



EVALUATION OF INFLAMMATORY MARKERS AND THEIR RELATIONSHIP TO DISEASE MORTALITY IN SEVERE COVID-19 PATIENTS AT PERIPHERAL CARE HOSPITAL, MUMBAI.

General Medicine

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ABSTRACT

Background: The etiology of the Coronavirus disease 2019 (COVID 19) is a RNA virus called severe acute respiratory syndrome coronavirus (SARS-CoV-2). The severity of COVID-19 is linked to inflammation. Elevated LDH levels are associated with a six-fold increase in the odds of developing severe COVID-19 disease and a sixteen-fold increase in the odds of mortality in COVID-19 patients. Therefore, we conducted a study of ICU-admitted COVID-19 patients to examine the relationship between inflammatory markers and mortality. **Methodology:** The present cross-sectional observational study was carried out on 166 COVID-19 positive patients of ICU. All the demographic data and inflammatory markers CRP, LDH, D-dimer and Serum Ferritin were taken. All the parameters were compared between discharged and dead patients. Sensitivity, specificity and cut off values of all the inflammatory parameters were calculated to predict outcome of the patients. The analysis was carried out using SPSS v21, descriptive statistical analysis was conducted to determine comparisons between the sociodemographic variables and the exposure variable. **Results:** 50 (30.1%) belong to age group 18 to 40 years. Mean age of the patients was 50.2±16.1 years ranging between 19 to 91 years. Males 88 (53%) slightly outnumbered females 78 (47%). 30 (18%) patients died and 136 (82%) discharged with recovery. Mean age of the patients who died, was significantly higher as compared to survived patients (48.42±16.29 and 58.17±12.99 years respectively). All the inflammatory parameters like CRP Level, Sr. Ferritin, D-Dimer and LDH were significantly high in patients who died. AUC of ROC curve for prediction of mortality was maximum for CRP Level (AUC 0.869) followed by Sr. Ferritin (AUC 0.865), LDH (AUC 0.829) and D-Dimer (AUC 0.737). All p values <0.01). CRP Level had 80% Sensitivity, 77.94% Specificity and Cut-off of 70.3 mg%, Sr. Ferritin had 80% Sensitivity, 79.41% Specificity and Cut-off of 690.4 mg%. LDH was 80% Sensitivity, 77.21% Specificity with Cut-off of 665.77 mg%. Sensitivity and Specificity of D-Dimer was minimum (70% and 66.91% respectively) with Cut-off of 1.29 mg%. **Conclusion:** All the inflammatory parameters like CRP Level, Sr. Ferritin, D-Dimer and LDH were significantly high in patients who died as compared to survived patients. Among routine investigations, CRP and Serum Ferritin have been considered the most accurate predictors of mortality in COVID-19 patients due to their high sensitivity and specificity.

KEYWORDS

Inflammatory, Mortality, Severe Covid-19, CRP Level, Sr. Ferritin and LDH

INTRODUCTION:

The etiology of the Coronavirus disease 2019 (COVID 19) is a ribonucleic acid (RNA) virus called severe acute respiratory syndrome coronavirus (SARS-CoV-2). The transmission of the COVID 19 virus occurs from one person to another through droplets from coughing, sneezing, talking, touching droplets on surfaces and contamination by hand-to-mouth routes⁽¹⁾. Symptoms of COVID 19 include cough, high temperature, loss of weight, headache, sore throat, and loss of smell. All ages are affected by the virus, but it is known to severely affect people with immunosuppression. The virus's incubation period ranges between about 2 to 12 days⁽²⁾.

Research has shown that the severity of COVID-19 is linked to inflammation⁽³⁾. Evidence indicates that during the cell lysis stage of COVID-19 viral replication, a cytokine storm caused by immune cells leads to elevated levels of C-reactive protein (CRP) and lactate dehydrogenase (LDH)⁽⁴⁾. This cytokine storm can result in severe multisystemic end-organ failure and is responsible for the high mortality rate. Therefore, monitoring inflammatory markers is crucial for the prognosis and management of COVID-19 patients. Studies have found a significant association between elevated CRP levels and a higher risk of COVID-19 infection. Severe COVID-19 patients tend to have higher CRP levels than non-severe patients, and CRP levels in the early stages of the disease correlate with disease severity⁽⁵⁾. CRP can serve as an early marker of COVID-19 infection and inflammation, enabling healthcare professionals to intervene earlier in high-risk populations⁽⁶⁾.

Elevated LDH levels are associated with a six-fold increase in the odds of developing severe COVID-19 disease and a sixteen-fold increase in the odds of mortality in COVID-19 patients⁽⁷⁾. While fewer studies have investigated the predictive role of CRP in COVID-19 mortality, there is a lack of research on the association between LDH, ferritin, and mortality among severe COVID-19 patients. Therefore, we conducted a study of ICU-admitted COVID-19 patients to examine the relationship between inflammatory markers and mortality.

MATERIAL AND METHODS:

The present cross-sectional observational study was carried out at dept of Medicine, Bhabha Hospital, Mumbai to investigate the study objectives. Data of 166 COVID-19 positive patients was taken who were admitted into ICU of the hospital between January 2021 to June 2021. The eligibility criteria were adult males and females 18 years old or older, admitted with a COVID-19 diagnosis. After taking Ethical Committee approval, study was started. Consent of the patients was taken. All the data about patients' demographics (e.g., age, sex, race/ethnicity, insurance) and health history, clinical examination and laboratory investigations were taken. The variables used for the study include CRP, LDH, D-dimer and Serum Ferritin and severity of COVID 19 measured by Saturation of Peripheral Oxygen (SPO2) and clinical variables.

Outcomes were measure in form of discharge (recovered) or deaths. All the parameters were compared between discharged and dead patients. Sensitivity, specificity and cut off values of all the inflammatory parameters were calculated to predict outcome if the patients. The analysis was carried out using SPSS v21, descriptive statistical analysis was conducted to determine comparisons between the sociodemographic variables and the exposure variable. One-way ANOVA and unpaired t-test analysis were conducted to determine the level of CRP (high vs low) against SPO2. The test is used to determine the level of significance between categorical and continuous variables. CRP, LDH, D-dimer, Serum Ferritin and SPO2 is the continuous variable.

RESULTS:

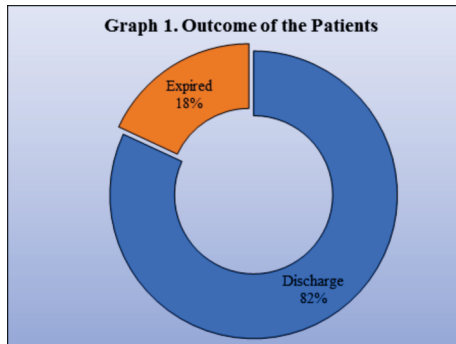
Table 1. Patient Characteristics:

Patient Characteristics		Frequency	Percent
Age groups	18 to 40 years	50	30.12
	41 to 60 years	76	45.78
	61 to 80 years	36	21.69
	≥ 80 years	04	2.41
Gender	Male	88	53.01
	Female	78	46.99
Co-morbidities	Diabetes	24	14.5

	Diabetes with Hypertension	19	11.5
	Hypertension	18	10.8
	IHD	3	1.8
	COPD	1	0.6
	No Co-morbidities	101	60.8
Total		166	100.0

In the present study, out of 166 patients Covid-19 patients, majority, 50 (30.1%) belong to age group 18 to 40 years followed by 76 (45.8%) from age group 41 to 60 years. Mean age of the patients was 50.2±16.1 years ranging between 19 to 91 years. Males 88 (53%) slightly outnumbered females 78 (47%) with male to female ratio of 1.1:1.

65 (39.2%) patients had co-morbidities with diabetes being most common (24, 14.5%) followed by Diabetes with hypertension in 19 (11.5%) and Hypertension only in 18 (10.8%) patients.



Above graph shows that out of 166 patients Covid-19 patients, 30 (18%) patients died and 136 (82%) discharged with recovery.

Comparison of Means of parameters between discharged and died patients:

Table 2 shows that mean age of the patients who died, was significantly higher as compared to survived patients (48.42±16.29 and 58.17±12.99 years respectively). Sr. Sodium, Sr. Potassium, Blood Urea, Sr. Creatinine, SGOT and Random Blood Sugar (RBS) were significantly high in patients who died as compared to survived patients. All the inflammatory parameters like CRP Level, Sr. Ferritin, D-Dimer and LDH were significantly high in patients who died as compared to survived patients (Table 2).

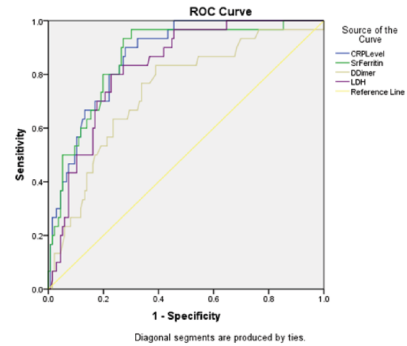
Table 2. Comparison of Means of parameters between discharged and died patients:

Variables	Outcomes		P value
	Discharge Mean ±Std. Dev.	Expired Mean ±Std. Dev.	
Age	48.42±16.29	58.17±12.99	0.003
Haemoglobin	12.33±1.69	14.72±16.63	0.101
Sr. Sodium	142.98±4.87	147.33±8.68	0.000
Sr. Potassium	4.61±0.50	4.39±0.65	0.045
Blood Urea	41.73±34.75	83.37±59.83	0.000
Sr. Creatinine	1.08±1.12	1.85±1.67	0.002
SGOT	42.35±32.37	64.77±40.07	0.001
SGPT	37.96±27.67	41.03±26.04	0.579
Random Blood	155.20±68.45	247.27±110.93	0.000
CRP Level	46.25±54.63	140.45±81.50	0.000
Sr. Ferritin	510.69±853.78	2178.61±2897.26	0.000
D-Dimer	2.17±3.73	4.87±5.73	0.002
LDH	598.81±694.53	910.98±356.94	0.018

Table 3. Correlation between LDH and Serum Ferritin with Blood Urea, Sr. Creatinine, Sr. Sodium and Sr. Potassium

Variables	LDH r2 value & p value	Sr. Ferritin r2 value & p value
Blood Urea	0.173 (0.025)	0.083 (0.289)
Sr. Creatinine	0.037 (0.639)	-0.017 (0.824)
Sr. Sodium	0.029 (0.714)	0.050 (0.523)
Sr. Potassium	-0.097 (0.213)	-0.226 (0.003)

There was significantly positive correlation between LDH and Blood Urea and significantly negative correlation between Sr. Ferritin and Sr. Potassium indicative of inflammation-mediated renal failure among patients.



Graph 2. ROC curve for prediction of mortality by different inflammatory markers:

Table 4a. Area Under the Curve:

Test Variables	Area	P value	Asymptotic 95% CI	
			Lower Bound	Upper Bound
CRP Level	0.869	0.000	0.811	0.928
Sr. Ferritin	0.865	0.000	0.797	0.934
LDH	0.829	0.000	0.759	0.898
D-Dimer	0.737	0.000	0.639	0.835

Table 4b. Sensitivity, Specificity and Cut-off level of inflammatory markers:

Test Variables	Sensitivity	Specificity	Cut-off level
CRP Level	80%	77.94%	70.3 mg%
Sr. Ferritin	80%	79.41%	690.4 mg%
LDH	80%	77.21%	665.77 mg%
D-Dimer	70%	66.91%	1.29 mg%

Graph 2 shows ROC curve for prediction of mortality by different inflammatory markers. Area Under the Curve was maximum for CRP Level (AUC 0.869 with 95% CI of 0.811 to 0.928) followed by Sr. Ferritin (AUC 0.865 with 95% CI of 0.797 to 0.934), LDH (AUC 0.829 with 95% CI of 0.759 to 0.898) and D-Dimer (AUC 0.737 with 95% CI of 0.639 to 0.835). All the p values were significant (<0.01).

CRP Level had 80% Sensitivity, 77.94% Specificity and Cut-off of 70.3 mg% for prediction of mortality. Sr. Ferritin had 80% Sensitivity, 79.41% Specificity and Cut-off of 690.4 mg%. LDH was found to have 80% Sensitivity, 77.21% Specificity with Cut-off of 665.77 mg%. Sensitivity and Specificity of D-Dimer was minimum (70% and 66.91% respectively) with Cut-off of 1.29 mg% (Table 4a and 4b).

DISCUSSION:

The purpose of this study was to examine the baseline laboratory features of very ill COVID-19 patients admitted to the intensive care unit and to analyse the association between inflammatory markers and death. In comparison to survivors, non-survivors had significantly greater levels of inflammatory markers. The relationship between inflammatory indicators and the general prognosis of COVID-19 patients has been investigated in a number of research. For instance, Ferritin can independently predict in-hospital mortality in the Kuwaiti population, according to **Alroomi et al**⁽⁸⁾. LDH has been linked to a higher risk of mortality, according to a different study by Huang et al. with a sizable sample size of 1751 Chinese patients⁽⁹⁾.

In contrast, LDH was found to be associated with a poor outcome in COVID-19 patients, according to a meta-analysis by **Martha et al**⁽¹⁰⁾. Ahmeidi et al. additionally hypothesised that increases in the blood inflammatory marker CRP may be used to predict the severity of COVID-19⁽¹¹⁾ and to identify the severity and mortality of the infection. However, because of the poor sample size and study methodology, their study had drawbacks. In COVID-19 patients, El-Shabrawy et al. demonstrated that the CRP/albumin ratio predicted 30-day death⁽¹²⁾.

Additionally, our study discovered a strong negative correlation between Sr. Ferritin and Sr. Potassium and a substantial positive correlation between LDH and Blood Urea, indicating that individuals with inflammation-mediated renal failure.

This result is consistent with Ng et al.'s study, which found that hospitalised COVID-19 patients with end-stage kidney disease had a higher mortality rate⁽¹³⁾. Numerous inflammatory indicators have been

found to evaluate severity and possible therapy targets because inflammatory responses play a critical role in the course of COVID-19⁽¹⁴⁾.

According to the current study, mortality may be predicted using CRP levels with a sensitivity of 80%, specificity of 77.94%, and a cut-off of 70.3 mg%. With sensitivity and specificity of 80%, 79.41%, and 77.21%, respectively, and matching cut-off values, Sr. Ferritin and LDH also shown predictive ability for death. Severe illness course has been independently linked to high blood ferritin concentrations at admission⁽¹⁵⁾. A separate risk factor for 3 acute respiratory distress syndrome (ARDS) in COVID-19 has also been found as hyperferritinemia⁽¹⁶⁾. However, despite the fact that hyperferritinemia 1 is linked to a more severe course of the illness, some investigations contend that it may not be associated with a worse prognosis⁽¹⁷⁾. Contrarily, the results of our investigation show that elevated serum ferritin levels, particularly before to the terminal event, are substantially related with a poor outcome.

Similar to this, we discovered that higher CRP levels before the terminal event—survival or non-survival—were more strongly linked to a worse final result than baseline CRP values or the absolute change in CRP levels during hospital admission. CRP levels at admission and just before release or death are indicators of a poor prognosis in COVID-19 patients, according to earlier reports⁽¹⁸⁾. Greater CT severity scores and significant lung involvement were linked to higher CRP levels in the early stages of the disease. Additionally, in comparable study cohorts, higher CRP values have been strongly linked with greater mortality in COVID-19 patients⁽¹⁹⁾.

Acute-phase protein CRP, which is produced with IL-6 and serves as a marker of tissue injury and inflammation, has been discovered to be higher in non-survivors. In our study, as cases progressed from asymptomatic to severe, the mean CRP levels increased considerably. As a result, we set a cut-off value for CRP to help in COVID-19 patient death prediction. Patients are more likely to die if their CRP levels are more than 70.3 mg/dL. This finding is consistent with those of Liu et al. who found that illness severity was correlated with a CRP level > 41.8 mg/dL⁽²⁰⁾.

These cytokines can act as potential indicators to distinguish between mild, moderate, and severe instances in addition to being elevated in severe symptoms. A poor prognosis and the emergence of severe symptoms as lung injury, 2 ARDS, multi-organ failure, and increased inflammatory responses are associated with SARS-CoV-2 infection⁽²¹⁾. In our study, non-survivors had considerably greater levels of biochemical markers such AST, urea, creatinine, LDH, D-dimer, and ferritin than survivors did. These anomalies point to a link between SARS-CoV-2 infection and organ damage, including hepatic, renal, myocardial, and other organs⁽²²⁾. Similar findings were made by Wang et al⁽²³⁾ who discovered that critical COVID-19 patients had noticeably elevated AST, ALT, LDH, and D-Dimer levels. Ferritin has a role in to the inflammatory response and is linked to catastrophic outcomes in COVID-19 patients when secreted simultaneously with CRP and IL-6. Epidemiological studies have shown that COVID-19 patients experience a rapid induction of the innate immune response, which is characterised by high levels of acute phase reactants like ESR, CRP, IL-6, and ferritin⁽²⁴⁾.

It's crucial to highlight that the fact that our study was done at a single peripheral healthcare facility and included just 166 patients as a sample size had some limitations.

CONCLUSION:

All the inflammatory parameters like CRP Level, Sr. Ferritin, D-Dimer and LDH were significantly high in patients who died as compared to survived patients. Among routine investigations, CRP and Serum Ferritin have been considered the most accurate predictors of mortality in COVID-19 patients due to their high sensitivity and specificity. Additionally, the measurement of LDH and D-dimer levels in the blood can provide valuable insights for predicting disease outcomes and identifying potential therapeutic targets in the treatment of COVID-19 patients.

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