Original Article

Predictive ability of complete blood count, mean platelet ratio, mean platelet volume, and neutrophil/lymphocyte ratio for severe pneumonia among RT-PCR or radiologically proven COVID-19 patients

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Abstract

Background: Immuno-inflammatory markers related to white blood cells, and platelets are shown to be associated with COVID-19 infection, and considered to be independent markers for clinical outcomes and mortality. The present study aimed to study the predictive value of these hematologic parameters in progression of COVID-19 to severe pneumonia. **Methods:** This was an analytical cross-sectional study conducted among RT-PCR or radiologically proven COVID-19 patients in a tertiary care hospital in Rajasthan. Semi-structured questionnaire was used to collect the epidemiological information of the patients with COVID-19. Complete blood count and other laboratory parameters were also studied among the patients. **Results:** Mean age of participants in the study was 52 years, with about 70% being males. Cough and breathlessness were the most common symptoms among the patients. It was found that the parameters related to white blood cells were significantly different between patients with COVID-19 infection and severe pneumonia (except absolute monocyte count). NLR was significantly higher among those with severe pneumonia. In the univariate analysis, age (OR - 1.02), NLR (OR - 1.16), and albumin (OR - 0.45) were found to be significant predictors of progression to severe pneumonia. In the final model, adjusted for confounders, only NLR and albumin levels significantly predicted progression to severe pneumonia among COVID-19 patients. **Conclusion:** The study consolidates the predictive ability of NLR for severe pneumonia. It is an important finding, as health facilities with limited access to laboratory investigations can rely on simple markers in routine practice to predict the progression of COVID-19 infection to severe pneumonia.

Keywords: COVID 19 severe pneumonia, mean platelet ratio, neutrophil-lymphocyte ratio `

Introduction

The twentieth century proved to be disastrous for the human race worldwide. And it all started in December 2019 when the novel coronavirus (2019-COVID) started ruining the whole world. Until November 2, 2020, the confirmed cases of COVID-19

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and deaths continued to rise. Overall, 4,59,68,799 confirmed cases and 11,92,911 deaths shook the whole world, and the number for India was equally horrifying, amounting to 1,84,082 confirmed cases and 1,22,111 total deaths since the start of the pandemic.[1] In Rajasthan, the picture of COVID-19 has been very gloomy. On December 21, 2020, there were 12,422 active cases and 2,83,957 cumulative cases, which included either discharged, cured, or migrated to other places. It has been observed that COVID-19-suspected patients usually presented with complaints of pyrexia, fatigue, dry cough/expectoration, upper respiratory congestion, and myalgia or joint pain, but rarely gastrointestinal symptoms.[2] The clinical spectrum of the disease has mostly remained toward the milder side but can present with severe manifestations that are unanticipated. These include sudden onset of respiratory manifestations like acute respiratory failure and acute respiratory distress syndrome. Others are septic shock, metabolic acidosis, and coagulopathies, which present unanticipated in the natural history of the disease.[3] While diagnostic criteria for severe pneumonia of COVID-19 is well established (fever with a suspected respiratory infection, plus one of the following: respiratory rate >30 breaths/min, or severe respiratory distress, or SpO2 ≤93% at room air), the progression toward the same is not well predicted or defined.[4] Morbidity or mortality related to progressive severe pneumonia could be minimized through early detection of risk factors with appropriate use of blood investigations, as the complex pathophysiology of the disease and systemic inflammatory response initiate reactions in various organs, which includes activation of coagulation cascade as well as damage to liver, myocardial and kidney.[5-7]

Immunological parameters play an important role in combating the disease in laboratories. These entire tests are seen to be expensive and time consuming.[8,9] The delay in the test results will ultimately affect the patient's treatment and outcome. Therefore, it is imperative to identify markers that are of low cost with rapid turn-around time and which are sensitive as well as specific. Complete blood count (CBC) is one of these markers. Neutrophils, lymphocytes, and platelets are the blood parameters that play an important role. It is well known that during an acute bacterial infection, neutrophils are increased, while in viremia, lymphocytes are decreased.[10,11] In systematic review and meta-analysis performed by Sarkar *et al.*,[12] they concluded that there is an association of neutrophil/lymphocyte ratio (NLR) with the progression of COVID-19 infection, and it can be utilized by physicians for identification of high risk or deteriorating patients at an early stage. Multiple studies have reported similar findings of NLR being an early warning sign of severe COVID-19 infection. It is considered as an independent marker for the poor outcome of the patient and mortality in COVID-19 infection.[12-16] Platelets are one of the important cellular components of inflammation and coagulation. Substances released by platelets serve a pivotal role in inflammation.[17] Platelet activation can be indicated by mean platelet volume (MPV), which could predict outcomes in critically ill patients.[18,19] MPV, MPR, PC, platelet–lymphocyte ratio (PLR), and other platelet indices could predict the mortality of the disease.[20-28]

Even to date, many laboratory investigations are far beyond reach for majority of the Indian population, and in public health facilities. So, the ability of a simple marker in routine practice, such as a CBC to predict the progression of such a severe disease, is a boon. In the context of this background, the present study was undertaken to study the predictive ability of these hematological parameters (especially MPV, MPR, and NLR) in progression of COVID-19 infection to severe pneumonia among RT-PCR or radiologically proven COVID-19 patients.

Materials and Methods

This was an analytical cross-sectional study conducted in the Bangur Hospital of Pali district, Rajasthan. After obtaining approval from the Institutional Ethics Committee (EC/NEW/INST/2020/555 dated March 05, 2021), de-identified data of COVID-19 patients (RT-PCR or radiologically proven) admitted in the hospital from April 1, 2020, to November 30, 2021) were included for the present study. Patients with a documented history of liver disease or on medications affecting platelet production and maturation were excluded from this study. A total of 729 patients were included in the present study. Sociodemographic information, clinical profile, investigation reports, and clinical outcomes were collected from the electronic medical records. WHO's definition of severe pneumonia of COVID-19[17] was utilized to categorize patients with severe pneumonia.

Data was entered in Microsoft Excel and checked for errors. The analyses were conducted using Jamovi and SPSS v. 23.0. Categorical variables are expressed in percentages or proportions. Continuous variables are expressed as medians (with Inter-quartile range (IQR)) or means (with SD). The association of sociodemographic variables with severe pneumonia was analyzed by Chi-square test. Comparison of hematologic and biochemical parameters among patients with infection and severe pneumonia was performed using Mann–Whitney U test. Univariate and multivariable analysis was performed to study the predictive variables for severe pneumonia among the patients.

Results

The mean age of the participants in the study was 52.2 years (SD - 17.9 years). There were 32 (4.4%) participants aged ≤18 years, while more than 60% of the participants were above 40 years of age. The prevalence of severe pneumonia in the study was 25.7% (187/729), and 8.9% (65/729) of participants succumbed to COVID-19 during the study [Table 1].

Cough was the most common symptom (433, 59.4%) reported among participants, followed by breathlessness (385, 52.8%) and fever (359, 49.2%). Participants experienced breathlessness for mean duration of 3.59 days (SD - 2.51 days) and fever for 4.26 days (SD - 1.94 days). About one-fourth of the participants (23%) reported diabetes and hypertension [Figure 1].

Azithromycin was used among almost all the participants (718, 98.5%), along with oseltamivir (706, 96.8%) as the next most commonly used drug. Other drugs used in the treatment of COVID-19 included ivermectin, hydroxychloroquine, lopinavir/ritonavir, and parenteral such as injection dexamethasone, remdesivir, and hydrocortisone. Plasma therapy was tried only among eight (1.1%) participants [Figure 2].

Severe pneumonia was reported higher among older persons, with a median age of 61 years (IQR - 19 years), with a statistically significant difference among those with no severe pneumonia [median - 53 years (IQR - 26.2 years)]. There was no statistically significant difference among males and females diagnosed with severe pneumonia [Table 2].

Among hematologic parameters, it was found that the parameters related to white blood cells were significantly different between the two groups (except absolute monocyte count). The median values related to indicators of acute infection (total WBC count, granulocyte (%), absolute granulocyte count) were higher in the group with severe pneumonia. It was found that NLR was significantly higher among those participants with severe pneumonia, but there was no such significance appreciated for the mean platelet ratio. Parameters related to red blood cells (except total RBC count) or platelets were found to have no statistically significant difference between the two groups [Table 3].

Post-prandial blood sugar and renal function parameters (S. urea and S. creatinine) were found to be significantly higher for those participants with severe pneumonia [Table 4].

It was found that increasing age was directly correlated with N/L ratio but indirectly with mean platelet ratio. Parameters related to acute infection (total WBC count, granulocyte (%), absolute granulocyte count) were directly correlated with N/L ratio and mean platelet ratio (except granulocyte (%)). Indicators of chronic infection (lymphocyte and monocyte) and eosinophils were indirectly correlated with the N/L ratio [Figure 3, Table 4]. Biochemical parameters such as post-prandial blood sugar, renal function parameters (S. urea and S. creatinine), total and direct bilirubin, liver enzymes (SGOT and SGPT), and albumin were also found to be directly correlated with N/L ratio. With regards to mean platelet ratio, it was found that the renal parameters, total and direct bilirubin, and liver enzymes (SGOT and SGPT) were indirectly correlated; there was no linear correlation between N/L ratio and mean platelet ratio [Table 5].

Considering the collinearity of the hematologic parameters with N/L ratio and mean platelet ratio, the variables related to white blood cells are not considered for regression analysis. From univariate analysis, it was found that increasing age, blood sugar, N/L ratio and blood urea, and decreasing levels of albumin were found to be significant predictors of severe pneumonia [Tables 6 and 7].

From multivariable analysis, it was found that increase in N/L ratio and decrease in albumin were significant predictors of severe pneumonia.

Table 1: Sociodemographic and clinical profile of Participants

Variables	*n* (%) [*n*=729]
Age (years)	
0-18	32 (4.4)
>18-40	154 (21.1)
41-60	282 (38.7)
>60	261 (35.8)
Gender	
Males	494 (67.9)
Females	235 (32.1)
Clinical profile	
Severe pneumonia	187 (25.7)
Dead	65 (8.9)
Positive contact history of COVID-19	32 (4.4)
Positive travel history	27 (3.7)

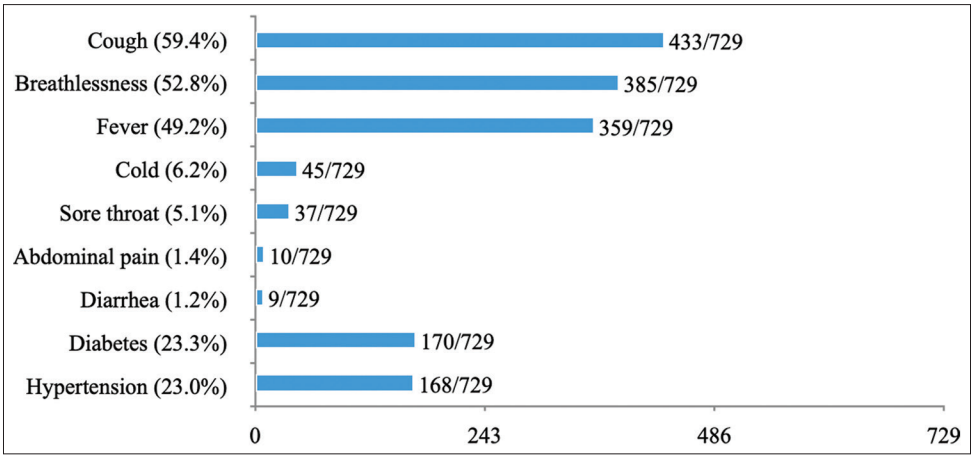

Figure 1: Symptoms and comorbidity profile of participants

Discussion

The present study assesses the predictive ability of hematologic as well as biochemical parameters for severe pneumonia in COVID-19 in more than 700 participants. More than 60% of the patients were above 40 years of age, with a minority being under 18 years of age. The prevalence of severe pneumonia and the proportion of the patients who succumbed to the disease in the study was comparable to that of other studies across the world.[9,12,13,21-24]

While previous studies[15,21] report no statistically significant differences in the hematologic parameters of those with severe pneumonia, the present study was able to demonstrate striking differences in these parameters, which could primarily be attributed to the large sample size of the present study. The present study demonstrated that there is a statistically significant change in the renal function tests and liver enzymes among patients with severe pneumonia. While some studies[15,22] were found to report similar findings, it was also found that a few[17] were not able to appreciate such differences. The present study indicates that NLR is a strong predictor of severe pneumonia among COVID-19-infected patients, subject to various conditions, which is in concordance with the findings of Lippi *et al.*[22] Median values related to acute inflammation (total WBCs count, Granulocyte (%), absolute granulocyte count) were higher in severe pneumonia as compared to non-severe pneumonia. From multivariable analysis, we found that an increase in N/L ratio and a decrease in albumin were significant predictors of severe pneumonia.

The present study showed that renal function tests (BUN and serum creatinine), total and direct bilirubin, and liver enzymes (SGOT and SGPT) were indirectly correlated to MPR. There was no linear correlation between N/L ratio and mean platelet ratio. Contrary to this, in the study by Zhong and Peng,[8] it was observed that the mean platelet ratio >7.44 fL was significantly associated with severe pneumonia in COVID-19 patients, and MPR directly correlated with AST, BUN, serum creatinine, and

Table 2: Comparison of sociodemographic characteristics with severe pneumonia status

Variable	Severe Pneumonia				*P*
	Yes		No		
	n	Median (IQR)	*n*	Median (IQR)	
Age (*n*=729)	187	61 (50.0-69.0)	542	53 (36.8-63.0)	<0.001[$]
Gender* (*n*=729)					
Male	127	17.4%	367	50.4%	0.841[#]
Female	60	8.2%	175	23.9%	

[$]Mann-Whitney *U*-test. *Values are expressed in frequency and percentages. [#]Chi-square test

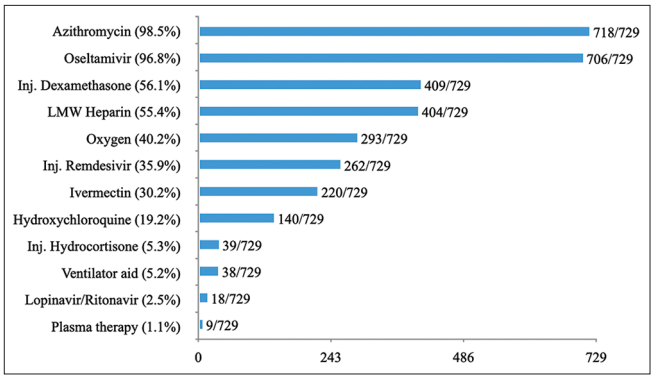

Figure 2: Treatment options for COVID-19 used among the participants

Table 3: Comparison of hematologic parameters with severe pneumonia status

Variable	Severe Pneumonia				*P* (Mann-Whitney *U* test)
	Yes		No		
	n	Median (IQR)	*n*	Median (IQR)	
Hemoglobin (g/dL)	169	12.9 (11.4-13.6)	511	12.7 (11.1-13.8)	0.940
Total RBC count (×10³/μL)	169	4.5 (4.0-4.9)	506	4.3 (3.7-4.8)	0.001
Hematocrit (%)	169	40.0 (34.0-44.0)	510	38.0 (34.0-42.0)	0.086
Total WBC count (×10³/μL)	169	8.5 (5.612.7)	510	7.1 (5.3-9.2)	<0.001
Granulocyte (%)	169	76 (69.5-86.0)	512	64.0 (53.3-75.0)	<0.001
Lymphocyte (%)	169	15.6 (9.7-21.9)	511	25.1 (17.4-35.1)	<0.001
Eosinophils (%)	164	0.2 (0.0-1.3)	468	1.0 (0.2-2.4)	<0.001
Monocyte (%)	169	5.4 (3.3-7.8)	511	7.1 (4.8-9.6)	<0.001
Absolute granulocyte count (×10³/μL)	169	6.4 (3.9-10.2)	507	4.5 (2.9-6.4)	<0.001
Absolute lymphocyte count (×10³/μL)	168	15.6 (9.7-21.7)	508	25.1 (17.435.0)	<0.001
Absolute eosinophil count (×10³/μL)	164	0.(0.0-0.1)	464	0.(0.0-0.1)	<0.001
Absolute monocyte count (×10³/μL)	169	0.4 (0.2-0.7)	506	0.5 (0.3-0.7)	0.083
Neutrophil/lymphocyte ratio	168	4.9 (3.3-8.9)	507	2.5 (1.5-4.2)	<0.001
Total platelet count (×10³/μL)	170	214 (156-272)	511	224 (163-280)	0.305
Mean platelet volume (fL)	157	9.4 (8.7-10.0)	462	9.5 (8.8-10.0)	0.467
Mean platelet ratio	157	22.9 (17.2-30.2)	462	23.8 (16.8-31.3)	0.596
Platelet crit (%)	155	0.(0.0-0.0)	445	0.0 (0.2-3.0)	0.307
Platelet distribution width (fL)	153	11.0 (10.0-16.0)	441	12.0 (10.0-16.0)	0.288
Platelet large cell ratio (%)	125	20.0 (17.0-27.0)	355	21.0 (17.0-28.0)	0.437

Table 4: Comparison of biochemical parameters with severe pneumonia status

Variable	Severe Pneumonia				*P*
	Yes		No		
	n	Median (IQR)	*n*	Median (IQR)	
Blood sugar (post-prandial) (mg/dL)	168	145.5 (108-585)	478	122.0 (76.9-558)	<0.001
Renal function tests					
Blood urea (mg/dL)	171	15.0 (27.9-242)	478	14.0 (20.8-226)	<0.001
Serum creatinine (mg/dL)	172	1.1 (0.9-1.2)	492	1.0 (0.8-1.1)	<0.001
Liver function tests					
Total bilirubin	172	0.7 (0.7-0.8)	470	0.7 (0.7-0.8)	0.947
Direct bilirubin	167	0.3 (0.2-0.3)	452	0.2 (0.2-0.3)	0.013
Indirect bilirubin	167	0.4 (0.40-0.55)	452	0.5 (0.4-0.6)	0.264
SGOT	173	39.0 (25.0-64.0)	481	30.0 (25.0-45.0)	<0.001
SGPT	173	43.0 (34.0-60.0)	479	35.0 (22.0-44.0)	<0.001
Alkaline phosphatase (IU/L)	138	84.0 (65.0-110.0)	279	74.0 (65.0-102.0)	0.085
Albumin (g/dL)	95	3.2 (2.9-3.5)	182	3.5 (3.1-4.0)	<0.001

Table 5: Correlation of sociodemographic, laboratory parameters with N/L Ratio and MPR

Variables	Neutrophil/Lymphocyte Ratio		Mean Platelet Ratio	
	Spearman's ϱ	*P*	Spearman's ϱ	*P*
Age	0.202	<0.001	-0.118	0.003
Hematologic parameters				
Total RBC count (x10^3/μL)	-0.105	0.006	0.156	<0.001
Hemoglobin (g/dL)	-0.063	0.105	-0.059	0.141
Hematocrit (%)	0.004	0.926	-0.075	0.064
Total WBC count (x10^3/μL)	0.467	<0.001	0.217	<0.001
Granulocyte (%)	0.960	<0.001	0.043	0.285
Lymphocyte (%)	-0.970	<0.001	-0.047	0.246
Eosinophils (%)	-0.432	<0.001	0.134	0.001
Monocyte (%)	-0.458	<0.001	-0.107	0.008
Absolute granulocyte count (×10^3/μL)	0.749	<0.001	0.162	<0.001
Absolute lymphocyte count (×10^3/μL)	-0.565	<0.001	0.146	<0.001
Absolute eosinophil count (×10^3/μL)	-0.224	<0.001	0.130	0.002
Absolute monocyte count (×10^3/μL)	-0.041	0.288	0.070	0.084
Biochemical parameters				
Blood sugar (post-prandial) (mg/dL)	0.267	<0.001	-0.029	0.487
Blood urea (mg/dL)	0.326	<0.001	-0.110	0.008
Serum creatinine (mg/dL)	0.214	<0.001	-0.132	0.001
Total bilirubin (mg/dL)	0.087	0.031	-0.119	0.004
Direct bilirubin (mg/dL)	0.186	<0.001	-0.129	0.003
Indirect bilirubin (mg/dL)	-0.015	0.710	-0.070	0.103
SGOT (IU/L)	0.204	<0.001	-0.181	<0.001
SGPT (IU/L)	0.307	<0.001	-0.135	0.001
Alkaline phosphatase (IU/L)	0.089	0.079	-0.045	0.391
Albumin (mg/dL)	-0.326	<0.001	0.048	0.459
D-Dimer	0.369	0.120	-0.324	0.280

indirectly with lymphocytes and albumin. In a retrospective cohort study[16] and cross-sectional study,[23] it was found that the MPR was also not a significant indicator of severity in COVID-19 patients. While studies[24] report a significantly lower value of MPV and MPR in COVID-19 patients as compared to those suffering from influenza, such a statistically significant difference could not be appreciated within the cohort of COVID-19 patients, i.e. between COVID-19 infection and COVID-19 severe pneumonia. However, a systematic review by Daniels *et al.*[25] showed that the MPV was higher in the severe COVID-19 patients than the non-severe patients. PLR and C-reactive protein (CRP), as well as decrease in Plateletcrit (PCT) percentage, were associated with mortality in COVID-19 infection.[28,29] We could not explore these parameters in our study.

In the wake of the pandemic, many diagnostic tests were experimented with, repurposed for precise results in a shorter span of time, and also to shift the burden away from the hubs (tertiary

Table 6: Predictors of severe pneumonia - Univariate analysis

Variable	Estimate	Unadjusted OR (95%CI)	*P*
Age	0.024	1.02 (1.01-1.04)	0.009
Blood sugar (post-prandial) (mg/dL)	0.003	1.00 (1.00-1.01)	0.027
Hematologic parameters			
Neutrophil/lymphocyte ratio	0.155	1.16 (1.07-1.26)	<0.001
Mean platelet ratio	0.003	1.00 (0.97-1.03)	0.827
Total RBC count ($\times 10^3/\mu L$)	-0.252	0.77 (0.54-1.11)	0.165
Renal function tests			
Blood urea (mg/dL)	0.017	1.02 (1.00-1.03)	0.032
Serum creatinine (mg/dL)	0.333	1.39 (0.95-2.05)	0.089
Liver function tests			
Total bilirubin (mg/dL)	0.005	1.01 (0.25-4.04)	0.994
Direct bilirubin (mg/dL)	1.428	4.17 (0.30-57.39)	0.286
Indirect bilirubin (mg/dL)	-0.729	0.48 (0.07-3.24)	0.453
SGOT (IU/L)	-	1.00 (0.99-1.00)	0.709
SGPT (IU/L)	0.003	1.00 (0.99-1.01)	0.314
Alkaline phosphatase (IU/L)	-	1.00 (0.99-1.01)	0.801
Albumin (mg/dL)	-0.789	0.45 (0.28-0.73)	0.001

*Estimate represents log odds of severe pneumonia

Table 7: Predictors of severe pneumonia - Multivariable analysis

Variable	Estimate	Adjusted OR (95%CI)	*P*
Model 1			
Age	0.014	1.01 (0.99-1.03)	0.139
Blood sugar (post-prandial) (mg/dL)	0.002	1.02 (0.99-1.00)	0.156
Blood urea (mg/dL)	-	1.00 (0.98-1.02)	1.000
Neutrophil/lymphocyte ratio	-0.680	1.11 (1.03-1.19)	0.005
Albumin (mg/dL)	0.100	0.51 (0.31-0.83)	0.006
Model 2			
Age	0.016	1.01 (0.99-1.04)	0.079
Neutrophil/lymphocyte ratio	0.107	1.11 (1.04-1.19)	0.007
Albumin (mg/dL)	-0.656	0.52 (0.32-0.84)	0.002
Model 3			
Neutrophil/lymphocyte ratio	0.110	1.11 (1.04-1.19)	0.002
Albumin (mg/dL)	-0.708	0.49 (0.30-0.79)	0.004

*Estimate represents log odds of severe pneumonia

care or centers of excellence) to the spokes (primary care or secondary care), and to be useful among resource-limited settings. In a developing country like India, where the public health systems are being strengthened and the coverage being slowly expanded for various services, the resources still remain constrained for conducting diagnostic tests using high-cost laboratory equipment such as RT-PCR. In such a scenario, the present study exhibits its potential in utilizing commonly available laboratory tests such as CBC, for the diagnosis or screening of COVID-19 and to showcase the predictive ability for progression to severe pneumonia. This shall be treated as an early warning sign, and the patient will be appropriately managed, or referred, based on the availability of resources.

While the present study was conducted in over 700 patients, it also presents its own share of limitations, the most important

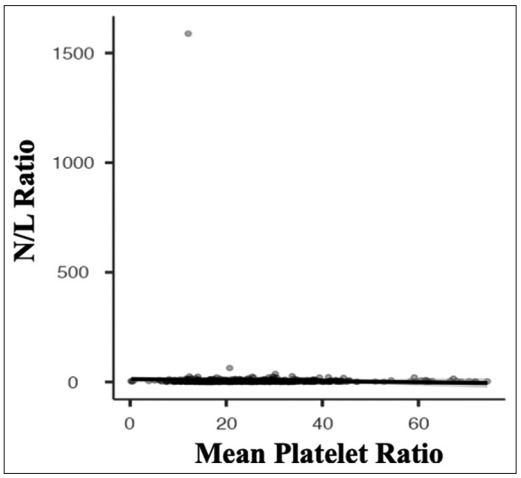

Figure 3: Scatterplot showing no correlation between mean platelet ration and nNeutrophil– lymphocytes ratio

of which is the use of data from electronic medical records. This was an important reason for a considerable number of missing cases for each variable. Also, it has prohibited the authors from including or considering other variables that could act as confounding variables.

Conclusion

The present study consolidates the evidence from the literature for the predictive ability of hematologic parameters (especially NLR) for severe pneumonia in COVID-19 patients. While there are uncertain differences from findings reported in the literature, it is imperative to understand that simple markers in the routine practice such as a CBC, could also help predict the severity of COVID-19 in routine practice. This comes as a major finding from the present study, as it could be extended to health facilities with limited access to laboratory investigations.

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Conflicts of interest

There are no conflicts of interest.

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