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Role of hematological parameters and biochemical markers as a predictor of severity of COVID-19 patients

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ABSTRACT

Background: The etiological agent for pandemic COVID-19 is severe acute respiratory syndrome corona virus 2. Hematological and biochemical parameters are the indicators of inflammation and coagulopathy. **Aims and Objectives:** The present study aimed to determine how effectively the hematological parameters and biochemical markers can help predict the severity of critically ill COVID-19 patients. **Materials and Methods:** The current retrospective cohort study was conducted among 200 COVID-19 patients admitted in the Sanjay Gandhi Memorial Hospital, Rewa, Madhya Pradesh, India. In our lab's computerized system, certain hematological and biochemical parameters of the patients were retrieved and recorded. Receiver operating characteristics (ROC) curve analysis was done to evaluate the diagnostic accuracy of hematological and biochemical parameters. **Results:** Total leukocyte count (TLC), absolute lymphocyte count (ALC), neutrophil to lymphocyte ratio (NLR), D-dimer, and serum ferritin had a significant relationship with severity among ICU patients ($P<0.05$). ALC, D-dimer, and serum ferritin can be used to predict the severity of COVID patients with area under the ROC-AUC curve values of 0.717, 0.725, and 0.710, respectively. Platelet to lymphocyte ratio, lymphocyte to monocyte ratio, and C-reactive protein were not useful to predict the severity of COVID illness. **Conclusion:** Hb concentration, TLC, NLR, D-dimer, and serum ferritin were significantly raised in critically ill COVID patients. ROC curve analysis showed that ALC, serum ferritin, and D-dimer were able to predict the severity of COVID illness effectively. Conclusively, these parameters can be used to track the prognosis of patients.

Key words: COVID-19; D-dimer; Hematological parameters; ICU; Serum ferritin

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INTRODUCTION

Recently, all countries are facing severe viral illness caused by novel severe acute respiratory syndrome corona virus 2. It has infected over 100 million individuals worldwide; resulting in an unparalleled global pandemic.[1] Disseminated intravascular coagulation (DIC) is seen in patients affected with COVID-19. Various hematological abnormalities such as thrombocytopenia, lymphopenia, and deranged coagulation profile are responsible for DIC in COVID-19 patients. DIC is associated with severe pneumonia.[2]Complete blood count is a cost-effective and less time consuming investigation. Hematological parameters provide important inflammatory markers and the ratios are considered as early markers of inflammation.[3]Some inflammatory biomarkers such as D-dimer, serum ferritin, and C-reactive protein (CRP) also play a significant role in the early prediction of disease severity and provide better guide for clinicians regarding the management of the patients.[4]

Aims and objectives

The present study aimed to assess the role of hematological parameters and biochemical markers as early predictors of severity among COVID-19 patients.

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MATERIALS AND METHODS

The current retrospective study was performed on 200 COVID-19 positive patients admitted from April to July 2021 in the Sanjay Gandhi Memorial Hospital, Rewa, Madhya Pradesh, India, after obtaining ethical clearance from the Institutional Ethical Committee. The study population was divided into ICU (n=64) and non-ICU (n=136) groups. Patients with negative RT-PCR test reports and suspected COVID-19 patients were excluded from the study. Datasets of basic hematological and biochemical investigations of positive COVID-19 patients were gathered from computerized records from the central pathology lab associated with the hospital. Hematological parameters included were Hb concentration, total leucocyte count (TLC), absolute neutrophil count (ANC), absolute lymphocyte count (ALC), absolute monocyte count (AMC), and total platelet count, while CRP, D-dimer, and serum ferritin levels were the biochemical parameters under study.

Cutoff points and interpretation of hematological parameters

A value of <12g/dl is considered as anemia, so the cutoff point was taken as 12g/dl for the analysis of hemoglobin concentration.[5]Leucopenia is defined as a value of TLC $<4\times10^9$/L and leukocytosis is defined as a value of $>10\times10^9$/L, so the reference range forthe analysis of TLC was taken 4–10×10^9/L. A value of ANC $<2\times10^9$/L is defined as neutropenia while a value of $>7\times10^9$/L is defined as neutrophilia so the reference range was taken as 2–7×10^9/L for the analysis of ANC. Lymphopenia is defined as a value $<1\times10^9$/L while lymphocytosis is defined as a value of $>3\times10^9$/L so the reference range was taken as 1–3×10^9/L. Monocytosis is defined as a value of more than 1×10^9/L while monocytopenia is defined as a value of $<0.2\times10^9$/L so the reference range was taken as 0.2–1.0×10^9/L. Thrombocytosis is defined as a value of more than 410×10^9/L and thrombocytopenia is defined as a value of $<150\times10^9$/L; hence, the reference range was taken as 150–410×10^9/L.[6]

Neutrophil to lymphocyte ratio (NLR) was calculated by dividing the relative percentage of neutrophils by lymphocytes. A NLR value of <3 was considered as normal because NLR value above 3 indicates acute stress and more than 9 indicates sepsis. Lymphocyte to monocyte ratio (LMR) was calculated by division of absolute lymphocyte count with absolute monocyte count. The normal range was considered as 3–9 with variations among different populations. Platelet to lymphocyte ratio (PLR) was calculated by division of absolute platelet count with absolute lymphocyte count. The normal range is 50–150.[7]

Cutoff points and interpretation of biochemical parameters

CRP values of patients were graded into normal (<0.3mg/L), minor elevation (0.3–1.0 mg/L), moderate elevation (1.0–10.0 mg/L), marked elevation (10–50 mg/L), andsevere elevation (>50.0 mg/L).[8] A D-dimervalue of 0.50 mg/Lor more was considered as positive result.[9]The cutoff point for serum ferritin was 250 μg/L.[6]

Statistical analysis

The statistical analysis was conducted by Medcalc version 20.023. Percentage was used to express the frequency of categorical data. Chi-square test was done for categorical data and aP<0.05 was considered as statistically significant. The sensitivity and specificity of the hematological parameters and biochemical markers were determined from multiple association Receiver operating characteristics (ROC) curve. Diagnostic accuracy of the parameters and biochemical markers was interpreted by calculating the area under curve (AUC) from the ROC curve. The diagnostic accuracy was interpreted as excellent, good, fair, poor, and not useful for the AUC values of 0.9–1.0, 0.8–0.9, 0.7–0.8,0.6–0.7, and <0.6.[10]

RESULTS

The current study was conducted in 200 patients positive for RT-PCR test, belonged to the age group between 20 and 86 years. The mean age of the study population was 51.8±12.98 years. Amongst 64 ICU and 136 non-ICU patients, 21.9% and 43.4% of patients had Hb value of <12g/dL, respectively. Statistically, the differences of Hb concentration between two groups were found to be significant (P=0.0076). TLC was found more than normal range among 64.06% of ICU patients and 47.58% of non-ICU patients. The value of TLC $<4\times10^9$/L was found in 26.56% patients admitted in ICU, while among non-ICU patients low TLC value was found in 9.55% of patients. The statistical differences of TLC among two groups were highly significant with P<0.001. Among ICU patients 82.81% had an ANC value of $>7\times10^9$/L and 46.32% of non-ICU patients had an ANC value of $>7\times10^9$/L. The statistical differences of ANC between two groups were found to be highly significant (P<0.001). Among ICU and non-ICU patients lymphopenia was found in 60.93% and 25.73%, respectively. The differences of ALC among two groups were found to be statistically significant with P<0.001. In both ICU and non-ICU patients, AMC value was nearly normal with 81.25% and 93.38%, respectively. The differences in the value of AMC among two groups were not statistically significant (P=0.03) (Table 1).

Table 1: Comparison of hematological parameters among ICU and non-ICU patients

1.	Hemoglobin (g/dl)			Total	Statistical analysis
	<12	12–16	>16		
ICU	14 (21.8%)	48 (75%)	2 (3.12%)	64 (100%)	χ^2=9.7376
Non ICU	59 (43.38%)	76 (55.88%)	1 (0.73%)	136 (100%)	df=2
					P=0.00768
					Statistically significant
2.	**Total leucocyte count (×10⁹/L)**			**Total**	
	<4	**4–10**	**>10**		
ICU	17 (26.56%)	6 (0.09%)	41 (64.06%)	64 (100%)	χ^2=26.27
Non ICU	13 (9.55%)	59 (43.38%)	64 (47.58%)	136 (100%)	df=2
					P<0.0001
					Statistically significant
3.	**Absolute neutrophil count (×10⁹/L)**			**Total**	
	<2	**2–7**	**>7**		
ICU	2 (3.12%)	9 (14.06%)	53 (82.81%)	64 (100%)	χ^2=2436
Non ICU	6 (4.41%)	67 (49.26%)	63 (46.32%)	136 (100%)	df=2
					P<0.0001
					Statistically significant
4.	**Absolute lymphocyte count(×10⁹/L)**			**Total**	
	<1	**1–3**	**>3**		
ICU	39 (60.93%)	10 (15.62%)	15 (23.43%)	64 (100%)	χ^2=43.27
Non ICU	35 (25.73%)	89 (65.44%)	12 (8.82%)	136 (100%)	df=2
					P<0.0001
					Statistically significant
5.	**Absolute monocyte count (×10⁹/L)**			**Total**	
	<0.2	**0.2–1**	**>1**		
ICU	2 (3.12%)	52 (81.25%)	10 (15.62%)	64 (100%)	χ^2=6.96
Non ICU	1 (0.73%)	127 (93.38%)	8 (5.88%)	136 (100%)	df=2
					P=0.03
					Statistically significant
6.	**Platelet count (×10⁹/L)**			**Total**	
	<1.5	**1.5–4.5**	**>4.5**		
ICU	24 (37.5%)	15 (23.43%)	25 (39.06%)	64 (100%)	χ^2=28.68
Non ICU	13 (9.55%)	76 (55.88%)	47 (34.55%)	136 (100%)	df=2
					P<0.0001
					Statistically significant

In our study, NLR value was found normal only in 9.37% of ICU patients. NLR value was found 3–9 and >9 in 73.43% and 17.18% of ICU patients, respectively. Among non-ICU patients 46.32% patients had normal NLR value, whereas rest of the non-ICU patients had NLR value of more than 3. The NLR value showed significant differences among ICU and non-ICU patients with P<0.0001. An increased PLR was found in 39.06% of ICU and 34.55% of non-ICU patients, whereas increased LMR was found among 10.93% of ICU and 8.82% of non-ICU patients. However, there were no significant differences seen among PLR and LMR (Table 2).

An increased D-dimer and serum ferritin was seen among 92.18% of ICU patients. Among non-ICU patients, D-dimer and serum ferritin wereincreased in 41.91% and 46.32% of patients, respectively. The value of D-dimer and serum ferritin showed significant differences among ICU and non-ICU patients with P<0.0001 (Table 3).

The ROC curve analysis showed that AUC for TLC was 0.574 with a sensitivity and specificity of 39.9% and 75.8%, respectively, which indicates that the diagnostic accuracy of TLC to predict severity of COVID-19 is not useful. The AUC value of ANC, AMC, and Hb concentration was found to be 0.663, 0.629, and 0.614, respectively, which indicates that the diagnostic accuracy of all these parameters to predict severity of COVID-19 is poor (Figure 1).

The present study also revealed that AUC value of ALC was 0.717 in ROC curve analysis which indicates that the diagnostic accuracy of ALC to predict the severity of COVID-19 is fair (Figure 2). The diagnostic accuracy of platelet count and NLR to predict severity of COVID-19 patients was poor with a AUC value of 0.642 and 0.636, respectively, while the diagnostic accuracy of PLR and LMR to predict the severity of COVID-19 was not useful with a AUC value of 0.521 and 0.527, respectively (Figures 2 and 3).

Table 2: Comparison of hematological parameter ratios among ICU and non-ICU patients

1.	Neutrophil to lymphocyte ratio			Total	Statistical analysis
	<3	3-9	>9		
ICU	6 (9.37%)	47 (73.43%)	11 (17.18%)	64 (100%)	χ^2=18.36 df=2 P<0.0001 Statistically significant
Non ICU	63 (46.32%)	49 (36.02%)	24 (17.64%)	136 (100%)	
2.	**Platelet to lymphocyte ratio**			**Total**	
	50–150		**>150**		
ICU	39 (60.93%)		25 (39.06%)	64 (100%)	χ^2=0.38 df=1 P=0.537 Statistically not significant
Non ICU	89 (65.44%)		47 (34.55%)	136 (100%)	
3.	**Lymphocyte to monocyte ratio**			**Total**	
	3–9		**>9**		
ICU	57 (89.06%)		7 (10.93%)	64 (100%)	χ^2=0.22 df=1 P=0.635 Statistically not significant
Non ICU	124 (91.17%)		12 (8.82%)	136 (100%)	

Table 3: Comparison of biochemical markers among ICU and non-ICU patients

1.	C-Reactive protein (mg/L)					Total	Statistical analysis
	<0.3	0.3–1	1–10	10–50	>50		
ICU	0	4 (6.25%)	17 (26.56%)	33 (51.56%)	10 (15.62%)	64 (100%)	χ^2=8.74 df=4 P=0.06 Statistically not significant
Non ICU	3 (2.2%)	14 (10.29%)	56 (41.17%)	45 (33.08%)	18 (13.23%)	136 (100%)	
2.	**D-dimer (mg/L)**					**Total**	
	<0.50			**>0.50**			
ICU	5 (7.81%)			59 (92.18%)		64 (100%)	χ^2=44.93 df=1 P<0.0001 Statistically significant
Non ICU	79 (58.08%)			57 (41.91%)		136 (100%)	
3.	**Serum ferritin (µg/ml)**					**Total**	
	<250			**>250**			
ICU	5 (7.81%)			59 (92.18%)		64 (100%)	χ^2=38.28 df=1 P<0.0001 Statistically significant
Non ICU	73 (53.67%)			63 (46.32%)		136 (100%)	

Figure 4, ROC curve analysis of biochemical markers diagnostic accuracy of serum ferritin and D-dimer to predict severity of COVID-19 patients was found to be fair with AUC value of 0.71 and 0.725, respectively, while the diagnostic accuracy of CRP was found poor to predict severity of COVID-19.

DISCUSSION

COVID-19 virus is apathogen of respiratory tract, which acts on the angiotensin converting enzyme 2 (ACE-2) receptor located in the lower respiratory tract. The virus invades the respiratory mucosa through the ACE-2 receptor and thus promotes the immune reactions that ultimately result in cytokine storm.[11]In our study, leukocytosis and neutrophilia were found to be significantly high in severely ill COVID-19 patients admitted in ICU (Table 1). These findings are in line with the study done by Taj et al.,[4] Seddigh-Shamsi et al.,[11] and Usul et al.,[3] Seddigh-Shamsi et al.[11] reported the development of lymphopenia in COVID positive patients, which is in accordance with our finding. Lymphopenia indicates a poor immune response to the contained viral infection.[12] In our study, thrombocytopenia was found predominantly in severe COVID-19 patients admitted in ICU (Table 1). Similar results were obtained by Usul et al.[3] with a significant association of thrombocytopenia in severe COVID-19 patients.

In ROC curve analysis, our study revealed that TLC was not useful to predict the severity of COVID-19 illness.

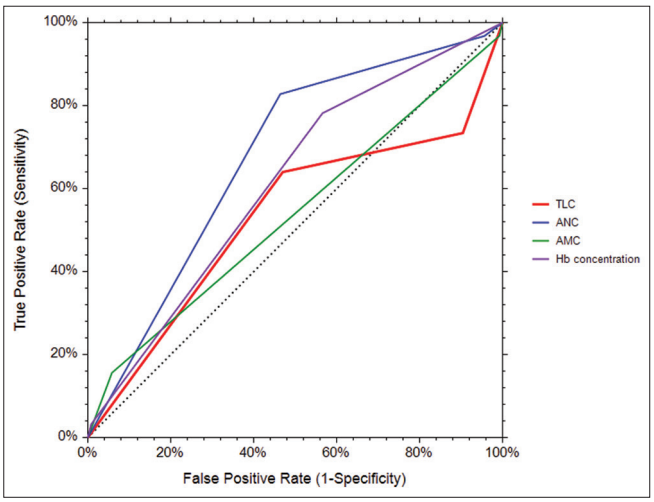

Figure 1: Receiver operating characteristics (ROC) curve analysis of absolute neutrophil count (TLC), absolute neutrophil count (ANC), absolute monocyte count (AMC) and Hb concentrations for predicting ICU admission. ROC curve for TLC (Red line), showed 39.0% sensitivity, 75.8% specificity and area under curve (AUC) value of 0.574. ROC curve for ANC (Blue line), showed 45.7% sensitivity, 86.9% specificity and AUC value of 0.663. ROC curve for AMC (Green line), showed 55.6% sensitivity, 70.3% specificity, and AUC value of 0.629. ROC curve for Hb concentrations (Purple line) showed an AUC value of 0.614 with a sensitivity of 38.7% and a specificity of 78.9%

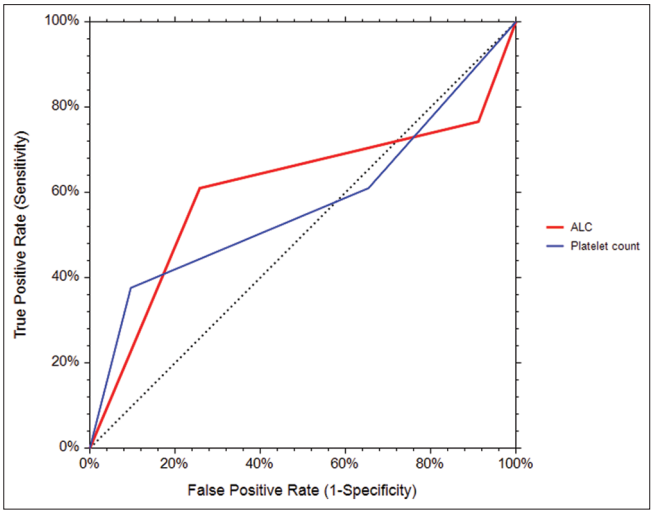

Figure 2: Receiver operating characteristics (ROC) curve analysis of absolute lymphocyte count (ALC) and platelet count for predicting ICU admission. ROC curve for ALC (Red line), showed an area under curve (AUC) value of 0.717 with a sensitivity 53.5% and a specificity of of 89.9%. The platelet count (Blue line) showed an AUC value of 0.642 with a sensitivity of 44.9% and a specificity of 83.5%

However, the AUC value of ANC, AMC, Hb concentration and platelet count indicates that these hematological parameters can be used to predict severity of COVID-19 illness, but the diagnostic accuracy of these parameters waspoor (Figures 1 and 2). In contrast to our findings,Usul et al.[3] and Keski,[13] reported that TLC and ANCcan be used as a good predictor to determine the severity of COVID-19 illness (Table 4).

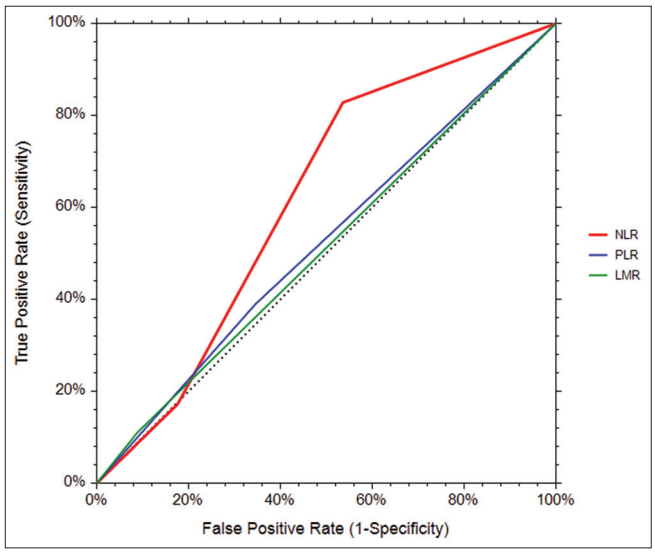

Figure 3: Receiver operating characteristics (ROC) curve analysis of neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR) and lymphocyte to monocyte ratio (LMR) for predicting ICU admission. ROC curve for NLR (Red line), showed an area under curve (AUC) value of 0.636 with a sensitivity of 42% and a specificity of 85.2%. The AUC value for PLR (Blue line) was 0.521 with a sensitivity of 34.7% and a specificity of 69.5%from the analysis. LMR (Green line) showed an AUC value of 0.527 with a sensitivity of 36.8% and a specificity of 68.5% from the ROC curve analysis

An elevated NLR is considered as a marker of inflammation and hemorrhagic transformation manifesting clinically in COVID-19 patients.[14] The present study showed a significant association of elevated NLR in severe COVID-19 patients admitted in ICU. This finding is line with the study done by earlier researchers.[4,7,11,14] The previous researchers reported that NLR can be used to predict the severity of COVID-19 illness with a good diagnostic accuracy.[3,13] Similarly we found that NLR can predict the severity of COVID-19 illness, but the accuracy was found to be poor.Our study also revealed that LMR and PLR were not useful to predict the severity the illness of COVID-19(Figure 3).

In COVID-19 patients, greater CRP levels were linked to the development of ARDS, cardiac damage, and death.[13] CRP is a useful marker for inflammation, infection, and tissue damage and it can be elevated in various medical conditions.[15] The present study revealed that CRP was not a useful predictor of severity in COVID-19 (Figure 4). The probable cause might be since it is a non-specific marker there can be associated medical conditions which caused the paradoxical elevation among both the groups. In contrast to our study Chen et al.[16] reported that the CRP can be useful to predict the severity of COVID-19 illness with good diagnostic accuracy.COVID-19 patients develop coagulation disorders particularly in the critically ill patients; hence, biochemical markers like D-dimer were elevated.[17] D-dimer is a fibrin degradation product and elevated

Table 4: Comparison of area under curve of different parameters with previous studies

Study	Total leukocyte count	Absolute neutrophil count	Absolute lymphocyte count	Platelet count	Neutrophil to lymphocyte ratio	D-dimer	Serum ferritin
Usul et al.[3]	0.8282	0.826	-	0.618	0.739	-	-
Keski[13]	0.771	0.823	0.723	-	0.861	0.843	0.803
Rahman et al.[10]	-	-	-	-	-	0.828	0.997
Bilgir et al.[20]	-	-	-	-	-	0.965	0.984
Present study	0.574	0.663	0.717	0.642	0.636	0.725	0.710

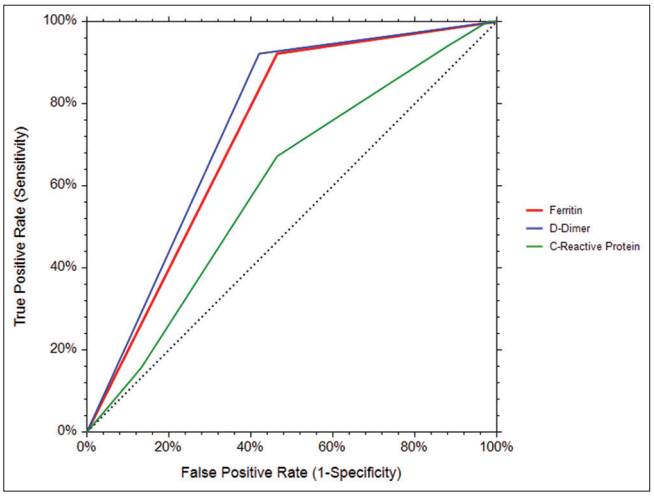

Figure 4: Receiver operating characteristics (ROC) curve analysis of serum ferritin, D-dimer and C-reactive protein (CRP) for predicting ICU admission. ROC curve for serum ferritin (Red line), showed an area under curve (AUC) value of 0.710 with a sensitivity of 48.5% and a specificity of 93.6%. The D-dimer (Blue line), showed an AUC value of 0.725 with a sensitivity of 50.9% and a specificity of 94%. CRP (Green line) showed an AUC value of 0.591 with a sensitivity of 40.6% and specificity of 77.6% from the ROC curve analysis

levels of D-dimer is a direct predictor of thrombotic manifestation and mortality of the patients.[18] It is postulated that the COVID-19 induced pro-inflammatory cytokines increase the release of serum ferritin, an inflammatory marker associated with the severity of the disease.[19] The AUC for D-dimer and serum ferritin in our study was found to be fair predictors of severity. The previous researchers found serum ferritin and D-dimer to be useful predictors for severity of COVID-19 illness with good to excellent diagnostic accuracy[3,10,13,20] whereas, our study revealed that D-dimer and serum ferritin were significantly elevated in critically ill COVID patients and both were useful to predict the severity of COVID illness with fair diagnostic accuracy (Table 4 and Figure 4). COVID-19 has an unclear future even though the current situation seems to be the ebb of the virus; if the virus continues to circulate among us for years, long-term consequences are likely to compound exponentially. Post-COVID-19 syndrome is an entity associated with low grade inflammation and elevated inflammatory markers. The inflammatory markers can be elevated among systemic inflammatory response and other bacterial and viral illness along with post COVID-19 syndrome.[21] Our study showed that biochemical and hematological parameters can be used for identifying high-risk cases and the systemic inflammatory response in certain illness. Thus, assist early management to prevent complications and mortality from severe viral infections.

Limitations of the study

The current investigation was conducted in a single center. As a result, the study's conclusions cannot be extrapolated to the broader population. The current study did not analyze several crucial laboratory indicators like LDH that potentially predict illness prognosis. The findings are preliminary, but they can be used to guide future research into the prognosis of COVID-19 patients. More longitudinal multicentric investigations are needed to corroborate the current study's findings, which are more generalizable.

CONCLUSION

Our study revealed that Hb concentration, TLC, ANC, ALC, AMC, NLR, and serum ferritin were significantly elevated among critically ill COVID patients, which indicates COVID is an inflammatory state. D-dimer was also elevated in ICU patients affected with COVID indicating a coagulation pathway dysfunction leading to multi-organ failure. ALC, serum ferritin, and D-dimer were able to predict the severity of COVID illness effectively. Conclusively, these parameters can be used by the clinicians to assess the prognosis of the patients affected with COVID and manage accordingly.

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