

The predictive role of red cell distribution width, neutrophil lymphocyte ratio and platelet lymphocyte ratio on mortality in COVID-19 patients admitted to intensive care units

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Abstract

Background: Coronavirus -19 (COVID-19) infection is associated with increased mortality and long-term complications. Aim: Comparison between neutrophil lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR) and red cell distribution width (RDW) in their role in mortality detection. Methods: A retrospective cohort study collecting data from medical records of 114 patients admitted to quarantine hospital intensive care unit in Ain-Shams University due to COVID-19 infection. Data was collected regarding demography, comorbidities, length of hospital stay. Blood samples were withdrawn including complete blood count and c-reactive protein. RDW was recorded, NLR and PLR were calculated. Patients were divided according to their outcome into cases including 57 patients who died and controls including 57 survivor patients with comparison between both groups. Regression analysis was performed to detect predictors of mortality. Results: The mean age of the study population was 73.61 and more than half of them were males. Diabetes mellitus and bronchial asthma were more prevalent in cases. By univariate regression analysis diabetes mellitus and NLR were associated with increased mortality. By multivariate analysis NLR is the only factor predicting mortality. NLR >12.4 had 57.89% sensitivity and 78.95% specificity for predicting mortality. Conclusion: NLR is the best inflammatory marker included the study and is associated with increased mortality in severe and critical COVID-19 patients. Diabetes mellitus is associated with increased mortality in those patients.

Keywords: COVID-19, mortality, Diabetes mellitus, inflammation, NLR

Introduction

Coronavirus 19 (COVID-19) infection is associated with severe respiratory disease, high rate of hospitalization, increased morbidity

and mortality and rising healthcare costs. The disease was first discovered in December 2019 in Wuhan with rapid spread all over the world thereafter (1). More than 6.0 million deaths were recorded

worldwide till March 2022 and in Egypt total recorded deaths exceeded 24,000 from the start of the pandemic (2).

Symptoms of COVID-19 ranges from mild symptoms like fever, cough and sore-throat to severe symptoms and the occurrence of complications such as sepsis, acute respiratory distress syndrome (ARDS), cytokine storm, multi-system organ failure and death (3).

Several studies and meta-analysis were performed to detect risk factors for severe COVID-19 infection with identification of different demographic, comorbid, clinical, laboratory risk factors such as old age, male gender, obesity, diabetes mellitus, hypertension, respiratory and cardiovascular disease, ARDS, decreased oxygen saturation, increased creatinine, anemia, lymphocyte level, d dimer, c-reactive proteins, interleukin-6, ferritin etc., and many of these factors were discovered as predictors of mortality (4,5, 6).

The neutrophil to lymphocyte ratio (NLR) is a routine blood test which is easily calculated by dividing absolute neutrophil count by absolute lymphocyte count. It has been reported as an indicator of heightened inflammatory state (7). Increase NLR was reported as a predictor of mortality not only in COVID-19

infection but also in cancer patients, those with cardiovascular events and intracerebral hemorrhage (8).

Red blood cell distribution width (RDW) is also a routine hematological parameter which is simple and easily measured. It was used in the past for differentiating thalassemia from iron deficiency anemia as it measures the heterogeneity in the size of circulating red blood cells (RBC) (9).

Recent studies have revealed that RDW is an inflammatory marker which can estimate the prognosis of various diseases like cancers, autoimmune diseases, cardiovascular diseases, and critical illness (10,11). It was found also to play a role in risk stratification in sepsis and some studies discussed its role in COVID-19 infection prognosis (12).

Platelet-to-lymphocyte ratio (PLR) has emerged as a novel inflammatory marker, has been suggested to predict the severity of COVID-19 patients (13). It an easy and available measure which was found to be elevated in patients with severe COVID-19 infection and suggested as a predictor of mortality (14).

Which parameter is better in predicting mortality in severe and critically ill COVID-19 infected patients? This is the aim of our study.

Subjects and Methods

A retrospective cohort study collecting data from medical records of 114 patients admitted to quarantine hospital intensive care unit (ICU) in Ain-Shams University due to COVID-19 infection during the period between December 2020 and June 2021 after contacting all patients or their proxies to take their approval and informed consent to record their medical data for scientific research with maintenance of privacy and confidentiality. The study was approved by Geriatrics and Gerontology research review council and ethical approval was granted by Faculty of Medicine ethical committee, Ain-Shams University.

Sample size was calculated by Community, Environmental and Occupational Medicine department in the 19th of September 2021, using NCSS PASS 11.0 and based on a study carried out by Wang et al., 2020. Group sample sizes of 50 patients; that would be further subdivided into 2 groups 25 patients with good prognosis and 25 patients with poor prognosis was recommended to achieve 92% power to detect a difference of -1.5 between the null hypothesis that both group means are 12.4 and the alternative hypothesis that the mean of group 2 is 14.0 with estimated group standard deviations of 0.5 and 1.3 and with a significance level (alpha) of 0.01000 using a two-sided two sample t-test. Sample size was inflated by 20% to

account for attrition problem in prospective studies.

Patients were diagnosed to have COVID-19 infection by nasopharyngeal swab for polymerase chain reaction (PCR) and by computerized tomography (CT) scan on chest to detect severity of infection. Patients had either severe or critical illness classified according to National Institute of Health (NIH) classification (16) whereas in severe illness patients had either SpO₂ <94% on room air, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO₂/FiO₂) <300 mm Hg, tachypnea with a respiratory rate >30 breaths/min, or lung infiltrates >50% in CT chest and in critical illness patients had respiratory failure, septic shock, and/or multiple organ failure.

Data was collected regarding demography, comorbidities, length of hospital stay and laboratory data regarding blood samples withdrawn during the 1st 24 hours after admission including complete blood count (CBC) and c-reactive protein (CRP). RDW was recorded, NLR and PLR were calculated. Patients were divided according to their outcome into cases including 57 patients who died and controls including 57 patients who were discharged home with comparison between both groups regarding demography, comorbidities, and laboratory data. Regression analysis was performed

to detect which parameter is a better predictor for mortality.

Statistical analysis

The collected data was analysed using statistical package for social science (SPSS 20). P-values indicated the level of significance and $p > 0.05$ indicated non-significant (NS), $p < 0.05$ meant significant (S), $p < 0.01$ was highly significant (HS). The mean and standard deviation (\pm SD) analysed the parametric numerical data. While the median and interquartile range (IQR) were used for non-parametric numerical data. Frequencies and percentages were used of non-numerical data. Chi-Square test was used to examine the relationship between two qualitative variables. The Mann-Whitney U test was used for nonparametric equivalent of the two-sample t-test. Correlation analysis (using Spearman's rho method) was used to assess the strength of association between two quantitative variables. The correlation coefficient "r" defines the strength and direction of the linear relationship between two variables.

Results

The mean age of the study population was 73.61 (\pm 7.71) and 55% of them were males as shown in table 1. Hypertension (HTN) was present in more than 40% of patients followed by diabetes mellitus (DM) and ischemic heart disease (ISHD). Our

cases and controls were matched with no significant difference between both groups regarding age, gender or smoking history as shown in table 2. Both DM and bronchial asthma (BA) were significantly higher in cases (p 0.014, 0.003 respectively) and BA was present in 14% cases while no one was asthmatic in controls. No significant difference was found regarding HTN, ISHD, other comorbidities or length of stay between both groups. When comparing different inflammatory markers in cases and controls, NLR showed a highly significant increase in cases (p 0.000). Although PLR and CRP were higher in cases, differences were still insignificant. RDW was somewhat higher in cases but with no significant difference. NLR was highly correlated with PLR but not correlated with age or length of hospital stay as shown in table 3. Also, it was not correlated with any other inflammatory markers. Table 4 shows cut-off point for NLR for predicting mortality. $NLR > 12.4$ has 57.89% sensitivity, 78.95% specificity, 73.3% positive predictive value and 65.2% negative predictive value for mortality detection. By performing univariate regression analysis in Table 5, DM and $NLR > 12.4$ are associated with increased mortality while multivariate analysis revealed that that $NLR > 12.4$ is the only factor associated with increased mortality (p 0.000).

Discussion

To our knowledge this is the first study in Egypt studying the predictive value of different inflammatory markers for mortality detection in COVID-19 infection patients. From the start of COVID-19 pandemic in December 2019, many studies were performed searching for pathogenesis, risk factors and predictors of mortality. It is well-known that COVID-19 infection is not just a viral infection but is associated with heightened inflammatory response in severe and critical cases, affection of the immune system, complications affecting various body systems and increased mortality.

DM and BA are more prevalent in patients with increased mortality and when performing univariate analysis DM was associated with increased mortality. A systemic review and meta-analysis performed by Saha and colleagues in 2021 revealed that in hospitalized COVID-19 patients, diabetes mellitus increased risk of mortality especially in patients with critical cases (17).

We studied different inflammatory markers in elderly patients and NLR was the only marker associated with increased mortality by univariate regression analysis and was the only factor associated with mortality by multivariate regression analysis. Many studies indicated that NLR was

one of the abnormal hemopoietic parameter in severe COVID-19 infection (18,19). Neutrophils compromise important part of the innate immune response and lymphocytes are the important cells in the inflammatory response. Some suggest that COVID-19 infection triggers NLRP3 inflammasome leading to destruction of lymphocytes with decreasing count or by activation of interleukin-6 (IL-6) leading to lymphocyte proptosis and lymphopenia (20). Therefore, high NLR indicate severe disease with increased inflammation and some studies declared its role in risk stratification and prediction of outcome and mortality (8,21,22).

RDW and PLR though elevated in cases, were not associated with increased mortality in our study. RDW is a marker of anisocytosis and many studies found that it was associated with increased mortality in COVID-19 patients. However, a meta-analysis performed by Sarkar and colleagues in 2021 (23) collecting 25 studies concluded that although it was associated in many studies with mortality, results were heterogenous and many were of low-quality evidence and needs further studies. It may be a mortality predictor in patients with adult respiratory distress syndrome from various causes.

PLR is a novel simple marker for detecting the prognosis and mortality

of COVID-19 infection. Meta-analysis performed by Simadibrata and colleagues in 2020 (13) concluded that PLR has a prognostic role in detecting severity of infection. Bozan and colleagues found that both elevated NLR and PLR were associated with increased mortality in COVID-19 patients (24). Although not associated with mortality in our study, it was highly correlated with NLR. This may be due to small sample size of our study or may be some of our patients had thrombocytopenia affecting results.

NLR >12.4 had 57.89% sensitivity and 78.95% specificity, 73.3% positive predictive value and 65.2% negative predictive value for predicting mortality. Fouad and colleagues (25) found in their retrospective on 338 patients that NLR cut-off point 7.53 [with an area under the curve (AUC) 0.644], has sensitivity 34.62%, specificity 87.21% in predicting COVID-19 severity. Also, Yan and colleagues (18) found in their multivariate logistic regression analysis that NLR more than 11.75 in COVID-19 patients was significantly correlated with all hospital mortality [odds ratio (OR) 44.3].

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Limitations of the study

The sample size is small, and the study was performed in one quarantine hospital in Cairo so results cannot be generalized to all elderly Egyptians.

Conclusion

Diabetes mellitus is associated with increased mortality in patients with severe and critical COVID-19 infection. NLR is the best inflammatory marker included in our study and is associated with increased mortality in those patients. It is simple, cost-effective measure that can be easily applied on admission to intensive care units.

Acknowledgment

We would like to thank the subjects and/or proxies who accepted to participate with their or their relatives' data in this study.

Conflict of interest

Authors declare no conflict of interest.

Funding sources

The study was self-funded.

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Table 1: demography and laboratory data of the study population

		Total no. = 114
Age (years)	Mean \pm SD	73.61 \pm 7.71
	Range	60 – 94
Gender	Female	51 (44.7%)
	Male	63 (55.3%)
Smoking	Non	99 (86.8%)
	Current smoker	7 (6.1%)
	Ex-smoker	8 (7.0%)
Length of stay	Median (IQR)	10 (5 – 13)
	Range	1 – 34
Co-morbidities	HTN	47 (41.2%)
	DM	34 (29.8%)
	Asthma	8 (7.0%)
	Chronic hematological disease	2 (1.8%)
	CKD	10 (8.8%)
	CLD	4 (3.5%)
	Chronic neurological disease	14 (12.3%)
	Cancer	10 (8.8%)
ISHD	24 (21.1%)	
Neutrophil to lymphocyte ratio	Median (IQR)	9.6 (4.01 – 19.8)
	Range	0.22 – 106.6
Platelet to lymphocyte ratio	Median (IQR)	235.6 (105.7 – 387.7)
	Range	1.85 – 3571.4
CRP	Median (IQR)	67.9 (31.7 – 163.2)
	Range	0.5 – 436.2
HGB	Mean \pm SD	11.17 \pm 2.46
	Range	2.6 – 17.7
RDW	Mean \pm SD	16.49 \pm 2.81
	Range	12.2 – 25.4

HTN= hypertension DM= diabetes mellitus CKD= chronic kidney disease CLD= chronic liver disease ISHD= ischemic heart disease CRP= C-reactive protein HGB= hemoglobin RDW= red cell distribution width

Table 2: comparison between cases and controls regarding demography, comorbidities, and laboratory data

		Discharge	Death	P-value
		No. = 57	No. = 57	
Age (years)	Mean ± SD	72.514 ± 7.67	74.70 ± 7.65	0.129
	Range	60 – 89	60 – 94	
Gender	Female	27 (47.4%)	24 (42.1%)	0.572
	Male	30 (52.6%)	33 (57.9%)	
Smoking	Non	49 (86.0%)	50 (87.7%)	0.721
	Current smoker	3 (5.3%)	4 (7.0%)	
	Ex-smoker	5 (8.8%)	3 (5.3%)	
Length of stay	Median (IQR)	11 (5 – 15)	9 (5 – 13)	0.139
	Range	1 – 34	1 – 33	
Comorbidities				
HTN		19 (33.3%)	28 (49.1%)	0.087
DM		11 (19.3%)	23 (40.4%)	0.014
Asthma		0 (0.0%)	8 (14.0%)	0.003
Chronic hematological disease		1 (1.8%)	1 (1.8%)	1.000
CKD		3 (5.3%)	7 (12.3%)	0.185
CLD		1 (1.8%)	3 (5.3%)	0.309
Chronic neurological disease		5 (8.8%)	9 (15.8%)	0.254
Cancer		5 (8.8%)	5 (8.8%)	1.000
ISHD		11 (19.3%)	13 (22.8%)	0.646
Neutrophil to lymphocyte ratio	Median (IQR)	6.2 (3.2 – 10.9)	14.7 (6.9 – 28.8)	0.000
	Range	0.22 – 54	0.4 – 106.6	
Platelet to lymphocyte ratio	Median (IQR)	213.8 (124.2 – 346.9)	273.6 (89.1 – 432.4)	0.414
	Range	1.85 – 950	11.6 – 3571.4	
CRP	Median (IQR)	56.7 (24.6 – 143.8)	91 (39.3 – 194.6)	0.069
	Range	0.5 – 311.2	1.4 – 436.2	
HGB	Mean ± SD	11.42 ± 1.95	10.91 ± 2.87	0.269
	Range	7.6 – 16.8	2.6 – 17.7	
RDW	Mean ± SD	16.04 ± 2.85	16.94 ± 2.72	0.090
	Range	12.2 – 22.7	12.9 – 25.4	

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant

*: Chi-square test; •: Independent t-test; ≠: Mann-Whitney test

HTN= hypertension DM= diabetes mellitus CKD= chronic kidney disease CLD= chronic liver disease ISHD= ischemic heart disease CRP= C-reactive protein HGB= hemoglobin RDW= red cell distribution width

Table 3 correlation between NLR, age, length of stay and laboratory parameters

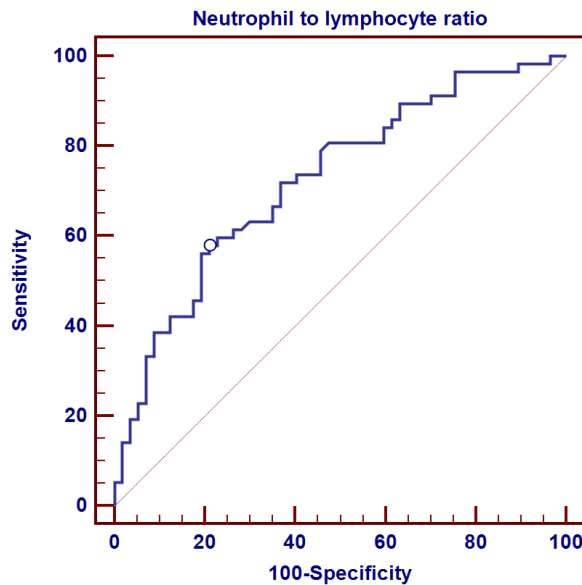
	NLR	
	r	P-value
Age (years)	0.033	0.727
Length of stay	-0.174	0.071
RDW	0.119	0.209
PLR	0.589	< 0.00001
CRP	0.075	0.427
HGB	-0.002	1

NLR= neutrophil lymphocyte ratio
CRP= C-reactive protein

RDW= red cell distribution width
HGB= hemoglobin

PLR= Platelet to lymphocyte ratio
r= spearman correlation

4- Table 4 and figure 1 show cutoff point for NLR for detecting mortality



Cut off point	AUC	Sensitivity	Specificity	+PV	-PV
>12.4	0.725	57.89	78.95	73.3	65.2

NLR= neutrophil lymphocyte ratio

AUC=area under the curve

+PV= positive predictive value

-PV= negative predictive value

5- Table 5 showing regression analysis for mortality

	Univariate				Multivariate			
	P-value	Odds ratio (OR)	95% C.I. for OR		P-value	Odds ratio (OR)	95% C.I. for OR	
			Lower	Upper			Lower	Upper
DM	0.016	2.829	1.216	6.581	0.059	2.381	0.967	5.863
NLR >12.4	0.000	5.156	2.258	11.775	0.000	4.729	2.042	10.951

DM= diabetes mellitus

NLR= neutrophil lymphocyte ratio