Research Square

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The prognostic role of inflammatory markers in COVID 19 patients – A retrospective analysis.

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Research Article

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Abstract

Background.

Approximately 5% of COVID-19 patients suffer near fatal disease. Clinical and radiologic features may predict severe disease albeit with limited specificity and radiation hazard. Laboratory biomarkers are eyed as simple, specific and point of care triage tools to optimize management decisions.This study aimed to study the role of inflammatory markers in prognosticating COVID-19 patients.

Methodology.

A hospital based retrospective study was conducted on COVID-19 adult inpatients classified into three groups **as** mild disease-recovered [Group I], severe disease-recovered [Group II] and dead [Group III]. Categorical outcomes were compared using Chi square test. Univariate binary logistic regression analysis was performed to test the association between the explanatory and outcome variables. Unadjusted OR along with 95% CI was calculated. The utility of lab parameters (Ferritin, LDH, D dimer, N/L ratio and PLT/L ratio) in predicting severity of COVID-19 was assessed by Receiver Operative Curve (ROC) analysis. P value < 0.05 was considered statistically significant.

Results.

The mean age was 49.32 +/- 17.1 years**.** Among study population, 378 were Group I, 66 Group II, and 56 Group III. Median levels of Ferritin among the 3 groups were 62ng/mL, 388.50 ng/mL and 1199.50 ng/mL. Median value of LDH were 95U/L, 720 and 982.50(p <0.001). D-dimer values of 3 groups were 23.20ng/mL, 104.30 ng/mL and 197.10 ng/mL (p <0.001). CRP done qualitatively was positive in 2 (0.53%), 30 (45.45%) and 53 (94.64%) of patients. The odds of patients suffering severe COVID-19 rose with rising values of ferritin, LDH and D-dimer [unadjusted OR 1.007, 1.004 &1.020]

Conclusion.

One time measurement of serum ferritin, LDH, D-dimer and CRP is promising to predict outcomes for COVID 19 inpatients. Single qualitative CRP was equally good but more cost effective than quantitative CRP. The most specific combination was NLR, Lymphocyte percentage and D-dimer levels done between 7^{th} – 10^{th} day of symptoms.

Introduction

The pandemic caused by novel Corona virus SARS-CoV-2 has swept through the globe casting a shadow of death and disability. Each wave of rising infections reminds the scientific community of our inadequate knowledge and limited capability [1]. The fatality rate has a wide range with considerable international variance [from 2.1% to as high as 5.25%][2]. Most COVID-19 patients experience mild illness

(80%), however a few end up with moderate (15%) to severe (5%) disease endangering survival [3]. Researchers in the field have identified clinical predictors of adverse outcomes albeit with limited specificity [4]. Experience gained so far reveals advanced age (> 65years), comorbid illnesses like diabetes, hypertension, obesity, Atherosclerotic Cardiovascular Diseases (ASCVD) and cancer to be significant associations which portend mortality [5]. Imaging modalities like CT scan do add to the predictive accuracy of clinical outcome but not without radiation hazard. This underscores the need for specific biomarkers which can predict outcome early enough in the disease course to facilitate triage and improve survival.

Animal studies and laboratory observations have given preliminary insight into the pathogenicity of SARS-CoV-2. The surface spike protein, primed by TMPRSS2 binds to the human ACE2 receptor thereby gaining cellular entry[6]. The clinicopathologic mechanism involved in COVID-19 disease is divided into 4 phases- Phase 1 whence patient becomes symptomatic, most commonly fever and cough. Phase 2 marks uncontrolled viral replication leading to macrophage activation, neutrophil infiltration and release of inflammatory cytokines like IL-1,IL-6.IL-8,TNF-α, IFN-γ, etc. The ensuing chain reaction activates procoagulant pathways whilst suppressing the antithrombotic mechanisms simultaneously. Phase 3 is marked by hyper-inflammatory and hypercoagulable state causing hypoxic respiratory failure and may explode into multi organ dysfunction, most notably the heart, kidneys and vascular system [Figure1]. Phase 4 is recovery stage with healing of lung lesions and resolution of hypoxia [7–10].

High levels of D-dimer, IL-6, C-reactive protein, procalcitonin, troponin, LDH, and ferritin are detected in severely ill patients [11]. However our knowledge about the optimal combination of these markers, timing of the tests, their validity in clinically mild disease and individual/cumulative predictive accuracy is far from complete. A single or combination of inflammatory markers which can forecast adverse end result in time to modulate treatment is the need of the hour. Our aim was to study the role of inflammatory markers in prognosticating COVID 19 patients admitted to the hospital.

Methodology

This retrospective study was conducted at Government Sivagangai Medical College and Hospital. All adult patients who were RT-PCR confirmed for COVID-19 admitted to the hospital between April 2020 and Jan 2021 were eligible participants. Inclusion criteria were symptom duration 7-10 days before admission, baseline investigations and inflammatory markers done on day 1 of admission and complete follow up records available up to death or discharge from hospital. Those referred to other centers, hematological malignancies and immune compromised status were excluded. As part of institutional protocol, basic blood investigations and inflammatory markers were performed for all patients at baseline. A total of 3089 patients were eligible among whom detailed scrutiny shortlisted 500 case records which fulfilled predefined enrolment criteria. From the final sample of 500, information retrieved included comorbidities, clinical signs, oxygen saturation, complete blood counts, neutrophil lymphocyte and platelet lymphocyte ratios and inflammatory markers like CRP, D- Dimer, LDH, Ferritin. The study

sample was divided into 3 groups based on outcome based criteria - mild COVID recovered [Group 1], severe COVID recovered [Group 2] and severe COVID died [Group 3] [Figure 2][12].

Ethical consideration.

The study was approved by Institutional Ethics Committee of Government Sivagangai Medical College and Hospital.

Statistical analysis.

Ferritin, LDH, CRP and D dimer were considered as primary outcome variables. Severity of COVID 19 was considered as primary explanatory variable. Age, gender, duration of hospitalization, clinical presentation, hemoglobin, neutrophil, lymphocyte and platelet count, packed cell volume, comorbidity & CT thorax findings were considered as other study relevant variable.

Descriptive analysis was carried out by mean and standard deviation for quantitative variables, frequency and proportion for categorical variables. Non normally distributed quantitative variables were summarized by median and interquartile range (IQR) and were compared across study groups using Kruskal Wallis test (> 2 groups). Shapiro- Wilk test was used to assess normal distribution.

Categorical outcomes were compared across study groups using Chi square test. Univariate binary logistic regression analysis was performed to test the association between the explanatory variables and outcome variables. Unadjusted Odds Ratio along with 95% CI was calculated. The utility of lab parameter (like Ferritin, LDH, D dimer, N/L ratio and PLT/L ratio) in predicting severity of COVID-19 was assessed by Receiver Operative Curve (ROC) analysis. P value < 0.05 was considered statistically significant. Software used was ADSS Corp. Released 2020. CoGuide **S**tatistics software, Version 1.0, India.

Results

Case records of 500 patients were analysed. The mean age was 49.32 +/- 17.1 years. 72.4% were < 60 years and male to female ratio was 3:2. Among the study population, 378(75.60%) had mild [Group 1], 66(13.20%) moderate [Group 2] and 56(11.20%) severe disease [Group 3]. The mean duration of hospital stay was 5.6 days ranging between 1 to 25 days. The comorbidity count included diabetes 168(33.6%), hypertension 122(24.4%), coronary artery disease 23(4.6%), hypothyroidism 3(6%) and others 33(6.6%). The values of Ferritin, LDH, D-dimer, NLR and PLR of patients in the 3 groups are depicted in Table 1.

The median levels of Ferritin among the 3 groups were 62ng/mL (24.60 ng/mL to 89 ng/mL) [mild], 388.50 ng/mL (195.50 ng/mL to 541 ng/mL) [moderate] and 1199.50 ng/mL (854 ng/mL to 1536 ng/mL) [severe]. The median LDH of Group I was 95U/L (IQR 35 to 105), Group II 720 (IQR 648.25 to 916) and Group III 982.50 (IQR 739 to 1119.25) [(P value <0.001). D-dimer values of the 3 groups were 23.20 ng/mL, 104.30 ng/mL and 197.10 ng/mL which on comparison had significance (p <0.001) [Figure 3]. CRP done qualitatively was positive in 2 (0.53%), 30 (45.45%) and 53 (94.64%) of patient Groups I, II and

III assuming statistical significance (p<0.001) [Table.1]. ROC assuming 95% confidence interval the odds of patients suffering severe COVID-19 rose with rising values of ferritin, LDH and D-dimer [unadjusted OR 1.007,1.004 &1.020] (Figure 4).

Other significant observations in the study population included a higher mean age [58.66 years], longer duration of hospitalisation [7 days], higher NLR [2.07(1.44 - 9.86)] to be statistically associated with severe COVID 19. (Figure 5).

Discussion

COVID-19 pandemic has affected all age groups, breached geo-political barriers, stunned the healthcare, economic and social systems of countries across the globe. The death toll is over a million till date[12]. The unpredictable course of COVID 19 mandates the need for early clinical and laboratory markers of outcome. In resource limited settings triage could prioritize patients who need hospitalization and intensive monitoring. To date, the search for such specific and cost effective biomarker is elusive to the scientific community [13]. Accumulating body of evidence suggest that inflammatory mediators like IL-6, ferritin, LDH and CRP play a critical role in the progression of COVID-19 [14]. Therefore, these biomarkers play an indispensable role in not just clinical management but timely screening of patients who are on the trajectory to severe disease. Though measurement of inflammatory markers can bear prognostic implications, uncertainties exist on the optimal timing and right combination. Whether their cumulative validity is additive is another grey area. We studied the association between one time measured biomarkers like ferritin, LDH, CRP and D-dimer on the 7-10 th day illness and the observed mortality.

It is common knowledge that underlying organ damage occurs due to activation of the complement system, inflammatory cascades and proinflammatory cytokines in severe COVID 19. Circulating levels of free thrombin activate platelets and dysregulated fibrinolysis portrayed by elevated D-dimer levels were observed to associate with severe COVID disease in previous research work[15]. Moreover they were instrumental in guiding anticoagulant therapy among COVID patients. Akin to other published reports, we observed a significant rise in D-dimer levels in our patients as well who suffered severe COVID [OR 1.020, p<0.001]. Interestingly we also found out that performing D-dimer for all admitted patients was not cost effective and the productivity was enhanced when done approximately 7th – 10th day of symptoms and on those requiring oxygen therapy to maintain SpO2 of > 94%.

CRP is a sensitive marker of acute-phase response in inflammation, infection, and tissue damage [16] whose potential has been exploited in COVID as well. In the study by Chen et al., although no statistically significant difference was found in the level of CRP between the nonsevere and the severe group, the mean level of CRP was higher in the latter [17]. Henry et al also reported significant increases in ferritin and CRP levels in patients with severe COVID-19, consistent with the earlier findings [18]. In our case series we measured CRP only by qualitative method however documented statistically significant CRP positivity with severe COVID 19 disease [p <0.001]. Two other pertinent findings surfaced in our study, firstly, qualitative method of CRP was sufficient to triage patients which could considerably reduce the cost

burden. Secondly, internal comparison among the study participants revealed that one-time performance of the test had the same prognostic accuracy as repeat measurements done on day 15 and 20 of symptoms.

Markers such as ferritin and CRP have an important role to play in a country like India, where IL-6 cannot be so widely estimated due to high cost. The elevated ferritin levels are probably due to secondary phagocytic lymphohistiocytosis and severe cytokine release syndrome [19, 20]. Pastora J et al. in a systematic review on the utility of ferritin in COVID-19 found that ferritin concentrations of COVID-19 patients were generally within the normal range of less than 400 ng/ml in non-severe disease [21] .However, hyperferritinemia (ferritin level > 400 µg/L), was observed in patients with severe disease on admission, precisely between 1.5 and 5.3 times higher. The author evaluated studies comparing ferritin levels on admission between COVID-19 survivors and non-survivors and demonstrated that non-survivors showed ferritin levels on admission around 1400 ng/mL, which is between 3 and 4 times higher than survivors. Our observations parallel that of other researchers with a mean ferritin value of 1199.50 ng/mL in severe group. The unadjusted odds for patients suffering severe covid was 1.007 in patients with elevated ferritin levels. The finding provides clinicians with a cost effective, point of care triage tool to optimize outcomes in resource limited settings.

A previous study found significantly higher levels of LDH in ICU patients than non-ICU patients (248 U/L vs 151 U/L, p=0.002). Since high levels of LDH continued in the ICU patients for a number of days post-admission (160 U/L vs 218 U/L, p=0.002), LDH was speculated to predict mortality. However, this being a single centre study was prone to selection bias with doubtful validity[22]. A multi-centric study involving 1099 patients reported strong evidence correlating extent of tissue damage and inflammation with increasing levels of LDH which corroborated well with CT scan scoring of severe COVID 19 pneumonia[23]. In our study LDH charted a significant rise among patients with severe COVID 19 [OR 1.004/p<0.001]. This increase observed in our series is consistent with the findings of Liu who correlated LDH, lymphocyte, neutrophil, and CRP abnormalities with severe COVID pneumonia [24].

The viral particles spread through the respiratory mucosa, first using the ACE2 receptor at the level of ciliated bronchial epithelial cells and then infecting other cells. Cytotoxic lymphocytes and natural killers play a key role in controlling the spread of infection which becomes relentless if lymphocyte count deplete. The number of lymphocytes particularly CD4 type can serve as a surrogate marker of severity and mortality in COVID 19 disease [25]. Lymphocytopenia directly correlates with disease severity and death with three-fold higher risk of poor outcome, in younger patients compared to older [26]. Other hematological markers of significance are high Neutrophil Lymphocyte Ratio and thrombocytopenia which have been associated with adverse outcomes in COVID 19 patients. Elevated NLR is conducive to a dysregulated cytokine elaboration whereas low platelet counts resulted from microthombi and vascular occlusion of pulmonary vessels (27). In our study, we documented a strong predilection between high NLR and poor outcome of COVID 19, however thrombocytopenia was not statistically significant.

Other relevant findings in our study included an older age and longer hospital duration being predictive of COVID mortality. Similar relevance to age factor has been reiterated in research work both regional and global [28].

Limitation

Though the sample size was adequate the method adopted was convenient sampling which might not represent the general population. CRP test done in the study was qualitative, hence the exact level of the parameter predicting severity could not be assessed.

Conclusion

Clinical decisions are not made in the laboratory and test results are best adjudged in the right clinical context, never piecemeal. Nevertheless, triage oriented, specific, and point of care biomarker is an elusive dream for COVID care physicians. We identified one time measurement of serum ferritin, LDH, D-dimer and CRP as promising tests to predict outcomes for COVID 19 inpatients. Interestingly, one time qualitative CRP was equally good but more cost effective than quantitative CRP and repeat measurements on day 15 and 20. The most specific combination was NLR, Lymphocyte percentage and D-dimer levels done between 7th – 10th day of symptoms. Advanced age and prolonged duration of hospitalization reinforced the same findings. The authors urge the need for larger multicentric research on these lines to end the long trail for the optimal biomarkers.

Declarations

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Financial support & sponsorship: None.

Conflicts of interest: None.

Abbreviations

ACE 2 receptor - Angiotensin Converting Enzymes 2 receptor

CRP - C - reactive protein

IL - Interleukin

ICU - Intensive Care Unit

LDH – Lactate Dehydrogenase

NLR – Neutrophil Lymphocyte Ratio

PLR – Platelet Lymphocyte Ratio

RT-PCR - Reverse Transcription–Polymerase Chain Reaction

TMPRSS2 - Transmembrane serine protease 2

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Tables

Table.1 Demographics and baseline characteristics of patients with COVID-19

meter	Mild	Moderate	Severe	p value
mean ± SD	48.24 ± 17.04	47.56 ± 16.62	58.66 ± 16.02	<0.001*
e ale	230 (60.85%) 148 (39.15%)	37 (56.06%) 29 (43.94%)	34 (60.71%) 22 (39.29%)	0.762
cal features				
r	165 (43.65%)	43 (65.15%)	32 (57.14%)	0.002*
gh	125 (33.07%)	29 (43.94%)	24 (42.86%)	0.114
l ache	34 (8.99%)	12 (18.18%)	15 (26.79%)	<0.001*
throat	34 (8.99%)	7 (10.61%)	9 (16.07%)	0.253
noea	26 (6.88%)	2 (3.03%)	2 (3.57%)	0.344
lgia	11 (2.91%)	12 (18.18%)	4 (7.14%)	<0.001*
orrhoea	15 (3.97%)	2 (3.03%)	2 (3.57%)	0.930
ıtion of the stay in Median (IQR)	5 (4 -6)	6 (5 - 7)	7 (5.25 - 8.50)	<0.001*
inding				
	128 (33.86%)	28 (42.42%)	49 (87.5%)	

	250 (66.14%)	38 (57.58%)	7 (12.5%)	<0.001*
orbidity	117 (30.95%)	26 (39.39%)	25 (44.64%)	
etes mellitus				0.073
ertension	89 (23.54%)	14 (21.21%)	19 (33.93%)	0.195
liovascular disease	13 (3.44%)	6 (9.09%)	4 (7.14%)	0.081
	22 (5.82%)	5 (7.58%)	6 (10.71%)	0.366
parameters				
	2 (0.53%)	30 (45.45%)	53 (94.64%)	<0.001*
itin(ng/mL) ian (IQR)	62 (24.60 - 89)	388.50 (195.50 - 541)	1199.50 (854 - -1536)	<0.001*
(U/L)	95 (35 - 105)	720 (648.25 - 916)	982.50(739 - 1119.25)	<0.001*
mer(ng/mL)	23.20(12.20 - 56.60)	104.30 (64 - 169.35)	197.10(130.63 - 257.78)	<0.001*
rophil/Lymphocyte o	2.07 (1.48 -3.16)	2.39 (1.65 - 6.50)	2.07(1.44 - 9.86)	<0.001*
elet/Lymphocyte ratio	0.078 (0.61 - 0.12)	0.092 (0.07 - 0.16)	0.09 (0.05 - 0.21)	0.018*

Abbreviations: IQR interquartile range. * P < 0.05 was considered statistically significant.

Figures

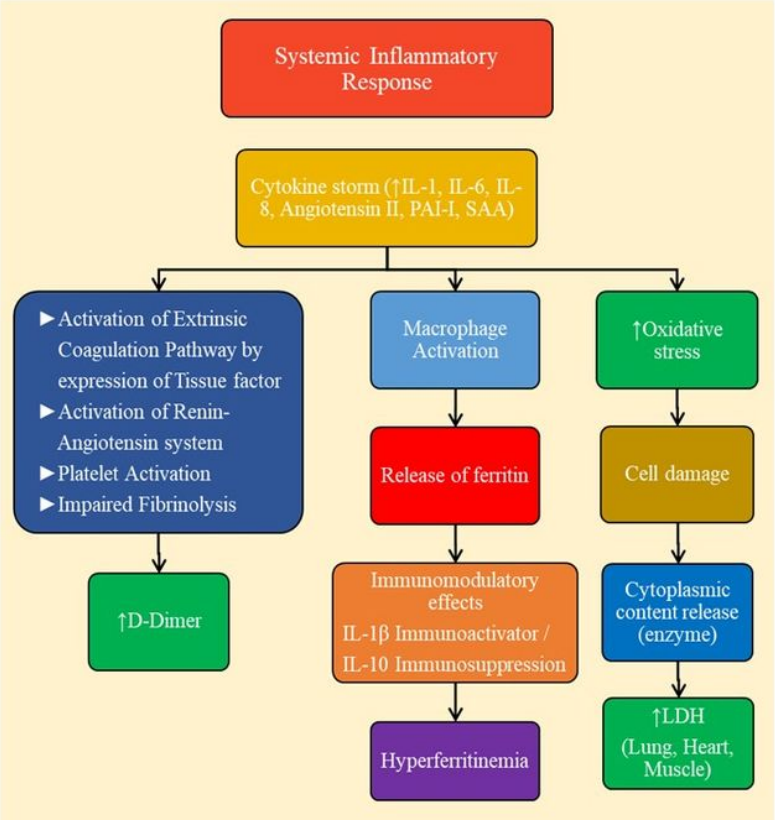

Figure 1

Interconnections between Covid 19 biomarkers of systemic inflammatory response leading to activation of extrinsic coagulation pathway, macrophage activation and oxidative stress.

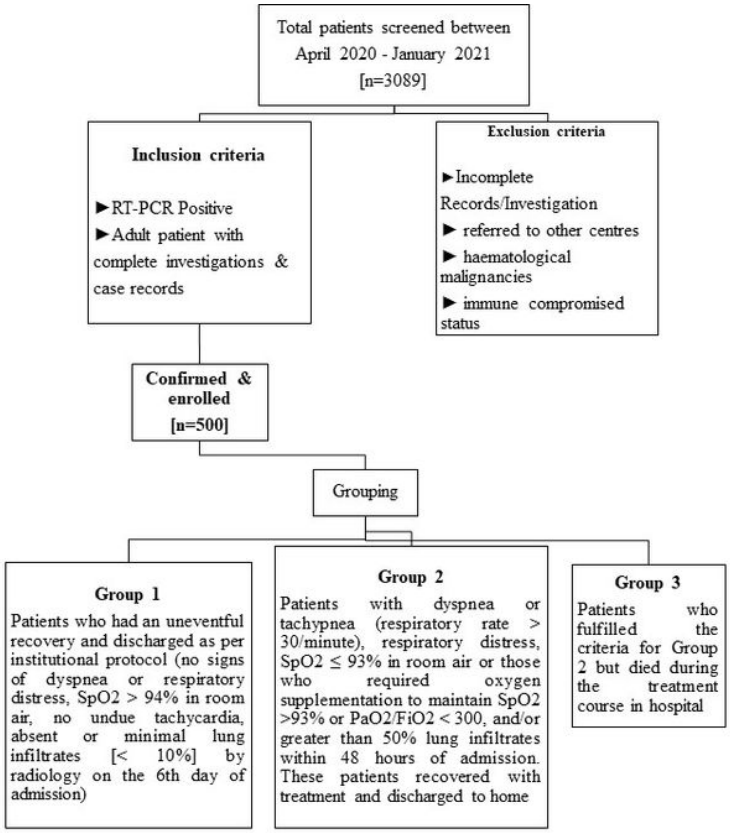

Figure 2

Flowchart of patient enrollment.

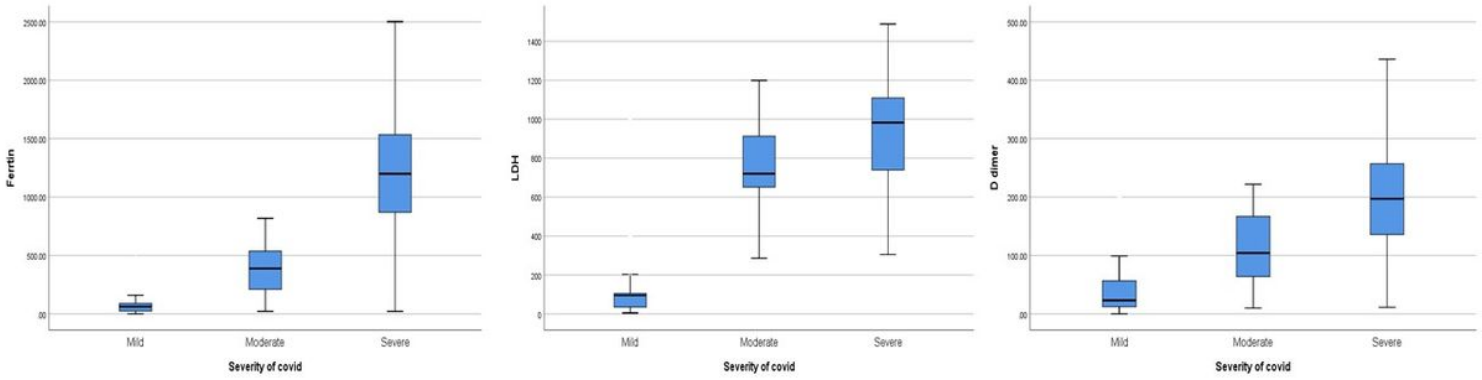

Figure 3

Box whisker plot of comparison of ferritin, LDH, D–Dimer across severity of COVID (N=500)

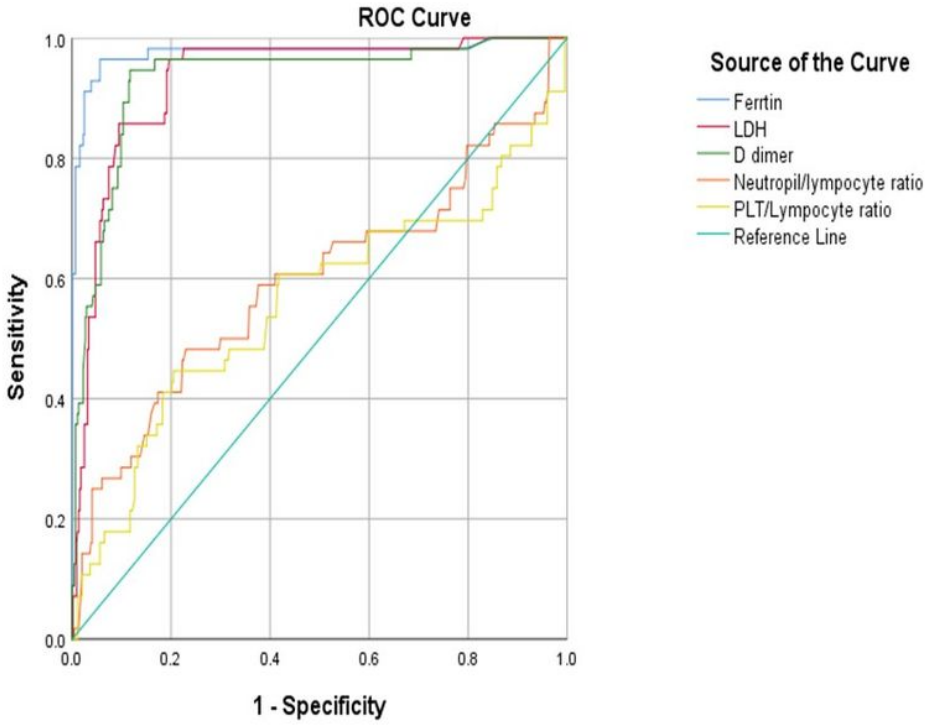

Figure 4

Predictive validity of lab parameter in predicting severity of COVID 19 (ROC analysis) (N=500)

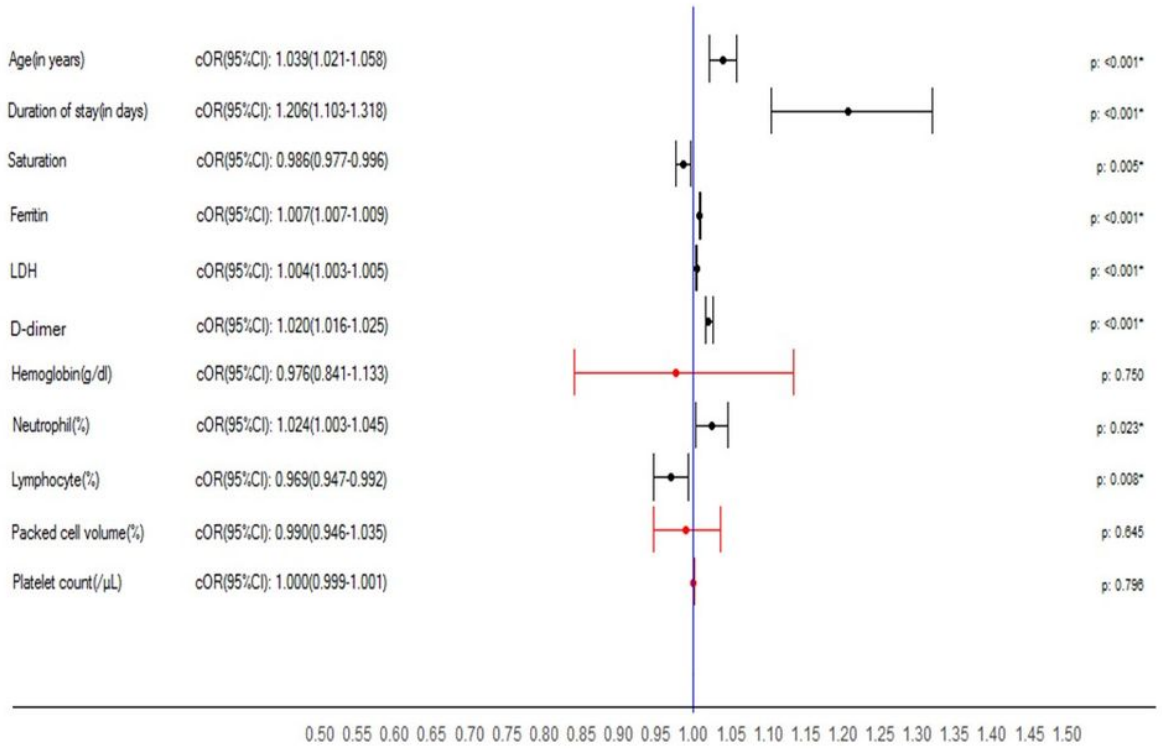

Figure 5

Forest plot for the factors associated with severe COVID 19 patients (N=500).