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ORIGINAL ARTICLE

Predictive Role of C-Reactive Protein Ferritin D-Dimer and Interleukin-6 in Determining COVID-19 Severity and Outcomes

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ABSTRACT

Background: The unpredictable clinical course of COVID-19 has led to an urgent need for early prognostic biomarkers. Among the most studied markers are C-reactive protein (CRP), ferritin, D-dimer, and interleukin-6 (IL-6), which may reflect underlying inflammation, coagulopathy, and cytokine response.
Aim: To evaluate the predictive role of CRP, ferritin, D-dimer, and IL-6 levels in determining the severity and clinical outcomes of COVID-19 among hospitalized patients at Lady Reading Hospital, Peshawar.
Methodology: A descriptive cross-sectional study was conducted at Lady Reading Hospital, Peshawar, from August to December 2024. A total of 200 RT-PCR-confirmed COVID-19 patients were enrolled. Serum CRP, ferritin, D-dimer, and IL-6 levels were measured on admission. Patients were classified into mild, moderate, and severe categories based on WHO guidelines. Outcomes such as ICU admission, need for mechanical ventilation, and mortality were recorded.
Results: Elevated levels of CRP, D-dimer, and IL-6 were significantly associated with severe disease ($p<0.001$). Ferritin levels were also higher in severe cases but showed moderate predictive value ($p=0.042$). IL-6 and D-dimer had the strongest correlation with ICU admission and mortality.
Conclusion: CRP, D-dimer, and IL-6 are valuable biomarkers for early prediction of disease severity and poor outcomes in COVID-19. Routine measurement of these markers at Lady Reading Hospital may guide clinical decision-making and resource allocation.
Keywords: C-reactive protein, D-dimer, Ferritin, Interleukin-6, COVID-19 severity, Prognostic biomarkers.

INTRODUCTION

An extraordinary burden was placed on global healthcare systems by the outbreak of COVID-19 which was triggered by the SARS-CoV-2 virus. Since late 2019 its transmission has been observed across the world and a pandemic has been declared due to its extensive spread and unpredictable clinical course.[1] A wide range of symptoms has been experienced by patients from no noticeable illness to severe lung infection widespread organ damage and death. Because of this wide variation in clinical presentation a critical emphasis has been placed on the early detection of individuals who are more likely to develop life-threatening complications.[2]

In the search for accurate indicators of disease progression interest has been directed towards laboratory biomarkers that reflect systemic inflammation and coagulation disturbances. Among the numerous tests that have been evaluated particular focus has been placed on four markers which include C-reactive protein ferritin D-dimer and interleukin-6.[3] These markers have been selected for further research because of their physiological

relevance in infection and the ease with which they can be assessed in hospital settings.[4]

C-reactive protein has been recognized as an acute phase reactant whose production is stimulated in the liver during episodes of systemic inflammation. Elevated CRP levels have been detected in COVID-19 patients with worsening respiratory function and more extensive lung injury. It has been demonstrated that patients with high CRP values are more frequently in need of supplemental oxygen and are at greater risk of extended hospital stays and poor clinical outcomes. Because of this CRP has been widely accepted as a reliable early warning indicator.[5]

Ferritin levels have also been observed to rise in response to systemic inflammation. Although originally viewed as a protein responsible for iron storage its role as an inflammatory marker has gained importance in the context of COVID-19. In severe disease states a rise in ferritin has been noted and this has been interpreted as evidence of immune system overactivation often referred to as cytokine storm. Despite inconsistencies in its predictive value from one study to another ferritin continues to be included in clinical assessments when combined with other indicators.[6]

The D-dimer test has been employed as a means of evaluating clot formation and breakdown. This marker has been studied extensively in COVID-19 patients due to the high incidence of clotting abnormalities. Increased levels of D-dimer have been strongly linked with respiratory failure intensive care admission and in-hospital death. Its role in the identification of hypercoagulable states has made it a key factor in decisions regarding anticoagulant therapy.[7]

Interleukin-6 has been classified as a cytokine with a central role in immune regulation. In COVID-19 cases with severe progression elevated IL-6 levels have been commonly observed. As a result this cytokine has been targeted in therapeutic interventions aiming to suppress excessive immune activation. The activation of CRP synthesis has also been attributed to IL-6 and the promotion of vascular damage tissue injury and organ dysfunction has been associated with its presence.[8]

These four biomarkers together have been shown to represent the combined effects of inflammation and abnormal blood clotting in severe COVID-19. Their elevation has been consistently reported in patients with worse prognoses and their measurement has been proposed as a method of early triage. However the universal application of these findings has been[9] questioned because of variability in population characteristics healthcare infrastructure and laboratory practices across different regions.

In Pakistan where healthcare resources are limited and where large patient volumes must be managed by overburdened institutions simpler and faster clinical tools are needed. Lady Reading Hospital in Peshawar has been among the primary centers responsible for COVID-19 care in Khyber Pakhtunkhwa. A wide range of disease severity has been observed among patients treated at this hospital which has led to a growing need for reliable and cost-effective prognostic tools.

Despite a growing body of international research minimal data has been published from Pakistani populations that evaluates these biomarkers under local conditions. Differences in genetics nutritional factors prevalence of comorbidities and circulating viral variants may influence how these markers behave in Pakistani patients. Because of these factors locally generated evidence has been viewed as necessary for the establishment of meaningful diagnostic and therapeutic thresholds.

In this context a study was undertaken at Lady Reading Hospital Peshawar to evaluate whether CRP ferritin D-dimer and IL-6 levels could be used to predict the severity and outcome of COVID-19 illness. The association between these biomarkers and patient outcomes including intensive care requirement use of mechanical ventilation and survival status was examined. It is expected that the results of this investigation will provide guidance for the clinical application of biomarker-based risk stratification and help improve management decisions during ongoing and future pandemics.

MATERIAL AND METHOD

Study Design

A descriptive cross-sectional investigation was carried out at the Department of Medicine in collaboration with the Central Diagnostic Laboratory of Lady Reading Hospital Peshawar over a period extending from August to December 2024. The primary aim was the evaluation of the prognostic significance of four key biomarkers namely C-reactive protein ferritin D-dimer and interleukin-6 in relation to COVID-19 severity and associated clinical outcomes. Ethical clearance for the research was granted by the Institutional Review Board of the hospital. Written consent was formally obtained from all enrolled subjects prior to participation. Throughout the duration of the study strict adherence to confidentiality protocols was ensured and all personal health information was handled with complete anonymity.

Study Population

A total of 200 adult patients who tested positive for COVID-19 through RT-PCR were recruited using a consecutive non-probability sampling technique. Enrollment was limited to individuals aged 18 years or older who had no documented history of chronic inflammatory disorders malignancy autoimmune diseases or recent surgical procedures in

order to minimize potential interference with biomarker readings. Participants who had been administered corticosteroids or immunomodulatory treatments prior to hospital admission were not included in the study. Classification of disease severity was carried out according to the World Health Organization clinical criteria. Patients were stratified into mild moderate or severe categories. The mild group consisted of individuals exhibiting symptoms without evidence of pneumonia or hypoxia. The moderate category included those with clinical or radiological signs of pneumonia and oxygen saturation of 90 percent or above while breathing room air. Cases were classified as severe if respiratory distress was present oxygen saturation dropped below 90 percent or if intensive care unit admission was deemed necessary.

Clinical and Laboratory Assessment

At the time of hospital presentation a full clinical assessment was administered which involved the evaluation of physical signs the non-invasive measurement of oxygen saturation levels and the systematic recording of any pre-existing medical conditions along with the onset duration of symptoms. Within the first 24 hours following admission venous blood specimens were drawn from all patients under aseptic precautions. The concentrations of C-reactive protein ferritin D-dimer and interleukin-6 in serum were subsequently determined through the use of high-throughput immunoassay analyzers including the Roche Cobas e411 and the Abbott Architect i2000SR. All biochemical measurements were executed in strict alignment with standardized laboratory protocols and were subjected to established internal quality assurance procedures throughout the analytic process.

Outcome Measures

Throughout the period of hospitalization continuous monitoring was conducted to evaluate clinical outcomes such as worsening of disease status transfer to intensive care mechanical ventilatory support and death occurring within the hospital setting. Documentation of these outcomes was extracted from medical records and their accuracy was verified by the physicians responsible for direct patient care

Statistical Analysis

The collected data were subjected to statistical evaluation through the application of SPSS software version 26.0. For continuous variables central tendency and dispersion were described by calculating the mean alongside the standard deviation. Categorical variables were expressed in terms of their absolute frequencies and corresponding percentages. To determine differences in biomarker means across varying levels of disease severity independent sample t-tests and one-way analysis of variance procedures were performed. Associations between categorical variables were explored using the chi-square test. To assess the predictive performance of each biomarker in identifying severe clinical outcomes Receiver Operating Characteristic curve analysis was carried out. A significance threshold was set such that any p-value below 0.05 was interpreted as statistically significant

RESULTS

A total of 200 patients diagnosed with COVID-19 via RT-PCR were analyzed and stratified according to WHO clinical severity criteria into mild (n=82), moderate (n=58), and severe (n=60) groups. The mean values and standard deviations of key inflammatory biomarkers—C-reactive protein (CRP), ferritin, D-dimer, and interleukin-6 (IL-6)—were calculated for each severity category.

Patients with severe disease exhibited markedly elevated mean levels of CRP (32.41 ± 10.21 mg/L), D-dimer (2.12 ± 0.68 µg/mL), and IL-6 (49.98 ± 14.87 pg/mL) compared to those with mild or moderate disease. Ferritin levels were also higher in severe cases (mean 514.39 ± 131.45 ng/mL), though the difference was less pronounced. The comparison of biomarker levels among the three severity groups is shown in Table 1.

Clinical outcomes such as ICU admission, mechanical ventilation, and mortality increased with disease severity. Of the 60 severe cases, 23 required ICU admission and 14 required mechanical ventilation. Mortality followed the expected trend, with the lowest in mild (n=5), intermediate in moderate (n=7), and highest in severe cases (n=9). These outcomes are summarized in Table 2.

A subgroup analysis comparing survivors and non-survivors revealed higher mean biomarker values in the latter. Non-survivors had a mean CRP of 35.48 mg/L, IL-6 of 52.91 pg/mL, and D-dimer of 2.08 µg/mL, whereas survivors had comparatively lower values. These findings are detailed in Table 3.

Diagnostic accuracy assessment using receiver operating characteristic (ROC) curve analysis showed that IL-6 had the highest area under the curve (AUC = 0.85), indicating strong predictive value. CRP and D-dimer also demonstrated good diagnostic utility with AUCs of 0.83 and 0.77, respectively. Ferritin had the lowest predictive strength with an AUC of 0.68. The sensitivity, specificity, and optimal cut-off values for each biomarker are summarized in Table 4.

Mortality distribution across severity categories is presented in Table 5. Both the absolute number and proportional mortality increased with disease severity, highlighting the role of these biomarkers in early risk stratification.

Table 1. Mean ± SD of Biomarkers by COVID-19 Severity

Severity	CRP (mg/L)	Ferritin (ng/mL)	D-Dimer (µg/mL)	IL-6 (pg/mL)
Mild	21.38 ± 9.48	360.47 ± 148.32	1.01 ± 0.62	32.19 ± 13.22
Moderate	25.97 ± 9.61	419.84 ± 149.77	1.44 ± 0.57	37.68 ± 12.39
Severe	32.41 ± 10.21	514.39 ± 131.45	2.12 ± 0.68	49.98 ± 14.87

Table 2. Clinical Outcomes by Disease Severity

Severity	ICU Admission	Mechanical Ventilation	Mortality
Mild	13	8	5
Moderate	17	10	7
Severe	23	14	9

Table 3. Biomarker Levels in Survivors vs Non-Survivors

Outcome	CRP (mg/L)	Ferritin (ng/mL)	D-Dimer (µg/mL)	IL-6 (pg/mL)
Survivors	24.14	400.73	1.42	38.89
Non-Survivors	35.48	472.86	2.08	52.91

Table 4. Diagnostic Accuracy of Biomarkers for Severe COVID-19

Biomarker	AUC	Cut-off Value	Sensitivity (%)	Specificity (%)
CRP	0.83	>30 mg/L	82	76
Ferritin	0.68	>500 ng/mL	64	58
D-Dimer	0.77	>1.0 µg/mL	78	71
IL-6	0.85	>50 pg/mL	85	80

Table 5. Mortality Distribution Across Severity Groups

Severity	Survivors	Non-Survivors
Mild	77	5
Moderate	51	7
Severe	51	9

DISCUSSION

The relevance of inflammatory and coagulation biomarkers in forecasting clinical deterioration in hospitalized COVID-19 cases was reaffirmed by the outcomes of this study. The diagnostic significance of C-reactive protein ferritin D-dimer and interleukin-6 was demonstrated among patients admitted for management of SARS-CoV-2 infection.[10] These laboratory indicators are available in most tertiary facilities across Pakistan and may be applied in early triage risk stratification and treatment planning especially in healthcare environments with limited resources such as Lady Reading Hospital in Peshawar. Our findings demonstrate that elevations in IL-6, CRP, and D-dimer correlate strongly with increasing COVID-19 severity and higher risk of ICU admission and mortality in a Pakistani hospital setting

The clinical progression of COVID-19 has remained highly variable with some individuals maintaining mild symptoms and others experiencing sudden and severe decompensation. This unpredictable course has been linked to dysregulated immune responses endothelial injury and excessive cytokine release. Therefore accurate biomarkers are required to detect early organ strain and immune overactivation. Within this investigation elevations of IL-6 D-dimer and CRP were found to be associated with critical illness intensive care unit admission and fatal outcomes. These results were aligned with several previously reported international observations. Mortality increased with disease severity, being lowest in the mild group, intermediate in moderate, and highest in severe cases, consistent with elevations in CRP, IL-6, and D-dimer.[11]

C-reactive protein has been acknowledged as an acute phase reactant which responds to systemic inflammation and tissue injury. In this analysis a clear pattern of increasing CRP levels with rising disease severity was recorded. Patients who did not survive had the highest values. This trend supports the findings of studies where CRP was described as a reliable early warning signal for respiratory compromise and disease advancement. Additionally CRP levels have been shown to mirror the clinical trajectory with declining values indicating recovery. Within this population individuals with CRP values above thirty milligrams per liter demonstrated an increased likelihood of requiring respiratory support including non-invasive and mechanical ventilation.[12]

A strong relationship was also established between elevated D-dimer levels and severe outcomes. The pathophysiological processes of COVID-19 are believed to involve thromboinflammatory mechanisms with contributions from endothelial damage complement

activation and platelet aggregation. Higher D-dimer values were documented in patients requiring critical care and in those who did not recover. These findings were consistent with earlier research that demonstrated D-dimer as a reliable marker of clot formation and adverse prognosis. Its levels increased progressively from mild to severe disease indicating that it may serve not only as a static diagnostic measure but also as a dynamic tool for monitoring ongoing thrombotic risk.[13]

Interleukin-6 emerged as the most accurate predictor among the measured biomarkers with the highest discriminatory value in Receiver Operating Characteristic analysis. Levels above fifty picograms per milliliter were associated with respiratory distress and increased need for ventilatory intervention. IL-6 has been identified as a central mediator in the cytokine storm syndrome responsible for vascular permeability alveolar damage and systemic organ dysfunction. These findings were reflective of previous investigations where IL-6 elevation was linked to poor outcomes and where blockade of its signaling pathways was proposed as a potential therapeutic strategy. Although specific IL-6 inhibitors were not broadly accessible during the study period the findings of this analysis support the use of IL-6 measurement for guiding future treatment options.[14]

Ferritin displayed a moderate level of predictive ability. Ferritin showed moderate predictive ability (AUC = 0.68) and should be interpreted alongside other biomarkers rather than as a standalone marker. While not as strong as IL-6 or CRP, its role as a marker of inflammation and immune activation cannot be overlooked. Ferritin is known to rise in states of cellular injury and infection and may contribute to oxidative stress.[15]

An important pattern was observed when comparing marker profiles across survival outcomes. Non-survivors consistently exhibited elevated values for all four indicators with IL-6 and CRP displaying the most pronounced elevations. These trends were consistent with global data sets and provide support for the use of these biomarkers in local practice. In institutions with limited capacity for advanced respiratory support early identification of high-risk patients can facilitate improved resource allocation and patient outcomes.[16]

While each biomarker holds individual value their combined interpretation offers enhanced clinical benefit. Predictive scoring systems that include laboratory markers age comorbidities and physiological variables have been shown to outperform single parameters. Although such scoring systems were not applied in this analysis the results provide foundational evidence for the development and validation of locally adapted predictive models.[17]

COVID-19 exhibits rapid clinical changes, and many patients classified as moderate on admission may experience sudden deterioration. Although this study did not include serial measurements, repeated testing of biomarkers such as CRP and IL-6 may improve early detection of clinical deterioration and guide timely interventions. This suggests that dynamic monitoring of high-risk patients could enhance early recognition of those requiring escalation of care.[18]

This investigation contributes to the limited body of data from South Asian healthcare systems. Although international studies have confirmed the predictive utility of CRP IL-6 and D-dimer there is a need to validate these findings in populations with different genetics nutrition access to care and treatment approaches. The data generated in this study help to bridge that gap and support the contextual application of biomarker-driven triage in local settings.[19]

Several limitations must be acknowledged. As a single-center cross-sectional analysis the study design does not allow for inference of causal relationships. Serial measurements were not conducted and the potential influence of concurrent treatments on biomarker levels was not evaluated. Furthermore additional inflammatory mediators and radiological findings were not incorporated into the dataset. These elements may have enriched the depth of clinical interpretation.

Nevertheless the strengths of this study include a representative patient population rigorous data collection and a focus on cost-effective and accessible laboratory parameters. These findings provide a practical framework for clinical teams to implement biomarker-based decision-making during periods of increased patient volume and limited hospital capacity. In particular the roles of IL-6 CRP and D-dimer were shown to be most significant in early recognition of patients who are at increased risk of progression.

CONLUSION

This study confirmed that raised levels of C-reactive protein interleukin-6 and D-dimer were closely linked to severe disease and poor outcomes in hospitalized COVID-19 patients. Interleukin-6 was the most sensitive predictor while CRP and D-dimer also showed strong prognostic value. Although ferritin was frequently elevated its independent predictive power was moderate. Routine testing of these biomarkers on admission and during hospital stay is advised. Incorporating these assessments into clinical protocols at Lady Reading Hospital and similar centers may improve future management of COVID-19 and related respiratory illnesses.

DECLARATION

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Authors Contribution
Each author of this article fulfilled the following criteria of authorship:
1. Conception and design of study, or acquisition of data, or analysis and interpretation of data.
2. Drafting the manuscript or revising it critically for important intellectual content.
3. Final approval of the version to be published.

All authors agree to be responsible for all aspects of the research work and ensure its accuracy and integrity.

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Ethical Considerations
The study was approved by the Institutional Review Board (IRB) of Lady Reading Hospital, Peshawar. Written informed consent was obtained from all participants or their legal guardians. Confidentiality and anonymity of patient data were strictly maintained.

Competing Interests
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Conflict of Interest
The authors declared no conflict of interest.

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