comorbidity						
Hypertension	311 (70.36%)	41 (74.5%)	270 (69.8%)	0.57	1.26 (0.68–2.49)	0.469
DM	281 (63.57%)	42 (76.4%)	239 (61.8%)	0.05	2.00 (1.06–3.99)	0.038
IHD	98 (22.17%)	23 (41.8%)	75 (19.4%)	<.001	2.99 (1.64–5.39)	0.0002
CKD	78 (17.65%)	19 (34.5%)	59 (15.2%)	<.001	2.93 (1.55–5.41)	0.0006
COPD	54 (12.22%)	13 (23.6%)	41 (10.6%)	0.011	2.61 (1.25–5.16)	0.007
CVA	20 (4.52%)	5 (9.1%)	15 (3.9%)	0.163	2.48 (0.78–6.71)	NA
Clinical feature						
Fever	399 (90.27%)	52 (94.5%)	353 (91.2%)	0.566	1.67 (0.57–7.10)	0.409
Cough	322 (72.85%)	36 (65.5%)	286 (73.9%)	0.248	0.66 (0.37–1.23)	0.19
SOB	294 (66.52%)	42 (76.4%)	252 (65.1%)	0.133	1.73 (0.92–3.45)	0.101
Fatigability	246 (55.66%)	33 (60%)	213 (55%)	0.584	1.23 (0.69–2.20)	0.489
Loss of smell	87 (19.68%)	9 (16.4%)	78 (20.2%)	0.631	0.77 (0.34–1.58)	0.509
Diarrhea	71 (16.06%)	11 (20%)	60 (15.5%)	0.513	1.36 (0.63–2.70)	0.397
Sore throat	47 (10.63%)	13 (23.6%)	34 (8.8%)	0.002	3.21 (1.53–6.45)	0.00137
Anorexia	13 (2.94%)	2 (3.6%)	11 (2.8%)	1	1.28 (0.19–4.97)	0.74
Chest pain	9 (2.04%)	0 (0%)	9 (2.3%)	0.527	NA	NA
Vomiting	4 (0.90%)	0 (0%)	4 (1%)	1	NA	NA
Headache	3 (0.68%)	1 (1.8%)	2 (0.5%)	0.824	3.56 (0.16–37.82)	0.303
Admission SpO_2	92 (88–95)	84 (73–93)	93 (89–96)	<0.001	0.91 (0.88–0.93)	0.001
LOS	8.7 ± 4.5	10.9 ± 7.3)	8.3 ± 3.8)	0.013	1.10(1.04–1.16)	0.0003

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVA cerebrovascular disease; DM, diabetes mellitus; IHD Ischemic heart disease; LOS, length of stay; OR, odds ratio; SpO_2, peripheral capillary oxygen ; SOB, shortness of breath saturation.

and percentages. The χ^2 test of independence was used to determine the association (difference) among categorical variables.

Multiple logistic regression models were used to identify the predictors of mortality. The variables that were significant at 10% level (cut-off point $p < 0.1$) in the univariate or bivariate analysis were included in the multivariate analysis. We measured the correlations between the various hemogram-derived indices and excluded the hemogram-derived ratios that were responsible for multicollinearity ($r > 0.8$) from the multivariate analysis. We also excluded the hemogram-derived ratios having a variance inflation factor of >5 to make sure that there was no multicollinearity in the multivariate logistic regression models. As there were high correlations among some of the hemogram-derived ratios and as all the ratios are important, we fitted three separate multiple logistic regression models to avoid multicollinearity (Table A1). Model findings were presented using odds ratio (OR) and 95% confidence interval (CI). A $p < 0.05$ was considered statistically significant. We used Youden Index to determine the optimal cut-off values for hemogram-derived ratios for predicting in-hospital mortality. Analysis was performed using R software. This study is reported following the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE)[12] statements.

3 | RESULTS

3.1 | Clinical characteristics and laboratory parameters of patients

The final analysis included 442 patients. Clinical characteristics of all patients are summarized (overall and by survivor status) and shown in Table 1. The proportion of patients who ended up with in-hospital death was 12.44%. The mean age of study subjects was 60.2 ± 13.7 years. The mean age of the non-survivor group was higher than the

TABLE 2 Lab findings on admission

Variables	Normal range	Nonsurvivor	Survivor	*p* value	Univariable analysis OR (95% CI)	*p* value
TC WBC (×10^9/L)	4–10	10.8 (6.80–14)	8.1 (6–11.3)	**0.003**	2.48 (1.34–4.58)	**0.003**
>10		29 (52.7%)	124 (32%)	**0.004**	**2.39 (1.35–4.25)**	**0.00273**
4–10		26 (47.3%)	252 (65.1%)	0.014		
<4		0.0%	11 (2.8%)	0.422		
Neutrophil (×10^9/L)	2.0–7.0	8.8 (4.84–12.59)	6.1 (4.15–9.37)	**<.001**	2.47 (1.47–4.14)	**0.0006**
Lymphocyte (×10^9/L)	0.8–4.5	1.18 (0.75-1.8)	1.4 (1.02–2.04)	0.122	0.61 (0.38–0.97)	**0.0393**
<0.8		40 (72.7%)	201 (51.9%)	**0.006**	**2.46 (**1.35–**4.74)**	**0.004**
0.8–4.5		15 (27.3%)	186 (48.1%)	0.006		
>4.5		0 (0%)	4 (1%)	1		
Platelet (×10^9/L)	150–350	209 (154–254)	230 (180–300)	0.05	0.48 (0.24–0.96)	**0.039**
<150		10 (18.2%)	39 (10.1%)	0.118	1.98 (0.88–4.11)	0.07
150–350		37 (67.3%)	283 (73.1%)	0.455		
>350		8 (14.5%)	65 (16.8%)	0.821		
D-dimer (ng/L)	0–500	900 (420–1411)	567 (300–1230)	0.12	1.26 (0.98–1.62)	0.0626
S. Ferritin	20–300	507 (181–981.32)	328 (169–748)	0.21	1.27 (0.98–1.65)	0.06
RBS	4.4–7.2	12 (8.9–14.7)	9.4 (7.6–13)	**0.005**	2.63 (1.32–5.22)	**0.005**

Note: Statistically significant values are highlighted in bold.

Abbreviations: CI, confidence interval; OR, odds ratio; RBS, random blood sugar; TC WBC, total count of white blood cells.

TABLE 3 Hematological ratios predicting mortality

Variables	Nonsurvivors	Survivors	*p* value	Univariable analysis OR (95% CI)	*p* value
NLR	7.08 (3.85–11.12)	4.05 (2.48–7.08)	0.005	2.02 (1.42–2.88)	0.001
d-NLR	4.88 (2.70–10.11)	3.34 (2.03–5.66)	0.001	2.30 (1.55–3.42)	0.001
NPR	3.59 (2.42–5.61)	2.47 (1.78–3.82)	0.003	2.77 (1.76–4.35)	0.001
PLR	1.96 (1.12–2.77)	1.57 (1.06–2.43)	0.879	1.10 (0.74–1.62)	0.623
SII	14.11 (7.63–25.50)	9.37 (5–17.52)	0.058	1.42 (1.06–1.89)	0.0156

Abbreviations: CI, confidence interval; D-NLR, derived neutrophil-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; NPR, neutrophil-to-platelet ratio; OR, odds ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index.

survivor group (69± 13 vs. 59 ± 14 years). Male comprises two-thirds of the study sample (65.84%).

Compared to survivors, nonsurvivors had higher prevalence of comorbidities like CKD (34.5% vs. 15.2%, [OR]: 2.93; 95% CI: 1.55–5.41; p = <0.001), COPD (23.6% vs. 10.6%, [OR]: 2.61; 95% CI: 1.25–5.16; p = 0.011), IHD (41.8% vs. 19.4%, [OR]: 2.99; 95% CI: 1.64–5.39; p < 0.001), DM (76.4% vs. 61.8%, [OR]: 2.00; 95% CI: 1.06–3.99; p = 0.05) and hypertension (74.5% vs. 69.8%, [OR]: 1.26; 95% CI: 0.68–2.49; p = 0.57).

Nonsurvivors had significantly lower SpO_2 at admission than survivors (median; 84 vs. 93; p < 0.001). Length of hospital stay was significantly higher in nonsurvivors (10.9± 7.3 vs. 8.3 ± 3.8, p = 0.013).

Regarding laboratory results (Table 2), median WBC count (10.8 vs. 8.1; p = 0.003) and neutrophil count (8.8 vs. 6.1; p < 0.001) were significantly higher while platelet (209 vs. 230; p = 0.05) and lymphocyte (1.18 vs. 1.4; p = 0.122) count was lower in nonsurvivors. Leukocytosis (52.7% vs. 32%; p = 0.004) and lymphocytopenia (72.7% vs. 51.9%; p = 0.006) were significantly higher in nonsurvivors. Nonsurvivors have higher median value of D-dimer (900 vs. 567), ferritin (507 vs. 328), and RBS (12 vs. 9.4).

Difference in hemogram-derived ratios between survivors and non-survivors are shown in Table 3. Median value of NLR (7.08 vs. 4.05; p = 0.005), d-NLR (4.88 vs. 3.34; p = 0.001) and NPR (3.59 vs. 2.47; p = 0.003) were significantly higher in nonsurvivor while,

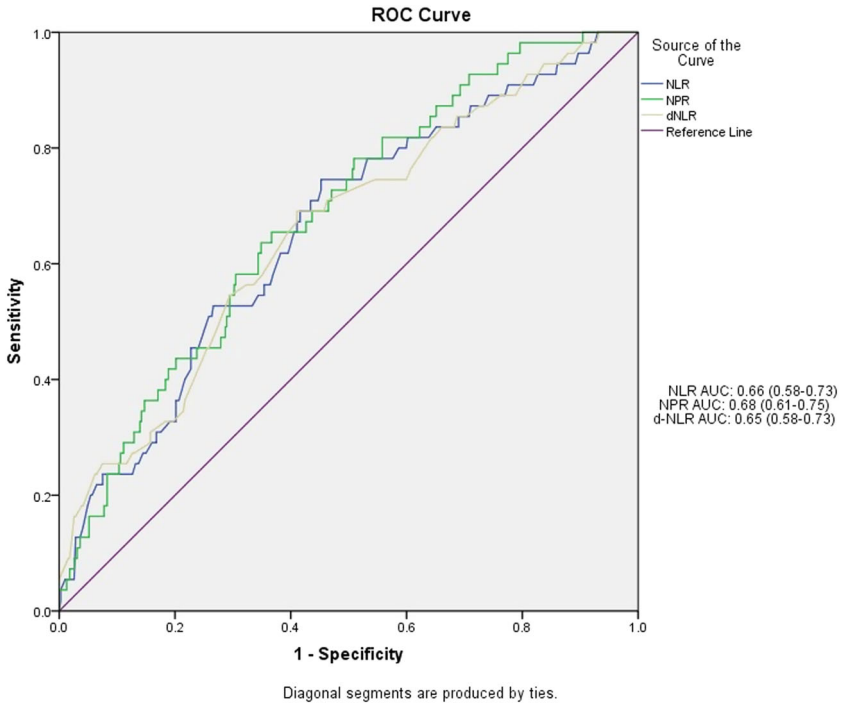

FIGURE 1 Receiver operating characteristic (ROC) curve for the different hemogram-derived ratios and their respective area under the curves (AUCs)

TABLE 4 Multivariable adjusted model for mortality prediction

Model	NLR OR (95% CI) *p* value	D-NLR	NPR OR (95% CI) *p* value	SII OR (95% CI) *p* value
Model A	-	1.08 (1.006–1.14) **0.033**	1.17 (1.06–1.29) **0.002**	-
Model B	-	-	1.20 (1.09–1.32) **<0.001**	1.004 (0.99–1.01) 0.505
Model C	1.05 (1.009-1.08) **0.014**	-	-	-

Note: Model A: Age, DM, CKD, COPD, RBS, D-dimer, Ferritin, NPR, d-NLR. Statistically significant values are highlighted in bold.

Model B: Age, DM, CKD, COPD, RBS, D-dimer, Ferritin, NPR, SII.

Model C: Age, DM, CKD, COPD, RBS, D-dimer, Ferritin, NLR.

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

though not statistically significant, median value of PLR (1.96 vs. 1.57; $p = 0.87$) and SII (14.11 vs. 9.37; $p = 0.05$) were also higher in nonsurvivors.

Independent mortality prediction ability is shown for each hemogram-derived ratio (receiver operating characteristic [ROC] curves are shown in Figure 1). The result of multivariable regression models that assessed the prognostic capability of different hemogram-derived ratios is shown in Table 4. Except for PLR and SII, all other ratios (NLR, d-NLR, and NPR) remain as significant predictors for mortality.

3.2 | ROC curve to determine optimal cut-off values of the hematological ratios

We analyzed the optimal cut-off values (Table 5) 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 0.66 (0.58–0.73), 0.65 (0.58–0.73), 0.68 (0.61–0.75), 0.55 (0.46–0.63), and 0.60 (0.52–0.67) respectively. The optimal cut-off values were NLR (7.57), d-NLR (5.52), NPR (3.87), PLR (2.26), and SII (19.68). PLR had the highest sensitivity (0.78), followed by d-NLR

TABLE 5 Optimal cut-off points for hemogram-derived ratios for prediction of mortality

Variable	Cut off	Sensitivity	Specificity
NLR	7.57	0.65	0.63
D-NLR	5.52	0.67	0.59
NPR	3.87	0.65	0.63
PLR	2.26	0.78	0.44
SII	19.68	0.43	0.75

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

(0.67) and then NLR and NPR (both 0.65). SII (0.75) has the highest specificity, followed by NLR and the NPR (both 0.63).

4 | DISCUSSION

4.1 | Statement of principal findings

This study analyzed the data on clinical characteristics and laboratory parameters of hospitalized COVID-19 patients with a particular focus on the predictive ability of hemogram-derived ratios on mortality. Non-survivors are of higher age and they had a higher prevalence of comorbidities. Length of hospital stay was more for non-survivors. At admission, nonsurvivors had a more severe degree of hypoxia than survivors. Leukocytosis and lymphocytopenia were more frequent in patients who died. The level of D-dimer, Ferritin, and RBS were higher in nonsurvivors. Adjusted multivariable models demonstrated that NLR, d-NLR, and NPR are significant predictors for mortality. The AUC was highest for NPR.

4.2 | Strengths and limitations

As this study included patients of four large hospitals of Sylhet city, it can be taken as representative of the wider population. Another strength of this study lies in the utilization of basic hematological parameters, which are widely available and can be measured even in a peripheral health center. However, Due to the retrospective nature of the present study, it has got some limitations. The questionnaire we used here was not a validated one. Data that could have the potential to influence the disease course like the presence of obesity, malignancy, smoking status, lab parameters like CRP, LDH, ALT, and troponin I were not available in the hospital records. So, their effects on the final outcome are overlooked here. Additionally, information on treatment before hospital admission was lacking in hospital records which could have modified the value of laboratory parameters. Besides, this study focuses on one region, a divisional city, not the whole of a country, that is why other studies involving large geographic areas need to be conducted to check the generalizability of these findings.

4.3 | Interpretation in the context of the wider literature

With a new upsurge of COVID-19 cases by emerging variants of coronavirus in the face of resource constraints, early prediction of mortality in COVID-19 is an important tool in the triage process and resource allocation. Existing scoring systems such as the Acute Physiology and Chronic Health Evaluation (APACHE) II score and COVID-GRAM are good prognostic clinical tools in COVID-19 patients.[13,14] However, both scoring systems require laboratory parameters such as arterial pH and fraction of inspired oxygen (FiO_2) in the APACHE II and lactate dehydrogenase in the COVID-GRAM, which is not available in resource-limited healthcare settings. Therefore, tools that are cost-effective and widely available with a potential for predicting the prognosis of COVID-19 patients are needed.

Presentation of COVID-19 is heterogeneous, ranging from asymptomatic infection to life-threatening critical illness requiring intensive care support. Several inflammatory markers have been evaluated as predictors of death among hospitalized patients with COVID-19.[15–18] Blood levels of different cytokines and inflammatory markers have been shown to predict the critical illness of COVID-19 disease,[19] but these are not readily available outside of tertiary-care medical centers. In this study, we investigated the predictive role of hematological parameters that are easily available at a low cost. Here we observed that NLR, d-NLR, and NPR can successfully predict mortality at the time of hospital admission.

Advanced age and the presence of comorbidities are considered independent predictors of in-hospital death in COVID-19.[20–22] In this current study, we adjusted age, comorbidities like DM, CKD, COPD, and IHD to reduce the influence of confounding factors.

Sex differences in mortality have been widely reported in COVID-19. Previous coronavirus outbreaks (SARS, MERS) demonstrated a higher risk of disease progression and high case fatality in males.[23–25] Male sex is also found to be associated with increased risk of severe disease, ICU admission, and mortality in COVID-19.[26–28] Several hypothesis or explanation has been put forward to explain this increased vulnerability of male. Sexual dimorphism plays a crucial role in the regulation of immune respnses, both innate and adaptive immune systems.[29] Female sex hormones Estradiol may have a protective effect against the development of hyperinflammation while male sex hormone testosterone has an immunosuppressive effect. The difference in the expression of ACE-2 receptor, which facilitates entry of SARS-CoV2 virus inside the cell and their regulation may also contribute to this sex bias. Besides sex-based differences in comorbidity also may play a role.[26] However, our study did not find the male sex as a significant predictor of mortality. This could be attributed to our demographically distinct population or racial difference. Few studies also reported findings similar to ours.[30,31]

NLR represents the relationship between two arms (innate and adaptive) of the immune system during different stages of diseases.[32] Higher NLR is a poor prognostic factor in infectious diseases, malignancy, cardiac disease, and autoimmune diseases.[33–36] In the present study, elevated NLR was a significant prognostic biomarker in COVID-19 patients. Our study finding is consistent with previous studies done to assess the relationship between NLR and the prognosis of COVID-19.[37,38] This may be due to the following reason. The inflammatory reactions could stimulate the production of neutrophils, which then migrate to the immune organs. Afterward, neutrophil releases vast amounts of reactive oxygen species that lead to cell damage. As a result, antibody-dependent cellular cytotoxicity may kill the virus directly. Besides, neutrophil production can be also triggered by factors released from the virus, such as IL-6 and IL-8, tumor necrosis factor-α, and interferon-γ.[39] In contrast, systemic inflammation promotes apoptosis of lymphocytes.[40] Lymphopenia also may be due to direct infection of bone marrow and lymphatic organ by SARS-CoV-2.[41,42] Furthermore, due to

low immune function, these patients are at risk of co-infection with bacteria, which could also explain the rise in the neutrophil count.[43] This study found that the associations between NLR and COVID-19 mortality are independent of age and underlying diseases.

Previous studies[44,45] showed that derived NLR (d-NLR) has a similar prognostic value to the NLR in cancer patients. The utility of d-NLR has also been investigated in COVID-19 and found to be a predictor of poor outcomes.[10,38] This study also found d-NLR as a prognostic marker.

NPR was found to be a marker of disease activity in Ulcerative colitis[46] and predictors of survival in a variety of cancers.[47] Our study suggests NPR can be used as a prognostic marker in COVID-19, which is consistent with other studies.[48,49]

The PLR reflects the interaction between platelet count and lymphocyte count, which represents aggregation, as well as inflammatory pathways. Like NLR, PLR has been demonstrated to be predictive of worse overall survival in cancer patients[50] and correlated with disease severity in patients with Rheumatoid arthritis.[51] Several systematic reviews and meta-analyses found the role of PLR as a prognostic marker in COVID-19.[52,53] However, in our study, PLR was not found to be a significant prognostic factor of mortality in multivariable analysis, which is consistent with previous studies.[54,55]

Although first reported in hepatocellular carcinoma, the prognostic value of SII has also been evaluated in other solid malignancies.[56,57] SII measured at admission can predict in-hospital mortality in COVID-19.[58,59] This current study found that SII can predict mortality in univariable analysis but not in multivariable analysis, which agrees with the study by Xue et al.[60]

To date, no cut-off value of the hematological ratio has been defined as optimal in COVID-19. The cut-off values of hemogram-derived ratios for the prediction of mortality in this study are 7.57, 5.52, 3.87, 2.26, and 19.68, respectively, for NLR. d-NLR, NPR, PLR, and SII. There is a wide variation in the cut-off value of these parameters in published studies.[61–63] The underlying reason may be due to differences in demographic characteristics of the study population[44,64,65] and differences in the technique applied to select the cut-off value. We used Youden Index to determine the optimal cut-off values. In line with our study, many other studies, including systematic review and meta-analysis[11,66] reported optimal cut-off values for NLR with moderate sensitivity and specificity. For example, Yildiz et al.[61] estimated that the optimal cut-off value of NLR was 6.4, with a sensitivity of 63% and specificity of 64%. Similarly, Cheng et al.[67] estimated an optimal cut-off value of NLR of 7.9, which corresponded to a sensitivity of 65% and Tahtasakal et al.[68] reported NLR cut-off >3.69 with a sensitivity of 78.68 and specificity of 66.08.

4.4 | Implications for policy, practice, and future research

The unpredictable course of COVID-19 disease, ranging from mild self-limiting illness to cytokine storms, multiorgan failure, and death has been posing a great challenge to health care workers because which particular patients will develop the progressive disease is difficult to predict at admission. Therefore, there is an urgent need to identify early prognostic biomarkers which are reliable and widely available at low cost. With these objectives in mind, this study evaluated the usefulness of hemogram-derived ratios, which can be calculated from the routine hematological test, and assessed their role as predictors of mortality in COVID-19.

We hope, the findings of this study will guide the clinician in risk-stratifying the patients upon admission and ensure better management with the best use of available resources. Considering the evolving nature of COVID-19, research directed at identifying early predictors of poor outcomes of COVID-19 needs to be continued.

5 | CONCLUSION

Risk-stratifying the patients based on prognostic markers can play a significant role in tackling the challenges of the ongoing COVID-19 pandemic. By allocating medical resources more rationally, this strategy will reduce the pressure on the already exhausted health system, alleviate the shortage of resources, and ultimately will contribute to lowering of public health burden. This study revealed that hemogram-derived ratios have a good predictive value on the mortality of COVID-19 patients. This cost-effective tool can help the clinician in early triaging of severe patients and to apply appropriate management in time.

AUTHOR CONTRIBUTIONS

MD Asaduzzaman: Data curation, formal analysis, methodology, writing –original draft, writing – review and editing. **Mohammad Romel Bhuia**: Methodology, validation, writing—review and editing. **ZHM Nazmul Alam**: Data curation, project administration, supervision. **Mohammad Zabed Jillul Bari**: Data curation, project administration, resources, supervision. **Tasnim Ferdousi**: Data curation, project administration, writing—review and editing.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

This study was conducted following the Declaration of Helsinki. We obtained ethical approval from the Ethical committee of Sylhet Women's Medical College, Sylhet, Bangladesh, and the committee waived the need for consent.

TRANSPARENCY STATEMENT

The corresponding author confirms that the "manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained".

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APPENDIX A

Table A1

TABLE A1 Model 1

Coefficients									
					Wald test			95% confidence interval (odds ratio scale)	
	Estimate	Standard error	Odds ratio	*z*	Wald statistic	*df*	*p*	Lower bound	Upper bound
(Intercept)	−7.373	1.034	6.277e-4	−7.130	50.842	1	<0.001	0.000	0.005
Age	0.051	0.013	1.053	3.934	15.475	1	<0.001	1.026	1.080
DM (yes)	0.245	0.403	1.278	0.608	0.370	1	0.543	0.580	2.818
CKD (yes)	0.721	0.373	2.056	1.934	3.740	1	0.053	0.990	4.267
COPD (yes)	0.595	0.433	1.813	1.374	1.889	1	0.169	0.776	4.234
RBS	0.057	0.031	1.059	1.872	3.503	1	0.061	0.997	1.125
D-dimer	−0.000	0.000	1.000	−1.060	1.124	1	0.289	1.000	1.000
Ferritin	0.000	0.000	1.000	0.717	0.514	1	0.474	1.000	1.001
NPR	0.157	0.050	1.170	3.157	9.965	1	0.002	1.061	1.291
d-NLR	0.072	0.034	1.075	2.127	4.526	1	0.033	1.006	1.148

Multicollinearity diagnostics		
	Tolerance	VIF
Age	0.901	1.110
DM	0.796	1.256
CKD	0.871	1.148
COPD	0.861	1.162
RBS	0.850	1.177
D-dimer	0.850	1.176
Ferritin	0.927	1.079
NPR	0.834	1.200
D-NLR	0.887	1.127

Note: Prognosis level "1" coded as class 1.

Abbreviations: COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; DM, diabetes mellitus; NPR, neutrophil-to-platelet ratio; RBS, random blood sugar; VIF, variance inflation factor.

APPENDIX B

Table B1

TABLE B1 Model 2

Coefficients									
					Wald rest			95% confidence interval (odds ratio scale)	
	Estimate	Standard error	Odds ratio	*z*	Wald statistic	*df*	*p*	Lower bound	Upper bound
(Intercept)	−7.422	1.036	5.978e-4	−7.163	51.316	1	<.001	0.000	0.005
Age	0.055	0.013	1.056	4.219	17.798	1	<.001	1.030	1.083
DM (yes)	0.338	0.402	1.403	0.842	0.710	1	0.400	0.638	3.082
CKD (yes)	0.715	0.369	2.045	1.940	3.763	1	0.052	0.993	4.213
COPD (yes)	0.711	0.425	2.035	1.671	2.791	1	0.095	0.884	4.686
RBS	0.055	0.030	1.057	1.816	3.297	1	0.069	0.996	1.121
D-dimer	−0.000	0.000	1.000	−1.115	1.244	1	0.265	1.000	1.000
Ferritin	0.000	0.000	1.000	0.827	0.684	1	0.408	1.000	1.001
NPR	0.184	0.050	1.202	3.712	13.781	1	<0.001	1.091	1.325
SII	0.004	0.006	1.004	0.666	0.444	1	0.505	0.993	1.015

Multicollinearity diagnostics		
	Tolerance	VIF
Age	0.903	1.108
DM	0.800	1.250
CKD	0.862	1.159
COPD	0.855	1.169
RBS	0.857	1.167
D-dimer	0.829	1.207
Ferritin	0.911	1.098
NPR	0.860	1.163
SII	0.922	1.084

Note. Prognosis level "1" coded as class 1.

Abbreviations: COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; DM, diabetes mellitus; NPR, neutrophil-to-platelet ratio; RBS, random blood sugar; VIF, variance inflation factor.

APPENDIX C

Table C1

TABLE C1 Model 3

Coefficients									
					Wald test			95% confidence interval (odds ratio scale)	
	Estimate	Standard error	Odds ratio	*z*	Wald statistic	*df*	*p*	Lower bound	Upper bound
(Intercept)	−6.666	0.970	0.001	−6.869	47.182	1	<0.001	0.000	0.009
Age	0.049	0.013	1.050	3.855	14.863	1	<0.001	1.024	1.077
DM (Yes)	0.213	0.387	1.238	0.550	0.303	1	0.582	0.579	2.644
CKD (Yes)	0.582	0.366	1.790	1.592	2.533	1	0.111	0.874	3.664
COPD (Yes)	0.771	0.420	2.161	1.834	3.363	1	0.067	0.948	4.926
RBS	0.062	0.030	1.064	2.093	4.381	1	0.036	1.004	1.128
D-dimer	−0.000	0.000	1.000	−0.544	0.296	1	0.586	1.000	1.000
Ferritin	0.000	0.000	1.000	0.923	0.852	1	0.356	1.000	1.001
NLR	0.047	0.019	1.048	2.449	5.997	1	0.014	1.009	1.089

Multicollinearity diagnostics		
	Tolerance	VIF
Age	0.926	1.080
DM	0.826	1.211
CKD	0.875	1.143
COPD	0.893	1.120
RBS	0.862	1.160
D-dimer	0.889	1.125
Ferritin	0.935	1.070
NLR	0.914	1.094

Note. Prognosis level "1" coded as class 1.

Abbreviations: COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; DM, diabetes mellitus; NPR, neutrophil-to-platelet ratio; RBS, random blood sugar; VIF, variance inflation factor.