Original Article

Predictive Efficacy of Haematological Biomarkers in COVID-19 infection

Nadeem Ikram[1], Asma Nafisa[2], Rabia Anjum[3]

[1] Associate Professor, Department of Pathology, Benazir Bhutto Hospital, Rawalpindi.
[2] Biochemist, Department of Pathology, Benazir Bhutto Hospital, Rawalpindi.
[3] Consultant Pathologist, Benazir Bhutto Hospital, Rawalpindi.

Author's Contribution
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[2] *Facilitation and Material analysis*

Corresponding Author
Dr. Nadeem Ikram,
Associate Professor,
Department of Pathology,
Benazir Bhutto Hospital,
Rawalpindi
Email: drnadeemikram@gmail.com

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Abstract

Introduction: The ongoing Corona Virus Pandemic is linked with high rates of morbidity and mortality globally. Early and effective predictors of clinical outcomes are urgently required to develop effective management protocols.

Objective: To investigate the predictive efficacy of haematological biomarkers in COVID-19 infection.

Material and Methods: Blood samples were drawn from COVID-19 infected pneumonia patients. Baseline clinical information was collected and quantification of the hemostatic variable was done. Laboratory data both groups expired and recovered were compared using t-test, Mann Whitney- U test, chi squared-test, and Kruskal Wallis test. Multivariate regression analysis was performed to determine the independent contribution of the haematological variable in COVID-19 related mortality. Receiver operating characteristic curves were drawn to find the predictive efficacy of significantly related parameters.

Results: Out of 191 patients 68.1% were male. D-dimer (median 800 ng/mL; IQR 200-3200) and NLR (median 10.40; IQR 3.20-22.80) were found to be predominantly raised and significantly correlated with Covid mortality in multivariate regression analysis. The optimum cutoff value of D-dimer to predict in-hospital mortality was 450 ng/ml with a sensitivity of 71.6% and a specificity of 95.8%. The optimum cut-off value of NLR to predict in-hospital mortality was 5.450 with a sensitivity of 70.1% and a specificity of 71%.

Conclusion: D-dimer and NLR could be used as the significant indicators in predicting the mortality of COVID-19.

Keywords: Predictive Efficacy, Haematological Biomarkers, Covid -19 infection, D-dimer, NLR.

Introduction

Despite the preventive infection measures, COVID-19 infection has taken on the proportions of pandemic around the globe. COVID-19 patients present with protean manifestations, from flu-like symptoms to multiple organ failure and death. Nearly 20% of patients, with COVID infection, become critically ill, with high mortality, ranging from 8% to 33%.[1-3] Excessive inflammation, platelet activation, endothelial dysfunction, hypercoagulability, and sepsis, along with many others, are held responsible for patho-physiological events in COVID infection. In-turn, these translate into different findings, which predict the course and prognosis of the disease. In this regard, haematological findings are also of paramount importance.[4,5]

Due to high morbidity and mortality, an early diagnosis of COVID infection is essential. The definitive diagnosis of this disease is made by a positive PCR test for the COVID antigen. Limited resources, insufficient training of the men's power, and many other confounding variables justify the identification of some inexpensive parameters which can reflect the presence of this disease. These, to a larger extent, can help manage the disease and can help differentiate severe from non-severe cases.[6] Standard guidelines for COVID-19 also give weightage to radiological, haematological, and biochemical parameters. Complete blood counts (CBC) are easily performed and inexpensive. Different parameters of CBC like, leucocyte count, absolute neutrophils, and lymphocytes count and their ratios are of importance in this regard.[7-9]

Out of different pathogenetic mechanisms, underlying the severity of COVID infection, cytokine storm is now well established. Interleukin-6 (IL-6) is a key molecule in stimulating cytokine storm. 10 Criterias, clinical and diagnostic, are proposed to find out the risk of the cytokine storm. In lab tests, parameters reflecting inflammation, immune dysregulation, and hypercoagulability are of pivotal significance, in diagnosing cytokine storm. The majority of the patients (84), in cytokine storm, validate these criterias.[11]

Haemostatic changes, observed in COVID patients, are detrimental in deciding the course and outcome of the COVID disease.[2,12] Pulmonary complications and acute respiratory distress syndrome, seen in COVID, have a clear thrombo-embolic component.[2] Endothelial cell infection can induce endothelial damage and dysfunction/activation, which in turn, triggers a coagulation cascade.[2,13-19]

Deranged hematological parameters and haemostatis are commonly observed in the progression of the COVID infection.[20,21] In this scenario speedy inexpensive laboratory testing can be helpful to provide clinicians with suitable information for rational medical resource allocation to reduce patient morbidity and mortality.[22] Because of its severity, it would be valuable to explore risk factors of severity and mortality in patients with COVID-19 disease. It can help in adopting timely measures and interventions, to enhance the cure rate.[23-25]

Materials and Methods

This prospective study was performed in the Department of Pathology, Benazir Bhutto Hospital, Rawalpindi Medical University between June to August 2020. Patients were classified as mild, moderate, severe, or critically ill and followed up till the outcome (discharged or died) (Commission NH, 2020). All COVID suspected patients had a clinical evaluation, blood tests, and PCR test. Throat and nasopharyngeal samples were collected from all patients for COVID-19 viral nucleic acid detection via a real-time reverse transcription-polymerase chain reaction. Blood complete counts were performed on an automated haematology analyzer. Absolute neutrophils and lymphocyte counts were determined to calculate Neutrophil to Lymphocyte Ratio (NLR). Value of NLR more than 3 was considered significant. In coagulation profile, Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT) and D-dimer was performed. D-dimer was measured on an automated chemistry analyzer, where immune complexes formed, between D-Dimer in the plasma and anti-human D-Dimer antibodies, in solution scatter light in proportion to their size, shape, and concentration. Turbidimeters measure the reduction of incident light due to reflection, absorption, or scatter.

All statistical analyses were performed using the SPSS 25 (SPSS Inc. Due to nonparametric distribution of data, results of continuous variables are given as median(interquartile range) and compared by using Mann–Whitney U test. Categorical variables are presented as number (percentage) and compared using the chi-squared test. Univariate and multivariate binary logistic regression analysis finds were performed. Receiver Operating Characteristic (ROC) curves were constructed to evaluate the sensitivity and specificity of age, D-dimer, and NLR in predicting

death. The area under the curve(AUC) was calculated, with higher values demonstrating better discriminatory ability. A p-value of <0.05 was considered statistically significant.

Results

A total of 191 RT-PCR confirmed COVID-19 patients were analyzed. The mean age of the subjects was 49.83 (SD 15.66) years, and 130 (68.1%) of the patients were male. At the time of data lock, 124 (65.26%)subjects recovered to be discharged and 67 (35.1%) proceeded to death. On presentation, 71 (37.2%) were classified as a mild group, 61 (38.8%) as a moderate group, and 59 (32.8%) as severe. In the mild group, 4 (6.0%) proceeded to ICU and death; in the moderate group, 9 (13.4%) developed the critical condition and died. In the severe group, 54 (80.6%) patients proceeded to death. Out of 67 diseased 37 were more than 60 years of age. Regarding haemostatic parameters, overall, 43 (22.5%) patients had thrombocytopenia, 8 (4.2%) developed thrombocytosis, 83 (43.3%) had neutrophilia (Table 1). Compared with the recovered group, expired subjects were significantly older 60.22 ± 14.44 versus 44.21 ± 13.28 years; (mean difference=16.01; t=7.51, 95% C.I., p-value=0.0001, P=0.001), had greater medians of D-dimer, PT, APTT, neutrophil count and NLR. Platelet count was lower in the expired group but the difference was not significant (Table 2). No significant difference was observed in the mortality rate in both genders (p=0.872). In Univariate analysis raised values of NLR, D-dimer, APTT, and PT showed a positive association with mortality (all P-value=0.0001). In Multivariate regression analysis after adjusting for all significantly associated variables in univariate regression analysis, age, odds ratio 95% CI; 1.13o (1.071, 1.194) D–dimer, OR, 95%CI; 1.007 (1.003, 1.010) NLR, OR, 95%CI; 1.342 (1.095, 1.644) come out to be the significant predictors of mortality (all p-value=0.0001).

Using recovered and died cases as the basis of positive division, the Receiver Operator Characteristics Curve Analyses for Age, peak D-dimer, PT, and NLR were performed. It revealed D-dimer, age, and NLR as significant biomarkers (Figure 1; Table 3). The Area Under the ROC Curve (AUC) (0.902) for D-dimer was higher than that of age (0.788) and NLR (0.745). The optimum cutoff value of D-dimer to predict in-hospital mortality was 450 ng/ml with a sensitivity of 71.6% and a specificity of 95.8%. There were 54 patients with D-dimer ≥450 ng/ml and 137 with d-dimer up to 450 ng/ml. The mortality rate for D-dimer ≥ 450 ng/ml group was significantly higher (88.9% vs 13.9) compared to D-dimer ≤ 450ng/ml ($\chi 2$=99.53; p-value=0.0001). A cut-off value of age ≥52.5 years showed the optimum balance of sensitivity (70.1%) and specificity (71.0%). There were 83 patients ≥ 52.5 years of age and 108 ≤ 52.5 years of age. The mortality rate of more than 52.5 years was greater than ≤ 52.5 years (57.6% vs 17.6%; $\chi 2$=34.018; p-value=0.0001). Additionally, for NLR cutoff value of 5.45 showed the optimum balance of sensitivity (73.1%) and specificity (71.0%) (Table 4).

Table 1: Clinical characteristics of Covid-19 patient

Parameters	Mild (n=75)	Moderate (=59)	Severe (n=57)	Total (n=191)	p-value
Age	39.73 ± 10.50	51.46 ± 13.74	61.42 ± 14.66	49.83 ± 15.66	0.0001
Sex%	46 (35.4%)	44 (33.8%)	40 (30.8%)	130 (68.1%)	0.663
D-dimer	200 (200-600)	400 (200-800)	800 (200-3200)	200 (200-3200)	0.0001
APTT	32 (32-54)	33 (32-46)	37 (32-82)	33 (32-82)	0.0001
PT	14 (14-19)	14 (14-19)	16 (14-36)	14 (14-36)	0.0001
Platelets#	198 (44-430)	269 (109-765)	200 (30-576)	209 (30-765)	0.002
Neutrophils#	4.9 (1.80-9.50)	7.70 (2.30-15.60)	10.20 (3.20-22.80)	7.50 (1.80-22.80)	0.0001
Lymphocytes#	1.60 (0.70-4.70)	1.30 (0.60-2.30)	1.50 (0.40-5.60)	1.50 (0.40-5.60)	0.010
NLR*	3.00 (1.26-9.00)	5.65 (1.63-14.14)	6.77 (1.07-24.22)	5.03 (1.07-24.22)	0.0001
Mortality %	4 (6.0%)	9 (13.4%)	54 (80.6%)	67 (35.1%)	0.0001

*NLR=Neutrophil to Lymphocytes Ration; Age; One way ANOVA, Sex and Mortality; Chi-Square Test; Heamatological markers; Kruskal Wallis test.

Table 2: Comparison of Haematological parameters between recovered group and deceased group

Parameters (N =191)	Normal range	Recovered group (n=124)	Deceased group (n=67)	p-vlaue
D-dimer (ng/ml)	125-250	200 (200-800)	800 (200-3200)	0.0001
APTT (Secs)	21-32	32 (32-48)	36 (32-82)	0.0001
PT (secs)	9.8-14 sec	14 (14-26)	16 (14-36)	0.0001
Platelets cmm2	150-450	215 (44-765)	205 (30-576)	0.182
Neutrophils count (absolute)	1.7-7.9	5.65 (1.80-19.50)	10.20 (3.20-22.80)	0.0001
Lymphocytes count (absolute)	1.0-4.8	1.60 (0.60-4.70)	1.50 (0.40-5.60)	0.788
NLR	Upto 3	4.29 (1.26- 14.14)	6.77 (1.07-24.22)	0.0001

Mann Whiteny U-test; Data shown as median (minimum-maximum).

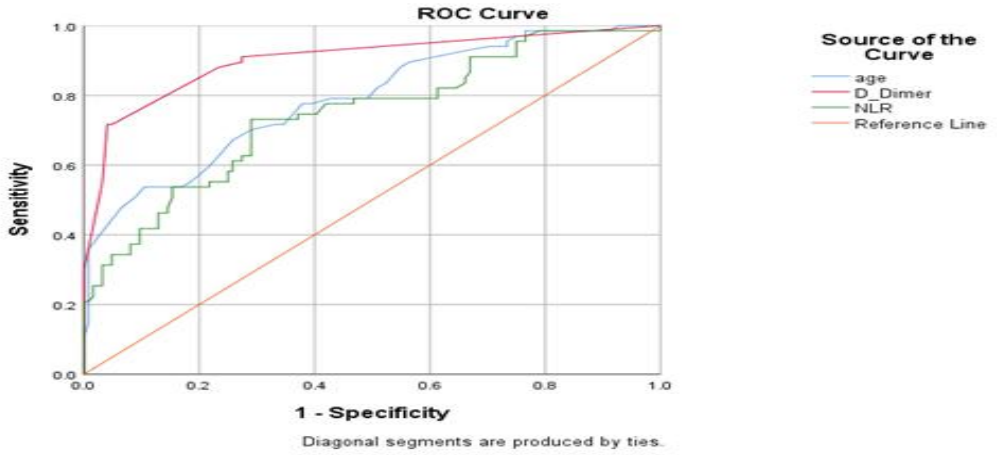

Figure 1: Receiver Operator Characteristics (ROC) Curve Analyses

Table 3: Association of haematological parameters with critical illness and mortality in Covid infection

	Univariate Regression Analysis		Multivariate Regression Analysis	
Variables	**OR (95%CI)**	**P-value**	**OR (95%CI)**	**P-value**
Age	1.087 (1.058, 1.117)	0.0001	1.130 (1.071, 1.194)	0.0001*
Sex	1.161 (.610, 2.209)	0.897		
D-dimer	1.008 (1.005, 1.010)	0.0001	1.007 (1.003, 1.010)	0.0001*
APTT	1.164 (1.085, 1.249)	0.0001	1.005 (0.870, 1.162)	0.941
PT	2.000 (1.5849, 2.525)	0.0001	1.457 (0.942, 2.256)	0.091
NLR	1.339(1.203, 1.491)	0.0001	1.342 (1.095, 1.644)	0.005*
Platelets	0.998 (0.996, 1.001)	0.240		

Table 4: Area under the ROC curve analysis

Parameters	AUC (95%CI)	Cuttoff-value	Sensitivity	Specificity	p-value
Age	0.788 (0.720-0.856	52.5 years	70.1%	71.0%	0.0001
D-Dimer	0.902 (0.851-0.952)	550 ng/ml	71.6%	96.0%	0.0001
NLR	0.745 (0.671-0.820)	5.45	73.1%	71.0%	0.0001

Discussion

The present study showed that besides age, haematological parameters including, NLR, D-dimer are significant predictors of disease severity and mortality. Results of raised D-Dimer levels, in the present study, are consistent with different studies that showed higher D-Dimer levels in expired COVID-19 patients compared to survive.[17,26-30] Elevated D-dimer level is a risk factor for the development of DVT or pulmonary embolism and can predict both severity and mortality.[2,31,32] British Thoracic Society, based on risk stratification, suggested prophylactic low dose heparin in COVID patients with D-dimer more than 3000 ng/ml, while D-dimer more than 1000 ng/ml is an independent risk factor for the critical disease.[4,14,33]

SARS-CoV2 infects type–II pneumonocytes via angiotensin-converting enzyme 2 (ACE 2) receptors. These, in–turn, triggers the phenomenon culminating in a characteristic Pulmonary Intravascular Coagulation (PIC).[34] Cytokine storm, increased expression of tissue factor on endothelium, and excessive recruitment of neutrophils and macrophages, all potentiate intrapulmonary activation of coagulation. Thrombosis observed is primarily intrapulmonary, but can proceed to systemic thrombosis in a subset of patients. This hypercoagulability may be attributed to endothelial dysfunction, elevated circulating platelet microparticles, neutrophil extracellular traps (NATs), and elevated inflammatory cytokines.[18,24,29,35,36] Resistance to fibrinolysis could be an additional underlying mechanism to the hypercoagulable state that predisposes to thrombosis.[37] Majority of the patients with COVID-19 infection show high levels of a pro-inflammatory cytokine, IL-6. IL-6 induces tissue factor gene expression in endothelial cells and monocytes, fibrinogen synthesis, and platelet production.[10]

Markedly increased D-dimers, increased fibrinogen, unusual anaemia and haemolysis, unpronounced PT/APTT prolongation, mild thrombocytopenia, uncommon bleeding, marked pulmonary involvement and evident thrombosis are characteristic findings in COVID coagulopathy. As compared to it, DIC is characterized by a moderate increase in D-dimers, decreased fibrinogen, evident anaemia and haemolysis, pronounced prolongation of PT/APTT, severe thrombocytopenia, unusual thrombosis, prominent bleeding, and mild pulmonary involvement.[12,28,39-41]

The initial and peak D-dimer and NLR, in the survivors, are found significantly lower, as compared with the deceased. High NLR with lymphopenia suggests aggravated infection and is difficult to control.[23] Present study findings of a lower count of lymphocytes and a higher count of neutrophils, with a high neutrophils-to-lymphocytes ratio (NLR) in the severely infected COVID-19 patients compared with the mildly infected group, are consistent with other studies.[1,42-47] Age more than 50 years with an NLR of more than 3.13 predicts course towards a critical illness.[43,48] In COVID-sepsis, neutrophils are hyper-activated along with depletion of CD4 lymphocytes, as a result of apoptosis.[40,49] Patients who died from COVID-19 are reported to have significantly lower lymphocytes count. This reflects exhausted adaptive immune system.[50-54]

Conclusion

1. Monitoring haematological and coagulation parameters might provide a reliable and convenient method for classifying and predicting the severity and outcomes of patients with COVID-19.
2. High NLR and elevated D-dimer levels can be considered as independent risk factors in assessing the severity of COVID-19 disease.

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