ORIGINAL ARTICLE

Supporting OPEN ACCESS Publishing

Inflammatory Markers for Prognosis of COVID-19 Mortality in Hospitalized Indian Patients: A Single-Center Retrospective Study

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ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) has emerged as a global pandemic associated with poor outcomes and mortality. Therefore, the present study aimed to assess the prognostic value of inflammatory markers in predicting COVID-19 mortality among patients hospitalized at a tertiary care hospital in India.

Methods: A retrospective cross-sectional study of 444 hospitalized patients with COVID-19 was conducted in Karnataka state, India from October 2020 to September 2021. Data on inflammatory markers for survivors and non-survivors of COVID-19 were retrieved and analyzed using the receiver operating characteristic (ROC) curve to determine their prognostic value for predicting mortality.

Results: Compared to survivors, the median values of all studied serum inflammatory markers were significantly higher in non-survivors of COVID-19. ROC analysis showed that LDH, D-dimer and ferritin were the best predictive markers of COVID-19 mortality.

Conclusion: Serum ferritin, LDH, CRP, PCT, IL-6 and D-dimer, are significantly elevated in non-survivors of COVID-19 than in survivors, with all can significantly predict disease mortality. Among these, LDH, D-dimer and ferritin are the best prognostic markers for predicting COVID-19 mortality, with good sensitivity and specificity.

Keywords: COVID-19 ▪ Inflammatory marker ▪ Prognosis ▪ Mortality ▪ India

1. Introduction

By the end of 2019, a severe acute respiratory syndrome (SARS) caused by SARS coronavirus 2 (SARS-CoV-2) emerged in the city of Wuhan in China,[1] which was later named coronavirus disease 2019 (COVID-19). Although most cases are asymptomatic or mildly symptomatic, many patients experience severe disease, often accompanied by a hyperinflammatory state known as a cytokine storm, which results from the hyperactivation of both innate and adaptive immune systems and is responsible for the high mortality associated with the severe course of COVID-19.[2] The disease has a spectrum of clinical severity ranging from mild pneumonia to severe pneumonia with acute respiratory distress syndrome (ARDS), as well as a poor prognosis with organ failure and death.[3]

Elderly people with comorbidities or compromised immune systems are more likely to be affected by COVID-19.[4] In many instances, healthcare services during the pandemic have not been able to meet the growing demands of infected populations. In addition to clinical evaluation, laboratory markers can offer additional information that can have a profound impact on many aspects of patient care and management.[5] During the pandemic, COVID-19 severity has been widely predicted using laboratory markers.[6] These markers can help in protocol-based patient admission, case staging, prognosis assessment and monitoring, which pose challenges to clinicians in an evolving pandemic.[7]

COVID-19 can cause abnormal findings in many laboratory investigations, including hematological, inflammatory, coagulative and biochemical parameters.[8] Interleukin-6 (IL-6) is one of the most widely studied inflammatory cytokines because it affects coagulation, which can in turn lead to disseminated intravascular coagulation (DIC), tissue hypoxia, hypotension and multiple organ failure.[9] Poor prognosis of COVID-19 has been linked to elevated levels of D-dimer and fibrinogen during early

infection.[10] In addition, the levels of serum ferritin, procalcitonin (PCT) and C-reactive protein (CRP) have been shown to increase in severe cases of COVID-19, making them prognostic markers.[11] Other biomarkers associated with COVID-19 severity include lactate dehydrogenase (LDH), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), troponin I and serum creatinine, besides neutrophilia and lymphopenia .[12]

Prognosis of COVID-19 severity has been predicted using different combinations of biomarkers. Understanding the dynamics of inflammatory markers and COVID-19 outcomes would help clinicians in predicting the disease prognosis, initiating appropriate therapy early and achieving better treatment outcomes. The present study assessed the prognostic significance of selected inflammatory markers in predicting COVID-19 mortality in Indian patients admitted to a tertiary care hospital.

2. Methods

2.1. Study design, population and setting

A retrospective cross-sectional study was conducted on COVID-19 patients admitted to KLE's Dr. Prabhakar Kore Hospital & Medical Research Center in Belgaum, district of Karnataka state in India from October 2020 to September 2021. A positive real-time reverse transcriptase polymerase chain reaction (RT-PCR) and/or rapid antigen test of nasal or pharyngeal swab specimens was used to confirm infection. The study included 444 patients aged 18 years and older with complete records. Those with incomplete electronic records were excluded.

2.2. Data collection

A pre-designed data collection sheet was used to extract demographic data, clinical features, co-morbidities and the inflammatory markers of serum

ferritin, LDH, CRP, PCT, IL-6 and D-dimer for survivors and non-survivors of COVID-19.

2.3. Statistical analysis

The IBM SPSS Statistics, version 23.0 software (IBM Corp., Armonk, NY, USA) was used to analyze data. The median values of serum inflammatory markers were compared between survivors and non-survivors using the Mann-Whitney U test. The optimal probability cut-off, sensitivity, specificity and area-under-the-curve (AUC) of inflammatory markers for the prognosis of COVID-19 mortality in hospitalized patients were determined using the receiver operating characteristic (ROC) curve. Statistical significance was set at a P-value of <0.05.

3. Results

3.1. Characteristics of study participants

Most patients with COVID-19 were males (67.6%) and aged ≥50 (62.6%), with a mean age (SD) of 54.4 (16.3) years. The mean length of hospital stay (SD) was 8.7 (6.5) days, with most patients staying for <8 days. Cough, dyspnea and fever were the most frequent clinical features among patients, affecting 63.5%, 63.1%, and 55.5% of them, respectively. The most frequent co-morbidities were hypertension (9.7%), diabetes mellitus (8.3%) and kidney disease (3.8%) (Table 1).

3.2. Distribution of hospitalized COVID-19 patients according to inflammatory marker findings

Most hospitalized COVID-19 patients had elevated levels of CRP (93.5%), LDH (92.1%), D-dimer (91.9%), IL-6 (87.4%) and ferritin (68.7%), while 24.8% of patients had elevated PCT levels (Figure 1).

3.3. Comparison of inflammatory markers between survivors and non-survivors admitted with COVID-19

Compared to survivors, the median values of all studied serum inflammatory markers were significantly higher in non-survivors of COVID-19 (Table 2).

Table 1: Characteristics of COVID-19 patients included in the present study*

Characteristics	n (%)
Sex	
Male	300 (67.6)
Female	144 (32.4)
Age (years)	
<50	166 (37.4)
≥50	278 (62.6)
Mean (SD): 54.4 (16.3)	
Length of hospital stay (days)	
<8	241 (54.3)
≥8	203 (45.7)
Mean (SD): 8.7 (6.5)	
Clinical features	
Cough	282 (63.5)
Dyspnea	280 (63.1)
Fever	246 (55.5)
Fatigue	63 (14.2)
Myalgia	33 (7.4)
Anorexia	15 (3.4)
Vomiting	12 (2.7)
Headache	11 (2.5)
Chest pain	10 (2.3)
Mucormycosis	1 (0.3)
Co-morbidities	
Hypertension	43 (9.7)
Diabetes mellitus	37 (8.3)
Kidney diseases	17 (3.8)
Thyroid disorder	10 (2.3)
Cardiac disease	13 (2.9)
Pulmonary disease	11 (2.5)

* The study included 444 patients; COVID-19, coronavirus disease 2019; SD, standard deviation.
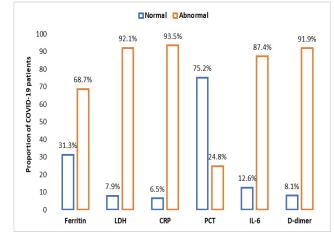

Figure 1: Distribution of COVID-19 patients admitted to a tertiary care hospital in Belgaum district, Karnataka state of India (2020–2021) according to inflammatory markers findings

Table 2: Comparison of inflammatory markers between survivors and non-survivors of COIVD-19 at a tertiary care hospital in Belgaum district, Karnataka state of India (2020–2021)

Inflammatory markers	Survivors (n = 308)	Non-survivors (n =136)	P-value
	Median (IQR)		
Ferritin (ng/ml)	478.0 (560)	957.5 (1032)	<0.001
LDH (U/L)	372.5 (221)	640.0 (408)	<0.001
CRP (mg/L)	62.0 (103)	134.0 (153)	<0.001
PCT (ng/ml)	0.0 (0)	0.0 (2)	<0.001
IL-6 (pg/ml)	39.5 (72)	99.0 (206)	<0.001
D-dimer (ng/ml)	528.5 (655)	1054.5 (4207)	<0.001

COVID-19, coronavirus disease 2019; IQR, interquartile range; LDH, lactate dehydrogenase; CRP, C-reactive protein; PCT, procalcitonin; IL-6, interleukin 6.

3.4. Prognostic performance of inflammatory markers of COVID-19 mortality

ROC analysis showed that LDH and D-dimer were the most predictive markers of COVID-19 mortality in hospitalized patients (Figure 2). All inflammatory markers had significant AUC values for predicting COVID-19 mortality, with LDH, D-dimer and ferritin being the best predictors with sensitivity levels of 71%, 67% and 65%, specificity levels of 70%, 66% and 64%, and AUC values of 0.791, 0.724 and 0.694. respectively. For other markers, sensitivity ranged from 44% for IL-6 to 63% for CRP, specificity ranged from 61% for CRP to 83% for Il-6, and AUC ranged from 0.646 for Il-6 to 0.700 for CRP (Table 3).
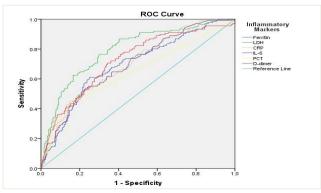

Figure 2: ROC curve of inflammatory markers as prognostic factors of COVID-19 mortality among patients admitted to a tertiary care hospital in Belgaum district, Karnataka state of India (2020–2021)

Table 3: Inflammatory markers' optimal probability cut-off, sensitivity, specificity and AUC in predicting COVID-19 mortality

Marker	Cut-off	Sen. (%)	Spec (%)	AUC (95% CI)	P-value
Ferritin (ng/ml)	633.5	65	64	0.694 (0.641–748)	<0.001
LDH (U/L)	483.5	71	70	0.791 (0.746–0.838)	<0.001
CRP (mg/L)	88.5	63	61	0.700 (0.649–0.752)	<0.001
PCT (ng/ml)	59.5	64	63	0.695 (0.643–0.747)	<0.001
IL-6 (pg/ml)	0.50	44	83	0.646 (0.588–0.706)	<0.001
D-dimer (ng/ml)	739.0	67	66	0.724 (0.673–0.777)	<0.001

AUC, area-under-the-curve; COVID-19, coronavirus disease 2019; CI, confidence interval; LDH, lactate dehydrogenase; CRP, C-reactive protein; PCT, procalcitonin; IL-6, interleukin 6.

4. Discussion

COVID-19 is an emerging pandemic that led to numerous cases and deaths all over the world. Despite having a good understanding of the clinical features of COVID-19, little is available about the prognostic value of inflammatory markers in predicting its mortality. In several instances, inflammatory cytokines and markers have been found to increase in severe cases of COVID-19.[8, 13] These markers have been reported to be useful in predicting COVID-19 mortality.[14–16] The present study revealed significant prognostic performance of all studied inflammatory markers in predicting mortality in hospitalized COVID-19 patients, with LDH, D-dimer, and ferritin having the strongest predictive values. This finding underscores the importance of evaluating and monitoring such markers in hospitalized patients to avert serious complications and deaths.

In the present study, the significantly higher elevation of serum LDH among non-survivors of COVID-19 than survivors could be attributed to severe tissue destruction. Tissue damage, necrosis and hypoxia during severe COVID-19 can substantially increase serum LDH.[17] The prognostic significance of serum LDH in predicting COVID-19 mortality in the present parallels

with that recently reported for COVID-19 patients admitted to tertiary care hospitals in South and East India.[18, 19] This finding is also consistent with findings reported elsewhere.[20–24] In Japan, serum LDH levels one week after hospital admission were found to be the strongest prognostic marker of in-hospital COVID-19 mortality.[25] Meanwhile, the prognostic performance of D-dimer in predicting mortality in the present study is in line with the dynamic changes revealed for D-dimer as a prognostic marker of COVID-19 mortality.[15, 16, 26]

Hyperferritinemia was found to be one of the best predictors of COVID-19 mortality in the present study. Consistent with this finding, a study among hospitalized COVID-19 patients in New Delhi found that higher ferritin levels were associated with poor COVID-19 prognosis.[2] The prognostic value of high serum ferritin agrees with that recently reported for COVID-19 patients admitted to tertiary care hospitals in South and East India.[18,19] Hyperferritinemia at admission has been independently linked to the severity of the disease and the development of ARDS.[27,28] In contrast to the present study, no association was found between serum ferritin and poor COVID-19 prognosis in Italian patients.[29]

The prognostic usefulness of elevated CRP in predicting mortality in the present study is consistent with that reported for COVID-19 patients in New Delhi,[2] where the risk of mortality significantly increased with elevated CRP levels. In a tertiary care hospital in South India, CRP was found to be an indicator of tissue oxygen availability in patients with COVID-19 and thus a useful marker for disease prognosis.[18] Likewise, it was also found to significantly predict COVID-19 mortality in hospitalized patients in East India.[19] In another context, CRP isoforms were found to be prognostic biomarkers of COVID-19 severity and mortality in hospitalized patients in Spain.[30] Several studies reported the prognostic utility of elevated CRP in predicting poor outcomes and mortality from COVID-19 at admission and before death.[31–33]

In the present study, IL-6 and PCT were not among the best markers to predict mortality in COVID-19 patients. However, their significant AUC values as useful prognostic markers for COVID-19 mortality are compatible with the hyperinflammatory state during the severe course of the disease and its poor outcomes. Patients with severe COVID-19 have been shown to die mostly from the cytokine storm brought on by pro-inflammatory cytokines.[32, 34–36] Despite not being a predictor of COVID-19 mortality, IL-6 can accurately predict the severity of COVID-19 with a pooled AUC of 0.850, according to a recent systematic review and meta-analysis.[37] On the other hand, a systematic review concluded that PCT can be a promising predictor of COVID-19 severity and mortality.[38]

Due to its retrospective nature in a single tertiary hospital, the present study has some limitations, possibly making its findings not generalizable to other parts of the country. Several other markers that would have helped to clarify the picture could not be studied as a result of secondary data acquisition from records. In addition, the use of anti-inflammatory drugs and other supportive measures could have affected disease progression and outcome, but these could not be assessed. Nevertheless, the findings of the present study underscore the importance of paying attention to dynamic variations in inflammatory markers, particularly LDH, D-dimer and ferritin, in the follow-up of hospitalized COVID-19 patients. To better understand the dynamics of inflammatory markers and their prognostic values, well-designed prospective cohort studies are recommended.

5. Conclusion

Serum inflammatory markers, including ferritin, LDH, CRP, PCT, IL-6 and D-dimer, are significantly elevated in non-survivors of COVID-19 than in survivors, being all significant prognostic factors for predicting mortality. Among these, LDH, D-dimer and ferritin are the best markers for predicting mortality from COVID-19, with good sensitivity and specificity. However, larger-scale longitudinal studies are needed to validate the

prognostic utility of inflammatory markers, individually or in combination, to predict COVID–19 mortality.

Ethical approval and consent

Ethical clearance was obtained with a waiver of consent from the Institutional Human Ethics Committee of Jawaharlal Nehru Medical College, KLE Academy of Higher Education and Research, Belagavi, Karnataka (Ref no.: MDC/DOME/243). Permission to use data records was obtained from the Clinical Services Administrator, Medical Director and Chief Executive Officer of KLE Hospital and the Medical Records Department. To ensure confidentiality and privacy, all the personal data were coded and anonymized prior to analysis.

Conflict of Interest

The authors declare no conflicts of interest.

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