International Journal of Health and Allied Sciences

Manuscript 1012

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ORIGINAL STUDY

Biochemical & Haematological Parameters to Predict Disease Severity and Mortality Among Patients Affected With COVID 19 Infection − A Retrospective Study☆

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Abstract

Introduction: **Coronavirus diseases (COVID-19), the global pandemic has posed a serious threat to the health of individuals across the world and is associated with increased morbidity and mortality. Several biochemical and hematological parameters are found to be altered in these patients and there is a need to identify a suitable biomarker that can help in better risk stratification of these patients. Hence in this study, we intend to evaluate the clinical utility of these parameters to predict severity and mortality in COVID-19 patients.**

Material & methods: **A retrospective, observational study was conducted in a tertiary care hospital involving Reverse Transcription Polymerase Chain Reaction (RT-PCR) positive COVID-19 patients (n-322). Data about patient's age, gender, co-morbidities, duration of hospital and intensive care unit (ICU) stay, need for mechanical ventilation and laboratory investigations were obtained from the Hospital Information System (HIS).**

Results: **The average duration of hospital stay was 10 days, and the ICU stay of these patients was 6.5 days. There was a statistically significant increase in C-reactive protein (CRP), ferritin, lactate dehydrogenase (LDH), aspartate aminotransferase (AST), neutrophils, and neutrophil/lymphocyte ratio (NLR), and lower mean lymphocytic count ($p = 0.05$), in patients who required ICU admission when compared to those who didn't and also among non-survivors compared to survivors.**

Conclusion: **Among the various biochemical & hematological markers, CRP, ferritin, LDH AST, and NLR were found to be better predictors of severity and mortality in COVID 19 patients. Timely monitoring of these markers would therefore help in better management and improved outcome for these patients.**

Keywords: COVID −19, Biomarkers, Inflammation, Mortality, Severity

Key messages

The COVID-19 pandemic has affected millions of individuals across the world. In our study, we have tried to evaluate the various biochemical & hematological markers in predicting the severity and outcome of COVID-19 patients. Among the various markers, CRP, ferritin, LDH AST and NLR were found to be better predictors of severity and mortality in COVID 19 patients.

☆ Presentation at a meeting: Poster Presentation February 15−17th 2021. Organisation: International Conference on COVID-19 organised by IFCC(Virtual).

Received 10 January 2022; revised 3 August 2022; accepted 22 August 2022.
Available online 16 December 2022

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https://doi.org/10.55691/2278-344X.1012

1. Introduction

The coronavirus disease (COVID-19) outbreak which started in Wuhan, China in December 2019, has spread rapidly across various countries and was declared a Public Health Emergency by the World Health Organization. This global pandemic has posed a serious threat to the health of individuals worldwide and is associated with increased morbidity and mortality. The disease has continued to have its effects even in 2021, entering into its second & third wave, with an alarming increase in the infection rate, affecting the lives of millions of people across the world [1]. Clinical presentation in patients with coronavirus infection varies from being asymptomatic or mild fever to typical presentation with symptoms of lower respiratory tract infections such as fever, cough, & dyspnea. Some patients have also presented with clinical manifestations involving gastrointestinal, renal, cardiovascular & neurological systems. In severe cases, they have manifested with acute respiratory distress syndrome (ARDS), sepsis, acute cardiac dysfunction, acute renal dysfunction, and multiorgan failure followed by death. Early diagnosis and timely management of these patients therefore can considerably reduce morbidity & mortality [2].

Several biomarkers have been linked to the severity of the disease & have been identified to play an important role in the management of COVID-19 patients. Studies have shown that there is a greater increase in inflammatory markers like C-reactive protein (CRP), ferritin, procalcitonin in critically ill patients with COVID-19. Other predictive markers associated with increased mortality were elevated lactate dehydrogenase (LDH) and D-dimer. Similarly, patients with severe disease presented with liver dysfunction when compared to those with mild COVID infection, characterized by an increase in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and serum bilirubin levels. Studies have also shown that critically ill COVID patients presented with a higher incidence of renal dysfunction with elevated levels of urea and creatinine; acute cardiac dysfunction characterized by elevated cardiac markers [3,4].

Another predominant feature of severe COVID-19 infection is, patients presenting with very low oxygen levels without dyspnea, termed silent hypoxemia, which was perplexing to the treating physicians. In one study, arterial blood gas indices estimated on admission was found to be associated with the pulmonary inflammatory process, correlating with the prognostic risk of these patients [5].

However, there is a dearth of knowledge related to the availability of specific markers that can be used to detect the occurrence of complications in the early stages of the disease. Hence, in this study, we planned to evaluate the clinical utility of the biochemical and hematological parameters as predictors of severity and mortality in COVID-19 patients in the Indian population.

Material & methods: A retrospective study was conducted in a tertiary care hospital in South India among the RT-PCR confirmed COVID positive patients after obtaining Institutional ethical committee approval. Details about age, gender, clinical history, associated comorbidities, duration of hospital stay, ICU stay, clinical outcome (death/discharge), biochemical and hematological parameters like CRP, LDH, procalcitonin, ferritin, D-Dimer, blood gas analysis, renal function tests, liver function test, complete blood count, erythrocyte sedimentation rate (ESR) on the day of admission were collected. These parameters were compared & correlated with the severity of the disease based on ICU admission and the clinical outcome of the patients (death/discharge).

Statistical methods: SPSS (Statistical Package for Social Sciences) version 20. [IBM SPSS statistics (IBM corp. Armonk, NY, USA released 2011)] was used to perform the statistical analysis. Data was entered in the excel spreadsheet. Data were subjected to a normalcy test (Shapiro−Wilk test). As the data showed non-normal distribution, non-parametric tests were applied. Descriptive statistics of the explanatory and outcome variables were calculated by median and interquartile range for quantitative variables, frequency, and proportions for qualitative variables. Mann−Whitney U test was applied to test the mean difference between two quantitative groups. Chi-square was applied to test the statistical association between qualitative variables. The receiver operating characteristic (ROC) curve was drawn along with the area under curves (AUC) to identify the best variables to detect mortality. Cut-off values, sensitivity, and specificity were calculated for the variables to detect mortality. Binary logistic regression was performed with mortality as dependent variable and biochemical variables as independent variables. The level of significance was set at 5%.

2. Results

A total of 322 RT-PCR positive COVID-19 patients were included in the study. The median age of the

patients was 56 years, with an IQR of 25. There was a statistically significant difference (p = 0.004) in the median age of the patients among the survivors & non-survivors. Males were more affected (66.8%) when compared to females (33.2%). Among the associated comorbidities, the number of hypertensives were significantly higher among the non-survivors (p = 0.014). Among the nonsurvivors, 52.2% were diabetics, whereas 47.1% of the survivors were diabetics (Table 1).

Out of the total 322 patients, 28.6% of patients required ICU admission, and 12.4% of patients required ventilatory support. Among the biochemical parameters CRP (p = 0.001), Ferritin (p = 0.006), and LDH (p = 0.001) were found to be significantly higher, as per table No.1 among the non-survivors (p = 0.05). Similarly, renal parameters like urea (p = 0.001) and creatinine (p = 0.008) were found to be significantly higher among the non-survivors (p = 0.05). Coagulation parameter like D Dimer was also significantly increased with a p-value of 0.002. The hematological parameters like neutrophil count, Neutrophil/Lymphocyte ratio (NLR) were significantly higher among the non-survivors (p = 0.001). Whereas other parameters like PCT, ALT, ALP, ESR, and electrolytes did not show any difference between the two groups (Table 1).

The study subjects were further assessed for the severity of the disease based on the ICU admission. There was a statistically significant difference (p = 0.002) in the median age of the patients requiring ICU admission. Males were more affected (67%) when compared to females (33%). Among the associated comorbidities, diabetes showed a statistically significant increase with the severity of the disease (p = 0.026), wherein 53% were diabetics among those requiring ICU admission and 47% among those not requiring ICU admission. However, there was no significant difference in the occurrence of hypertension among the two groups (Table 2).

Table 1. Comparison of baseline characteristics, biochemical and hematological parameters among survivors & non-survivors.

Variables	Total (n = 322)	Survivors (n = 276)	Non-survivors (n = 46)	p-value
Age (years)	56 (24)	55 (26)	62 (19)	0.004*
Gender				
Male	215 (66.8%)	187 (67.8)	28 (60.9%)	0.359
Female	107 (33.2%)	89 (32.2)	18 (39.1%)	
Diabetes	154 (47.8%)	130 (47.1%)	24 (52.2%)	0.524
Hypertension	163 (50.6%)	132 (47.8%)	31 (67.4%)	0.014*
On ventilator	40 (12.4%)	9 (3.3%)	31 (67.4%)	0.001*
ICU stay (days)	–	0 (0)	6.5 (8)	0.001*
Hospital Stay (days)	10 (8)	10 (9)	9 (8)	0.471
CRP (mg/L)	53 (93)	46 (85)	93.5 (133)	0.001*
PCT (ng/mL)	0.236 (0.155)	0.238 (0.15)	0.227 (0.175)	0.317
Ferritin (ng/mL)	333 (529)	283.5 (522)	454 (744)	0.006*
LDH (U/L)	297 (173)	289 (144)	413 (242)	0.001*
D Dimer (μgFEU/mL)	0.5 (0.6)	0.5 (0.5)	0.755 (1.6)	0.002*
Uric acid (mg/dL)	4.2 (2.6)	4.2 (2.5)	4.9 (3.15)	0.204
AST (U/L)	31 (24)	30 (24)	39.5 (31)	0.006*
ALT (U/L)	26 (24)	26 (25)	24 (25)	0.932
ALP (U/L)	81.5 (44)	80.5 (44)	91 (66)	0.114
Urea (mg/dL)	27 (20)	27 (17)	35.5 (37)	0.001*
Creatinine (mg/dL)	0.88 (0.44)	0.87 (0.407)	1.06 (1.14)	0.008*
Hb (g/dL)	12 (3)	12 (3)	12 (2)	0.254
ESR (mm in 1 h)	70 (60)	70 (60)	70 (60)	0.525
PCO2 (mm Hg)	35 (8)	35 (7)	36 (11)	0.467
PO2 (mm Hg)	74 (34)	75 (34)	60.5 (40)	0.07
SO2 (%)	92 (13)	92 (11)	89 (18)	0.194
HCO3 (mmol/L)	22 (4)	22 (3)	21.5 (7)	0.207
Sodium (mEq/L)	135 (5.2)	135 (5)	135 (7.25)	0.591
Potassium (mEq/L)	4.15 (0.7)	4.1 (0.6)	4.2 (0.93)	0.622
Ionised calcium (mmol/L)	1.12 (0.2)	1.13 (0.18)	1.01 (0.272)	0.005*
Total Count (cells/cumm)	7750 (47600)	7570 (4103)	10060 (7508)	0.001*
Neutrophils (%)	80 (14)	79 (15)	90 (9)	0.001*
Lymphocytes (%)	15 (13.25)	18 (14)	8 (7.5)	0.001*
Platelet Count (lakh/cumm)	2.26 (1.135)	2.28 (1.158)	2.035 (1.11)	0.256
Neutrophil/Lymphocyte	5.12 (5.9)	4.5 (4.9)	11.4 (11.4)	0.001*

Data are presented as median (IQR) or n(%).
*P < 0.05.

Table 2. Comparison of baseline characteristics, biochemical and hematological parameters among patients requiring ICU stay.

Variables	Total (n = 322)	ICU stay		p value
		Yes (n = 92)	No (n = 230)	
Age (years)	56 (24)	61 (17)	53.5 (26)	0.002*
Gender				
Male	215 (66.8%)	154 (67%)	61 (66.3%)	0.911
Female	107 (33.2%)	76 (33%)	31 (33.7%)	
Diabetic	154 (47.8%)	53 (57.6%)	101 (43.9%)	0.026*
Hypertension	163 (50.6%)	54 (58.7%)	109 (47.4%)	0.067
On ventilator	40 (12.4%)	40 (43.5%)	0	NA
Hospital Stay (days)	10 (9)	12 (12)	10 (8)	0.003*
CRP (mg/L)	52.5 (93)	86 (114)	44 (87)	0.000*
PCT (ng/mL)	0.236 (0.155)	0.236 (0.183)	0.238 (0.151)	0.839
Ferritin (ng/mL)	333 (534)	456 (712)	255 (518)	0.000*
LDH (U/L)	296 (172)	396 (241)	277.5 (138)	0.000*
D Dimer (μgFEU/mL)	0.5 (0.6)	0.5 (0.9)	0.4 (0.5)	0.003*
Uric acid (mg/dL)	4.2 (2.6)	4.55 (3.15)	4.2 (2.5)	0.469
AST (U/L)	31 (24)	40.5 (30)	29 (23)	0.000*
ALT (U/L)	26 (24)	27 (26)	25 (24)	0.458
ALP (U/L)	81.5 (44)	85.5 (58)	80 (42)	0.197
Urea (mg/dL)	27 (20)	31.5 (33)	26 (17)	0.000*
Creatinine (mg/dL)	0.88 (0.44)	0.98 (0.41)	0.855 (0.41)	0.015
Total count (cells/cumm)	7750 (4760)	8835 (6430)	7615 (4068)	0.003*
Neutrophils (%)	80 (14)	86 (13)	78 (15)	0.000*
Lymphocytes (%)	15 (13)	10 (12)	18 (13)	0.000*
Platelet Count (lakh/cumm)	2.26 (1.135)	10 (11.75)	18 (13)	0.883
Neutrophil/Lymphocyte ratio	5.1 (5.9)	8.7 (11.1)	4.4 (4)	0.000*

Data are presented as median (IQR) or n(%).
*P < 0.05.

Among the biochemical parameters CRP (p = 0.001), ferritin (p = 0.001), LDH (p = 0.001), AST (p = 0.001), urea (p = 0.000), creatinine (p = 0.015), ionized calcium (p = 0.001) and D Dimer (p = 0.003) were found to be significantly higher among the patients who required ICU admission. The hematological parameters like neutrophil count, NLR were significantly higher in ICU patients (p = 0.001), as shown in Table 2.

ROC analysis was done to detect the predictive ability of these biomarkers. The AUC for CRP levels was 0.675 with a sensitivity of 0.804 and specificity of 0.43 for predicting the mortality when the cut-off level of CRP was 37.50 mg/L. The cut-off level for LDH was set at 321.00 U/L, with a sensitivity of 0.739 and a specificity of 0.62 with an AUC of 0.715. The AUC of the neutrophil count was 0.793 with a sensitivity of 0.848 and a specificity of 0.53 when the cut-off level was 79.5% and the AUC of NLR was 0.786 with a sensitivity of 0.848 and a specificity of 0.610 when the cut-off was 5.65, as shown in Fig. 1 & Table 3.

Further, binary regression analysis showed patients requiring ICU stay & ventilator, D-dimer, and ionized calcium were independent predictors of mortality with p = 0.05 (Table 4).

3. Discussion

In this study, we tried to assess the role of biochemical and hematological markers in improving the management of COVID-19 patients. In our study, we found that the median age of the subjects was higher among the non-survivors and those who required ICU admission, which indicated that advanced age is a predisposing factor for increased severity and mortality. Our findings are in line with earlier studies, and the increased risk of severe infection & mortality could be due to diminished immune functions as age advances and greater prevalence of comorbidities [6,7]. Many studies have shown that males are at higher risk of developing complications of COVID [8]. However, in our study, we found that there was no statistically significant difference in the clinical outcome & ICU admission between males and females, although 66.85% of the subjects were males in the study group. Among the associated comorbidities, there was a significant increase in the risk of ICU admission in patients with hypertension & Type 2 diabetes mellitus and an increased risk of mortality in hypertensive patients. Similar findings were shown in earlier studies, where hypertension & diabetes have

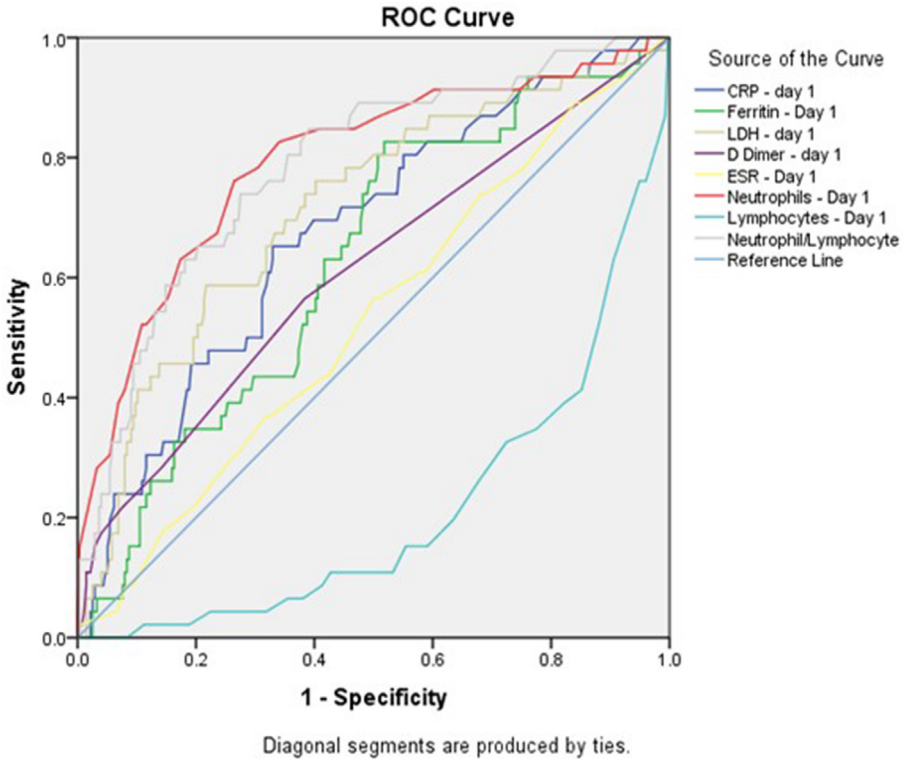

Fig. 1. ROC curve for biochemical and hematological parameters.

Table 3. The area under the curve, cut off values, sensitivity, and specificity for the markers for prediction of mortality.

Variables	AUC	95% CI		p-value	Cut off	Sensitivity	Specificity
		Lower bound	Upper bound				
CRP - day 1 (mg/L)	.675	.593	.758	.000	37.50	.804	0.43
Ferritin - Day 1 (ng/mL)	.627	.544	.710	.006	321.50	.717	0.52
LDH - day 1 (U/L)	.715	.632	.797	.000	321.00	.739	0.62
D Dimer - day 1 (μgFEU/mL)	.644	.554	.733	.002	.50	.565	0.62
ESR - Day 1 (mm in 1 h)	.529	.440	.618	.526	51.00	.609	0.41
Neutrophils - Day 1 (%)	.793	.717	.870	.000	79.50	.848	0.53
Lymphocytes - Day 1 (%)	.212	.143	.281	.000	6.50	.630	0.09
Neutrophil/Lymphocyte	.786	.713	.858	.000	5.650	.848	0.61

Table 4. Independent determinants of mortality using binary logistic regression analysis.

Variables	B	S.E.	Wald	df	OR	p value
Age (years)	−.001	.020	.003	1	.999	.953
Hypertension	−1.070	.607	3.108	1	.343	.078
On ventilator	−3.696	.738	25.098	1	.025	.000*
ICU Stay	1.684	.665	6.413	1	5.385	.011*
CRP	−.001	.004	.116	1	.999	.733
Ferritin	.000	.000	.990	1	1.000	.320
LDH	.002	.002	.868	1	1.002	.352
D Dimer	.233	.101	5.300	1	1.262	.021*
AST	−.007	.009	.625	1	.993	.429
Urea	.003	.004	.467	1	1.003	.494
Ionised calcium	3.202	1.533	4.363	1	24.588	.037*
Total count	.000	.000	.721	1	1.000	.396
Neutrophils	−.015	.056	.071	1	.985	.790
Lymphocytes	−.084	.082	1.050	1	.920	.305
Neutrophil/Lymphocyte	−.010	.051	.041	1	.990	.840

*P < 0.05.

been identified as leading comorbidities in COVID-19 deaths [9].

Among the various biomarkers, inflammatory markers like CRP, ferritin, LDH, showed a statistically significant difference between the survivors and non-survivors. Similar differences were observed in patients requiring ICU admission and those not requiring ICU admission. Our findings are in line with Mardani et al. & Chen et al. [4,10], who showed that patients with positive RT-PCR had significantly increased CRP & LDH levels in serum. Lactate dehydrogenase (LDH) is a cytoplasmic enzyme, which converts pyruvate to lactate in anaerobic conditions. It is a marker of enhanced inflammatory status & increased vascular permeability; as a result of immune-mediated lung injury [11]. An increase in the inflammatory markers like

CRP, ferritin reflects the systemic inflammatory response due to viral particles induced 'Cytokine Storm', resulting in the release of inflammatory cytokines which in turn leads to extensive tissue damage [12]. Interestingly, Procalcitonin (PCT), a marker of sepsis, did not show any significant difference in relation to severity or clinical outcome in these patients.

Studies have identified varying degrees of liver dysfunction with altered liver enzymes; as a result of direct infection of the virus on the liver cells. However, in our study, apart from AST, other liver parameters did not show any significant differences among the study groups in contrast to few other studies which have shown alteration in ALT & AST levels [13,14]. Severe hypoxemia has been the characteristic feature identified in COVID-19 patients. The discrepancy between features of respiratory distress & severe hypoxemia termed as "Silent Hypoxia/Happy Hypoxia' has been identified, especially among patients with severe disease and those associated with comorbidities like diabetes & hypertension. In our study, the mean PO_2 level was 74 mm Hg, though there was no statistically significant difference between survivors & non-survivors. Severe Hypoxemia in these patients has been attributed to extensive interstitial & alveolar inflammation resulting in impaired gas exchange in the alveoli [15]. We observed significant decrease in the ionized calcium levels among non survivors and in ICU patients. Similar findings have been reported by few other studies and several pathophysiological mechanisms have been proposed for hypocalcemia in COVID19 patients. Decrease in calcium levels has been attributed to the viral infection induced alteration in calcium permeability through the ion channels, disruption of calcium homeostasis due to impaired absorption, undernourishment and malnutrition in severe illness, imbalance in the PTH and vitamin D mediated calcium regulation etc. [16,17].

Among the coagulation parameters, D-Dimer was found to be significantly higher among patients requiring ICU stay & among non-survivors. Our findings are in agreement with previous studies, where it was shown that D-dimer levels at the time of admission are indicative of severe COVID infection. Association of D-dimer in COVID 19 patients is found to be due to infection-induced coagulopathy, secondary hyper-fibrinolysis, and pulmonary thrombosis [18,19]. Studies have identified acute kidney injury in COVID patients & Cheng et al. showed elevated creatinine levels with poor clinical outcomes [20]. In our study, urea & creatinine levels were significantly increased among the non-survivors & those patients requiring ICU admission. Acute kidney injury has been attributed to the binding of Sars-Cov2 to Angiotensin-Converting Enzyme-2 (ACE-2) receptors in the kidneys and cytokine storm-mediated renal dysfunction [21].

Among the hematological parameters, our study demonstrated a significant increase in total leukocyte count, neutrophils, and NLR. Our findings are consistent with the studies done by Thirumalaisamy P. Velavan et al. and Liao D et al. [22,23] In our study, AUC for the neutrophil count and NLR was highest among all the parameters, which indicates that NLR and neutrophils were better predictors of the mortality in COVID-19 patients when compared to other parameters. Neutrophils form a major component of innate immunity & lymphocytes, a part of adaptive immunity and are involved in the regulation of inflammatory response. Lymphocytopenia is one of the characteristic features identified in patients with severe infection. This is due to Sars-Cov2 viral infection mediated depression of cellular immunity, with a decrease in CD3, CD4, and CD8 T cells. An increase in total count & neutrophils is due to the early inflammatory process induced by the damaged cells, mainly, by the macrophages & granulocytes [24,25].

The binding of Sars-Cov 2 spike protein to ACE-2 receptors in the alveolar macrophages, initiates the inflammatory response by stimulating the release of inflammatory mediators & chemokines. The release of reactive oxygen species & proinflammatory cytokines by activated neutrophils results in tissue damage & systemic inflammatory response. ACE-2 is expressed in alveolar cells, endothelial cells, smooth cells of various organs like liver, kidney, brain, stomach, intestines, etc. This diffuse expression of the ACE-2 receptors elucidates the wide range of systemic manifestations in COVID-19. The altered levels of the biochemical & hematological parameters are indicative of underlying pathophysiological processes such as inflammation, hypercoagulable state, sepsis, thrombosis, and disseminated intravascular coagulation (DIC) [12,23,26].

Identification of these alterations would therefore help in the initiation of the treatment strategies in the early stages, which helps in improving the prognosis of these patients. Since many of these parameters were identified as useful predictors of severity & mortality, any one of these or a combination of these parameters can be used as early markers to detect the involvement of any organ system or to assess the prognosis in these patients. Some of the routine parameters like AST, urea, creatinine & CBC can be utilized in peripheral

centers, where facilities of blood gas analysis, D-dimer, CRP, LDH, Ferritin are not available. Our study further emphasizes the need for clinicians and laboratory physicians to work in coordination, so that they can come out with simpler risk predictive models, decide on intervals at which these tests are repeated, choose the tests which can help in adjusting the treatment modalities and so on. Such strategies will further reduce the overall economic burden on the patients as well as laboratories, which are facing difficulty in procuring the reagents & consumables so as to meet the unforeseen increase in the demand during the COVID crisis.

The limitations of our study are that it is a retrospective study, details of clinical progression of these patients & variations of these biomarkers upon treatment could not be traced. Details of these biomarkers on different days from the time of admission till death/discharge, was not available for all the patients to study the temporal changes of each of these markers in relation to the prognosis of the disease. A prospective study to evaluate such changes would help in identifying an ideal biomarker in COVID patients.

4. Conclusion

Our study showed that estimation of CRP, ferritin, D-Dimer, ionized calcium, LDH, AST, urea, creatinine, neutrophils, lymphocytes, and NLR at the time of admission are useful predictors of severity and outcome in patients with COVID-19 infection. Among these parameters, neutrophils, neutrophil to lymphocyte ratio, and LDH were better predictors of mortality compared to other parameters. Patients requiring ICU stay & ventilator, D-dimer, and ionized calcium were the independent predictors of mortality, when compared to other parameters. Timely monitoring of these markers in COVID-19 patients would therefore help in better risk stratification & management of these patients and to improve the disease outcome.

Funding source

Nil.

Conflict of interest

The authors declare that they have no conflict of interests.

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