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Can Dynamic Changes in Inflammatory Markers Predict Outcomes in COVID-19 Infection?

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ABSTRACT

Objective: To determine the role of dynamic changes in inflammatory markers over initial 48 hours after admission in predicting outcomes of COVID-19 infection.

Study Design: Cross-sectional study.

Place and Duration of Study: Department of Medicine, Combined Military Hospital, Peshawar Pakistan, from Sep to Dec 2020.

Methodology: Indoor patients with positive polymerase chain reaction test for SARS-CoV-2 were included in the study. Serum C-reactive protein, Ferritin and LDH levels were tested within 60 minutes of admission and the course of these markers was monitored over 48 hrs. In-hospital mortality was also recorded.

Results: There were 92 patients in this study, having a mean age of 53.80±16.20 years. In-hospital, 14 patients (15.22%) died whereas the rest were discharged. Median and interquartile ranges for changes in Serum CRP, Ferritin and LDH over the first 48 hours of admission were -10.00(-56.35–2.68) mg/L, -5.50(-100.00–193.50) ng/ml and -23.50(-162.00–81.50) U/L respectively. Increase in Serum Ferritin ≥128.5 ng/ml had 64.29% sensitivity and 74.36% specificity for predicting in- hospital mortality. Changes in C-reactive protein and Lactate Dehydrogenase did not have a predictive role in our study.

Conclusion: Rise in Serum Ferritin levels over first two days of admission was associated with increased risk of death.

Keywords: COVID-19, Biomarker, Ferritin, Mortality.

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INTRODUCTION

COVID-19 pandemic has affected the whole world as according to World Health Organization, as of 6 August 2021, there have been 200,840,180 confirmed cases of COVID-19, including 4,265,903 deaths.[1] It is primarily a respiratory disease but has a wide spectrum of presentation, from asymptomatic patients to those with critical disease requiring ventilatory support. Once the virus enters the body an inflammatory response starts with an overproduction of proinflammatory cytokines that amass in the lungs leading to the damage of lung parenchyma, with resultant tissue hypoxia and acute respiratory distress syndrome.[2-3] This buildup of cytokines may lead to widespread tissue damage, referred to as Cytokine Release Syndrome, resulting in capillary leak, thrombosis and organ malfunction, leading to serious clinical consequences, including death.[4]

Thus, there is a dire need to implement strategies to reduce mortality, which begins with identifying at-risk patients. Hematological markers, like Interleukin-6 (IL-6) and Procalcitonin, might play an important role in this regard. Some of these are not routinely tested at most centers in Pakistan, others like Serum Ferritin, C-Reactive Protein (CRP) and Lactate Dehydrogenase (LDH) are routinely monitored in the vast majority of patients. Many studies on the role of these biomarkers have been conducted in various parts of the world.[5,6] A study conducted at our hospital during the first wave of COVID-19 pandemic showed that levels of the latter three markers in the early hours of hospitalization predicted mortality in COVID-19 infection, with Serum Ferritin outperforming the others.[7] One of the limitations of that study was that these parameters were checked at only one point in time only, and the effect of quantitative change in inflammatory markers over the initial period of admission was not clear.[8]

We, therefore, planned this study to see the association of dynamic changes in inflammatory markers with poor outcomes in our patients with different levels of disease severity. The results would help identify patients with greater risk of death during hospital stay, who could benefit from earlier aggressive and preferential treatment escalation.

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METHODOLOGY

The cross-sectional study was undertaken at the Department of Medicine, Combined Military Hospital, Peshawar Pakistan, from September to December 2020 after attaining prior approval from Ethics Review Committee (Reference number 37). Sample size was calculated using EasyROC, a web-tool for ROC curve analysis (ver. 1.3.1). Sampling technique used was convenience sampling.

Inclusion Criteria: Indoor patients of either gender, aged 18 years or older, with confirmed COVID-19 infection, based on a positive Polymerase Chain Reaction (PCR) for SARS-CoV-2 performed on nasopharyngeal samples, were included.

Exclusion Criteria: Patients with suggestive findings on HRCT chest but negative polymerase chain reaction for SARS-CoV-2, home isolated patients, those dying within 48 hours of admission or having incomplete data and unwilling patients were excluded.

At the time of this study, there was no literature available on the role of dynamic changes in commonly used inflammatory markers as markers of mortality in COVID-19 infection. We, therefore, assumed that the expected area under ROC curve for change in Serum Ferritin levels would be 0.915 and based our calculation of sample size on an allocation ratio of 10 (corresponding to anticipated mortality of 10%) as documented in a previous study from our hospital.[7] Clinical disease severity was assessed using World Health Organization interim guidance on clinical management of COVID-19.[8] All patients had blood sampling for inflammatory markers including Serum CRP, Ferritin and LDH within 60 minutes of arrival in ward, as per institutional policy. Blood samples for quantification of inflammatory markers were collected again twice at 24 hours' intervals. All of these patients were treated according to disease severity as per hospital guidelines and monitored for duration of hospital stay and disease progression. In- hospital mortality was also recorded for all patients.

Data was analyzed by using Statistical Package for the Social Sciences (SPSS) version 23. Quantitative data with normal distribution was described as Mean± standard deviation, whereas non-parametric distribution was described as median and interquartile range. Changes in levels of different inflammatory markers were calculated and Receiver Operating Characteristic (ROC) curve analysis was done to identify the optimal cut- off for different inflammatory markers for predicting in- hospital mortality. The *p* value of ≤0.05 was considered statistically significant.

RESULTS

There were 92 patients included in this study, having a mean age of 53.80±16.20 years. Their baseline characteristics are shown in Table-I. Of them, 14 patients (15.22%) died in hospital, whereas the rest got discharged after recovering from COVID-19 infection. Median levels of inflammatory markers at baseline, 24 hours and 48 hours of admission are shown in Figure-1. Median and interquartile ranges for changes in serum CRP, ferritin and LDH over the first 48 hours of admission were -10.00(-56.35–2.68) mg/L, -5.50(-100.00–193.50) ng/ml and -23.50 (-162.00–81.50) U/L respectively. As shown in Table-II, only the change in serum ferritin levels was predictive of mortality, whereas the other two inflammatory markers did not have a significant relationship. Increase in serum ferritin ≥128.5 ng/ml had 64.29% sensitivity and 74.36% specificity for predicting in- hospital mortality. ROC curves for changes in the three inflammatory markers as predictors of mortality are shown in Figure-2.

Table-I: Demographic Characteristics of Patients (n=92)

Characteristics		n(%)
Gender	Male	72(78.26%)
	Female	20(21.74%)
Duration of hospital stay (days)		9.15± 4.70
Outcomes	Death	14(15.22%)
	Discharged	78(84.78%)
Requirement for respiratory support	Non Invasive Ventilation	7(7.61%)
	Mechanical ventilation	4(4.35%)
Disease severity	Mild	52(56.52%)
	Moderate	27(29.35%)
	Severe	13(14.13%)

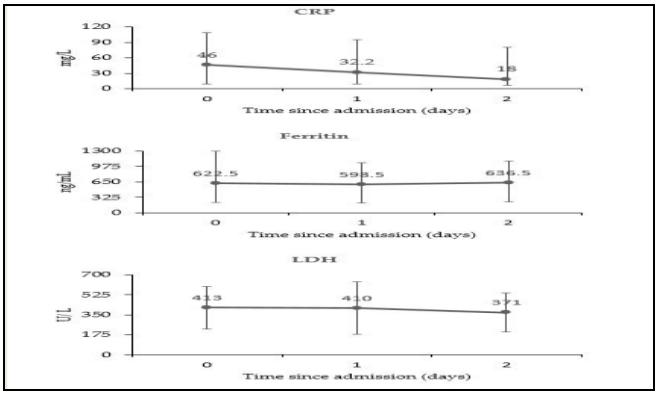

Figure-1: Serum Levels of Inflammatory Markers on Admission and at 24 and 48 Hours Intervals (Error Bars show Interquartile Ranges)

Table-II: Areas under Receiver Operating Characteristic (ROC) Curve Analysis for Changes in Inflammatory Markers Over Initial 48 Hours of Admission (n=92)

Variables	AUC (95% CI)	*p*-value
Change in CRP	0.605(0.438-0.772)	0.213
Change in Ferritin	0.690(0.512-0.869)	0.024
Change in LDH	0.647(0.511-0.784)	0.080

(AUC: Area Under Curve, CRP: C Reactive Protein, LDH: Lactate Dehydrogenase)

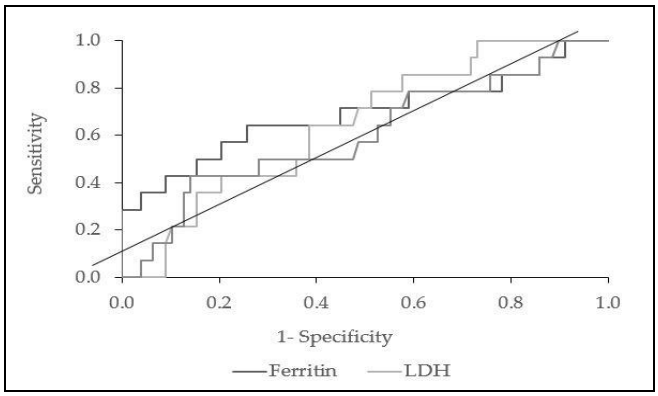

Figure-2: Receiver Operating Characteristic (ROC) Curves Showing Changes in Different Inflammatory Makers over Initial 48 hours of Admission (LDH: Lactate dehydrogenase, CRP: C-Reactive Protein)

DISCUSSION

In this study, we analyzed changes in inflammatory markers including Serum CRP, LDH and Ferritin amongst patients with confirmed COVID-19 infection during the initial period of hospitalization and their relationship with in-hospital outcomes. Our results show that elevation in Serum Ferritin levels over the first two days of admission is associated with poor prognosis, whereas changes in CRP and LDH were not predictive of mortality in our patient population.

A retrospective cohort study done at Boston (USA) during 2020 analyzed patients' level of inflammation associated with severity of illness, by looking at the CRP levels in 100 admitted patients.[9] A rapid rise was seen during the first two to three days and was predictive of subsequent worsening of respiratory status and requirement for intubation. This rise had a better sensitivity than the absolute CRP levels at the time of admission in predicting poor respiratory outcomes. Similarly, Herold *et al* identified peak levels of CRP and interleukin-6 (IL-6) as predictors of the need for mechanical ventilation.[10] This observation might seem interesting but is not practically helpful since maximal levels of these inflammatory markers could only be identified in retrospect. Elevated Ferritin levels in COVID-19 infection are either due to an increased production by proinflammatory cytokines such as IL-6 and tumor necrosis factor-α or as a result of release from damaged cells.[11] A study conducted by Bozgurt *et al*. on a total of 93 Turkish patients with a positive PCR for COVID-19 showed that Ferritin was considerably higher amongst patients with severe COVID pneumonia and was found to be the only noteworthy predictor of disease severity.[12] In this study, several other laboratory and biochemical parameters were notably different between the severe and mild groups of COVID 19 infected patients, and only CRP, IL-6, and Ferritin levels were found to be abnormally elevated. In another study conducted in Brazil, Serum Ferritin was superior to other inflammatory markers in predicting the risk of death; and a strong relation of Serum Ferritin with overall mortality was seen.[13] Findings of another study suggest that monitoring IL-6, D-dimer, CRP, LDH and Ferritin levels is clinically useful.[14]

Some studies done previously have already highlighted multiple poor prognostic factors, such as advancing age, male gender, poor respiratory function, low lymphocyte count, high Sequential Organ Failure Assessment score, and elevated levels of inflammatory markers including CRP, Procalcitonin, LDH, and d-dimers.[15] CRP is an acute phase protein and an inflammatory marker used to predict the disease severity. However, in our study the mortality was not well predicted by CRP levels. These findings are in contrast to other studies in which CRP level correlated with the severity of COVID-19 infection. Amongst 27 patients from China, Tan *et al*. found that CRP levels increased significantly during the initial stage of severe COVID-19 infection even before the radiological changes became apparent, while there was no significant difference in computed tomography imaging between the severe group and the mild group.[16] In a study by Chen et al. patients in the severe group had higher CRP levels than those in the non-severe group, though this difference did not reach statistical significance.[17] Retrospective review of 268 adult patients admitted with COVID-19 pneumonia in Atlanta showed that the rate of rise in CRP levels in the first week of hospitalization could predict evolution of the disease and the need for an early transfer to ICU.[18]

LDH is an enzyme in human tissues that catalyzes the conversion of pyruvate to lactate reversibly.[19] Our study showed no significant relation

between rising serum LDH levels and severity/ outcomes of COVID 19 infection. Our findings differ from the results of survey conducted by Wu *et al*. in which higher levels of LDH at diagnosis were seen in patients with severe covid pneumonia and this biomarker was authenticated as a marker of disease severity and treatment response.[20] Another pooled analysis of 9 studies involving 1532 patients also showed association of increased LDH levels and poor outcomes in COVID 19 patients, wherein, there was a six times increase risk of severe disease and a 16 times increase in risk of death.[21] LDH and CRP are useful parameters that could help identify patients requiring closer monitoring of respiratory function with an aim to institute more aggressive treatment modalities to avoid poor outcomes.[22]

LIMITATION OF THE STUDY

In our study, gender bias couldn't be eliminated as most of the patients were males. Another limitation we faced was that IL-6 and procalcitonin levels could not be done on all patients due to financial constraints. Patients with incomplete data were not included in the study, so the sample size studied remained small.

CONCLUSION

In contrast to Serum CRP and LDH, progressive increase in Serum Ferritin levels over the first 48 hours of admission is predictive of mortality amongst indoor patients with COVID-19 infection. These results would help focus more on such patients to improve outcomes during the pandemic.

Conflict of Interest: None.

Authors Contribution

Following authors have made substantial contributions to the manuscript as under:

TU: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

SM, ARA: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

MAM, YT: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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