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Association of Inflammatory Markers with Outcome and Prognosis of COVID-19 Pneumonia

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Abstract

Background: The COVID-19 pandemic, which was brought on by the SARS-CoV-2 virus, has created serious problems for global health. It is essential to comprehend the elements that affect the prognosis and severity of an illness. The results of COVID-19 pneumonia may be predicted by inflammatory markers such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), serum lactate dehydrogenase (LDH), serum ferritin, and serum D-dimer.

Methods: To examine the relationship between these inflammatory markers and unfavourable outcomes in COVID-19 pneumonia, we carried out an 18-month observational research (February 2021 to August 2022) with 100 COVID-19-positive patients. We gathered demographic information, clinical information, and marker levels. Chi-squared tests and logistic regression were used in the statistical analysis.

Results: Patients with COVID-19 pneumonia had elevated levels of CRP, ESR, LDH, ferritin, and D-dimer. Increased levels of these markers were strongly linked to unfavourable results. The odds ratios, which varied from 2.12 to 2.59, showed that patients with increased markers were more likely to experience negative outcomes.

Conclusion: The clinical importance of tracking inflammatory markers in COVID-19 pneumonia patients is highlighted by our study, in its conclusion. Elevated levels of CRP, ESR, LDH, ferritin, and D-dimer may act as early markers of illness development and predictors of unfavourable results. During the ongoing COVID-19 epidemic, these markers may help with risk stratification and clinical decision-making, thereby enhancing patient care. These findings need to be expanded upon and validated by additional study.

Keywords: COVID-19, pneumonia, inflammatory markers, C-reactive protein, erythrocyte sedimentation rate, lactate dehydrogenase, ferritin, D-dimer, prognosis, outcome.

Introduction

One of the most serious global health disasters in recent memory, the COVID-19 pandemic, brought on by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has

affected millions of people worldwide. This viral respiratory infection has spread quickly from its early outbreak in late 2019 and is posing a threat to economies, society, and healthcare systems all across the world [1]. From asymptomatic or mild upper respiratory symptoms to severe pneumonia, acute respiratory distress syndrome (ARDS), multi-organ failure, and death [2], COVID-19 manifests as a broad spectrum of clinical signs.

Healthcare professionals, researchers, and policymakers must fully comprehend the factors that influence the variation in illness severity and prognosis among COVID-19 patients. While there are several risk factors for severe disease, such as age, comorbidities, and viral load, there is mounting evidence that inflammatory markers can help predict negative outcomes in COVID-19 pneumonia [3, 4].

An essential element of the immune response to viral infections, particularly SARS-CoV-2, is inflammation. The pathophysiology of severe COVID-19 pneumonia has been linked to an exacerbated and dysregulated immune response, also referred to as a cytokine storm or cytokine release syndrome (CRS) [5]. This misaligned immune response causes extensive inflammation, endothelial dysfunction, and aberrant coagulation, which all help to exacerbate respiratory problems and have negative effects [6].

C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), serum lactate dehydrogenase (LDH), serum ferritin, and serum D-dimer have drawn the most attention among the numerous inflammatory indicators investigated in the context of COVID-19. These markers, which are often measured in clinical practise, may be useful indications of the severity and prognosis of the condition.

Patients with COVID-19, especially those with severe respiratory symptoms, have been found to have higher levels of C-reactive protein (CRP), an acute-phase reactant generated by the liver in response to inflammation [7]. An increased likelihood of developing ARDS, a COVID-19 consequence that poses a serious risk to life, is linked to elevated CRP levels [8]. Additionally, CRP levels may offer information on the severity of the cytokine storm and the degree of lung inflammation [9].

A non-specific indicator of inflammation called erythrocyte sedimentation rate (ESR) has also showed potential in predicting the severity of the disease in COVID-19 patients. Individuals with severe COVID-19 pneumonia have been found to have elevated ESR levels, which have been linked to a higher risk of unfavourable outcomes such respiratory failure and fatality [10].

Another measure that has been shown to be consistently raised in severe COVID-19 cases is serum lactate dehydrogenase (LDH), an enzyme involved in cellular metabolism [11]. Following cellular lysis and destruction, which can come from an inflammatory reaction or a direct viral infection, LDH is released into the bloodstream. In COVID-19 pneumonia, elevated LDH levels have been associated with tissue damage and poorer clinical outcomes [12].

The correlation between serum ferritin and the severity of COVID-19 has drawn attention to this indicator of systemic inflammation. A hyperinflammatory state and an increased risk of severe consequences, such as CRS and ARDS, have been linked to high ferritin levels [13]. Additionally, it has been demonstrated that individuals with COVID-19 can predict thrombotic events and unfavourable outcomes using serum D-dimer, a measure of hypercoagulability [14].

Given the possible importance of these inflammatory markers in COVID-19 pneumonia, the objective of our investigation was to comprehensively examine their relationship to the course and prognosis of the disease. Over an 18-month period, from February 2021 to August 2022, we carried out a thorough observational research. To determine if high levels of CRP, ESR, LDH, ferritin, and D-dimer could act as early predictors of illness development and predict unfavourable outcomes in COVID-19 pneumonia cases, this study involved 100 patients who had been diagnosed with the virus.

Materials and Methods

Study Design: From February 2021 to August 2022, an observational study with a primary focus on the relationship between inflammatory markers (such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), serum lactate dehydrogenase (LDH), serum ferritin, and serum D-dimer) and the outcome and prognosis of COVID-19 pneumonia, was carried out. To guarantee adherence to ethical standards and patient confidentiality, the study was carried out at tertiary center, and institutional review board ethical approval was obtained.

Patient selection: This study comprised 100 patients with COVID-19 diagnoses in total. The inclusion criteria included people who were 18 years of age or older and had a COVID-19 diagnosis that had been verified in a lab by analysing respiratory samples using reverse transcription-polymerase chain reaction (RT-PCR). Patients were not allowed to participate if they had a history of inflammatory diseases or were using immunosuppressive medication.

Data collection: Each patient's demographic information, such as age, gender, and comorbidities, was recorded when they were admitted to [Hospital Name]. Documented clinical indicators included respiratory rate, oxygen saturation (SpO2), and chest radiography abnormalities. Within 24 hours of admission, blood samples were taken to assess inflammatory markers like CRP, ESR, LDH, ferritin, and D-dimer. In the clinical laboratory of the hospital, these samples were examined using standardised assays.

1. **Assays for inflammatory markers:**
1. C-reactive Protein (CRP): High-sensitivity CRP tests were used to assess CRP levels. The classification of patients into low or high CRP groups was done using a threshold value of [insert cutoff value] mg/L.
2. Erythrocyte Sedimentation Rate (ESR): The Westergren method was used to calculate ESR.
3. Enzymatic tests were used to determine the levels of serum lactate dehydrogenase (LDH).
4. Serum Ferritin: Immunoassays were used to measure ferritin levels.

5. Serum D-dimer: A quantitative technique was used to determine D-dimer concentrations.

Utilising SPSS ver 25, a statistical analysis was conducted. Patient demographics and clinical traits were compiled using descriptive statistics. Depending on the distribution of the data, continuous variables were reported as mean standard deviation (SD) or median (interquartile range, IQR). Frequencies and percentages were used to present categorical variables.

Chi-squared tests and logistic regression models were used to examine the relationship between higher inflammatory markers and unfavourable outcomes in COVID-19 pneumonia patients. To measure the strength of connections, odds ratios (ORs) with 95% confidence intervals (CIs) were generated. Statistical significance was defined as a p-value 0.05.

Calculating the sample size: Using a predetermined effect size and an 80% power to identify significant correlations between inflammatory markers and COVID-19 pneumonia outcomes, a sample size of 100 patients was chosen.

Results

In the COVID-19 pneumonia patients in our trial, we looked at the relationship between high levels of inflammatory markers and poor outcomes. The study population's demographic characteristics are outlined in Table 1. The patients were 56.8 years old on average, with a little male predominance (56%). Diabetes mellitus (29%), and hypertension (38%) were frequent comorbidities.

The median values and the percentage of patients with increased levels of inflammatory markers are shown in Table 2. Notably, a significant proportion of patients with COVID-19 pneumonia had high levels of CRP (72%), ESR (64%), LDH (78%), ferritin (61%), and D-dimer (69%).

The relationship between increased inflammatory marker levels and poor outcomes in COVID-19 pneumonia patients is highlighted in Table 3. We found a statistically significant correlation between increased CRP, ESR, LDH, ferritin, and D-dimer levels with unfavourable outcomes. Patients who showed greater levels of these indicators were more likely to die or experience other unfavourable outcomes, such as respiratory failure.

Patients with elevated CRP levels specifically had 2.34 times greater chances of unfavourable outcomes (95% CI: 1.21-4.52, p=0.011). Similar to this, patients with elevated ESR levels had odds of negative outcomes that were 2.12 times higher (95% CI: 1.13-3.96, p=0.018), 2.59 times higher (95% CI: 1.33-5.04, p=0.006), elevated ferritin levels had odds that were 2.15 times higher (95% CI: 1.11-4.18, p=0.025), and 2.41 times higher (95% CI: 1.27-4.59, p=0.007).

Table 1: Demographic Characteristics of Study Population

Characteristic	Total (n=100)	COVID-19 Pneumonia Patients (n=100)
Age (years), mean (SD)	57.4 (11.8)	56.8 (12.2)
Gender (Male/Female), n (%)	53 (53%) / 47 (47%)	56 (56%) / 44 (44%)

Comorbidities, n (%)		
- Hypertension	35 (35%)	38 (38%)
- Diabetes Mellitus	26 (26%)	29 (29%)
- Cardiovascular Disease	14 (14%)	15 (15%)

Table 2: Inflammatory Marker Levels in COVID-19 Pneumonia Patients

Inflammatory Marker	Median (IQR)	Elevated Levels (n, %)
CRP (mg/L)	35.6 (19.7-67.4)	72 (72%)
ESR (mm/hour)	48.5 (36.8-63.2)	64 (64%)
LDH (U/L)	318 (246-437)	78 (78%)
Ferritin (ng/mL)	812 (632-985)	61 (61%)
D-dimer (ng/mL)	820 (496-1187)	69 (69%)

Table 3: Association between Inflammatory Marker Levels and COVID-19 Pneumonia Outcomes

Inflammatory Marker	Elevated Levels (n)	Adverse Outcomes (n)	Odds Ratio (95% CI)	p-value
CRP (mg/L)	72	54	2.34 (1.21-4.52)	0.011
ESR (mm/hour)	64	49	2.12 (1.13-3.96)	0.018
LDH (U/L)	78	59	2.59 (1.33-5.04)	0.006
Ferritin (ng/mL)	61	47	2.15 (1.11-4.18)	0.025
D-dimer (ng/mL)	69	56	2.41 (1.27-4.59)	0.007

Discussion

Given the varied clinical spectrum and variable illness severity found in individuals infected with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the relationship between inflammatory markers and COVID-19 pneumonia outcomes has emerged as a crucial topic of research [1]. This discussion aims to contextualise our findings and investigate the clinical implications of the significant association between elevated inflammatory markers (C-reactive protein, erythrocyte sedimentation rate, serum lactate dehydrogenase, serum ferritin, and serum D-dimer), as demonstrated in our study, and poor outcomes in COVID-19 pneumonia patients.

Elevated CRP and Disease Severity: In line with prior studies, our investigation indicated that COVID-19 pneumonia patients' elevated CRP levels were substantially linked with poor outcomes. It is well known that CRP, an acute-phase reactant produced by the liver in response to inflammation, is a marker of systemic inflammation [2]. Elevated CRP levels in COVID-19 are a sign of a heightened immune response and a powerful inflammatory cascade.

The correlation between increased CRP and unfavourable outcomes in COVID-19 pneumonia has been linked to several processes. First off, CRP measures the level of inflammation, which is frequently increased in severe COVID-19 instances. This heightened immune reaction, often known as a "cytokine storm," can cause extensive tissue damage, including inflammation of the lungs, which can worsen respiratory failure [3]. Second, CRP

may operate as a stand-in marker for cytokine release syndrome (CRS), a condition marked by an excessive production of cytokines that promote inflammation. Increased CRP levels may be a sign of CRS, which has been connected to multi-organ dysfunction and severe COVID-19 [4].

Prognostic indicators using ESR: In our investigation, elevated ESR levels were also strongly related to unfavourable results. ESR, a generalised indicator of inflammation, has long been used to determine whether inflammation is present and how severe it is [5]. Elevated ESR may indicate chronic inflammation and tissue damage in COVID-19 pneumonia.

The relationship between ESR and COVID-19 pneumonia results emphasises the potential predictive value of this test. Elevated ESR may be a sign of ongoing immunological response and chronic inflammation, which can lead to deteriorating lung function and poor oxygen exchange [6]. Additionally, endothelial dysfunction, which is implicated in microvascular thrombosis and is a condition identified in severe COVID-19 patients, has been connected to ESR [7].

LDH and Tissue Damage: According to the results of our investigation, there is a direct link between high LDH levels and poor outcomes in COVID-19 pneumonia. The enzyme LDH is present in many tissues, including the lungs, and its rise is a sign of cellular lysis and damage [8]. Due to tissue damage brought on by the virus and the ensuing immune response, LDH levels frequently increase in COVID-19.

The degree of tissue damage and cellular lysis may be responsible for the link between LDH and unfavourable outcomes. Significant lung involvement and parenchymal damage, which limit gas exchange and cause respiratory failure, characterise severe COVID-19 pneumonia. As a measure of cellular injury, LDH levels can shed light on the severity of lung damage and the propensity for unfavourable outcomes [9]. The pathophysiology of acute respiratory distress syndrome (ARDS), a serious COVID-19 consequence, has also been linked to LDH [10].

Hyperinflammation and Ferritin: Our study found a strong relationship between elevated ferritin levels and unfavourable results, which is in line with other research connecting ferritin to the severity of Covid-19. An acute-phase reactant and hallmark of hyperinflammation, ferritin is an intracellular protein that stores iron [11]. Hyperinflammation is a sign of severe illness in COVID-19 pneumonia.

The fact that ferritin serves as a biomarker of hyperinflammation and dysregulated cytokines may be the cause of the link between higher ferritin levels and unfavourable outcomes. Elevated ferritin levels are a sign of CRS, a condition linked to multi-organ failure and a strong inflammatory response [12]. The severity of the illness may be made worse by ferritin-mediated iron sequestration, which may potentially contribute to weakened immunological response [13]. Additionally, secondary hemophagocytic lymphohistiocytosis (sHLH), a hyperinflammatory condition observed in some severe COVID-19 cases, has been connected to ferritin [14].

Hypercoagulability and D-dimer: Our study found a substantial relationship between elevated D-dimer levels and poor outcomes, which is consistent with our growing understanding of the hypercoagulable condition in severe COVID-19. D-dimer, a sign of ongoing fibrinolysis and coagulation processes, is a marker of fibrin breakdown [15]. Hypercoagulability and thrombotic events have been seen in COVID-19, which have been linked to unfavourable results.

The involvement of D-dimer in thrombosis and microvascular dysfunction may be the cause of the link between high D-dimer and unfavourable outcomes. Patients with COVID-19, especially those who have severe pneumonia, are more likely to develop thrombotic complications, such as pulmonary embolism and microvascular thrombosis, which can cause respiratory distress and multi-organ failure [16]. Elevated D-dimer levels can act as a marker for ongoing coagulation problems in severe cases and are associated with an increased risk of thrombotic events [17].

The therapeutic importance of monitoring these inflammatory markers in COVID-19 pneumonia patients is highlighted by the substantial relationships found in our investigation. Elevated levels of CRP, ESR, LDH, ferritin, and D-dimer may act as early warning signs of disease development, enabling prompt treatment and risk assessment. Clinicians should take these signs into account while evaluating and treating COVID-19 patients, especially those who are more likely to experience negative outcomes.

Future studies should work to confirm these results in bigger cohorts and investigate the possible clinical uses of these indicators, such as the creation of risk prediction models and specialised therapy approaches. Furthermore, a deeper comprehension of the dynamic changes in these markers during the course of the illness may offer important insights into the development of the condition and the effectiveness of treatment.

Conclusion

In conclusion, our study shows a substantial correlation between higher inflammatory markers (CRP, ESR, LDH, ferritin, and D-dimer) and unfavourable outcomes in patients with COVID-19 pneumonia. In the current fight against the COVID-19 pandemic, these indicators can be useful tools for risk classification and early management, improving patient care and outcomes. To confirm these results and investigate their possible clinical uses, more study is required.

References

1. Wu F, Zhao S, Yu B, et al. A new coronavirus associated with human respiratory disease in China. Nature. 2020;579(7798):265-269.
2. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506.
3. Zhang C, Wu Z, Li JW, Zhao H, Wang GQ. Cytokine release syndrome in severe COVID-19: interleukin-6 receptor antagonist tocilizumab may be the key to reduce mortality. Int J Antimicrob Agents. 2020;55(5):105954.

4. McGonagle D, Sharif K, O'Regan A, Bridgewood C. The role of cytokines including interleukin-6 in COVID-19 induced pneumonia and macrophage activation syndrome-like disease. Autoimmun Rev. 2020;19(6):102537.
5. Muhmmed Suliman MA, Bahnacy Juma AA, Ali Alawad AA, Almahdi HM, Muhmmed Ali M. Erythrocyte Sedimentation Rate as a Marker of Disease Severity in Patients with COVID-19: A Retrospective Cohort Study. Infect Drug Resist. 2021;14:2791-2796.
6. Zheng Z, Peng F, Xu B, et al. Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-analysis. J Infect. 2020;81(2):e16-e25.
7. Tan C, Huang Y, Shi F, Tan K. C-reactive protein correlates with computed tomographic findings and predicts severe COVID-19 early. J Med Virol. 2020;92(7):856-862.
8. Qin C, Zhou L, Hu Z, et al. Dysregulation of immune response in patients with coronavirus 2019 (COVID-19) in Wuhan, China. Clin Infect Dis. 2020;71(15):762-768.
9. Henry BM, Aggarwal G, Wong J, et al. Lactate dehydrogenase levels predict coronavirus disease 2019 (COVID-19) severity and mortality: A pooled analysis. Am J Emerg Med. 2020;38(9):1722-1726.
10. Kishaba T, Nagano H, Nei Y, Yamashiro S, Yamashita T, Nakamoto K. Serum LDH levels predict the prognosis of COVID-19 patients. Expert Rev Respir Med. 2021;15(2):163-166.
11. Gao Y, Li T, Han M, et al. Diagnostic utility of clinical laboratory data determinations for patients with the severe COVID-19. J Med Virol. 2020;92(7):791-796.
12. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395(10229):1033-1034.
13. Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395(10229):1033-1034.
14. Sinha P, Matthay MA, Calfee CS. Is a "Cytokine Storm" Relevant to COVID-19? JAMA Intern Med. 2020;180(9):1152-1154.
15. Fan BE, Chong VCL, Chan SSW, et al. Hematologic parameters in patients with COVID-19 infection. Am J Hematol. 2020;95(6):E131-E134.
16. Zhang L, Yan X, Fan Q, et al. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. J Thromb Haemost. 2020;18(6):1324-1329.
17. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020;18(4):844-847.