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Clinical outcome and its correlation with inflammatory markers in SARS-COV-2 patients

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Abstract



Coronaviruses, characterized by a single-stranded RNA genome, present a challenge due to the unclear relationship between elevated inflammatory markers and disease severity. This study examines the correlation between inflammatory markers (D-dimer, serum ferritin, serum LDH, CRP) and clinical outcomes in 62 COVID-19 patients at a medical center in Puducherry, India. Patients were categorized into mild, moderate, or severe based on WHO guidelines. CBC, RFT, D-dimer, serum LDH, serum ferritin, and CRP levels were evaluated at admission and after 72 hours. Most patients with moderate and severe disease experienced ARDS and required oxygen support, with ventilator assistance limited to severe cases. Severe cases were also associated with pulmonary embolism and DIC, leading to mortality in all six severe cases. Higher CRP positivity was noted in moderate and severe cases on days 1 and 3, along with elevated D-dimer, ferritin, and LDH levels, indicating severity. In conclusion, severe illness was marked by significantly elevated levels of CRP, D-dimer, ferritin, and LDH, suggesting their potential as prognostic indicators. Repeated monitoring of these markers may aid in predicting outcomes for severe cases in clinical practice.

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INTRODUCTION

In December 2019, the city of Wuhan, China, witnessed the emergence of an unprecedented outbreak of pneumonia of unknown etiology. This outbreak, driven by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), swiftly escalated into a global pandemic. While the origins of the outbreak are suspected to involve zoonotic transmission, recent evidence suggests significant person-to-person spread within family and healthcare settings, primarily through direct

contact or respiratory droplets expelled by infected individuals.

The clinical and epidemiological profile of SARS-CoV-2, the virus responsible for COVID-19, indicates its potential to induce severe respiratory illness, often necessitating high-dependency care and associated with a considerable fatality rate. As a novel and highly transmissible viral infection in humans, the underlying pathophysiological mechanisms driving the unusually high pathogenicity of SARS-CoV-2 remain elusive.

Previous observations have noted elevated levels of inflammatory markers in patients with coronavirus diseases, yet the precise relationship between these markers and the severity of illness remains poorly understood.

Objective

This study aims to assess the clinical outcomes among SARS-CoV-2-infected individuals by evaluating levels of D-dimer, serum ferritin, serum LDH, and CRP. Specifically, we will investigate the duration of hospitalization, the incidence of complications (including AKI, DIC, ARDS, and pulmonary embolism), the need for oxygen support and ventilator assistance, and overall mortality rates among RT-PCR-positive SARS-CoV-2 patients.

MATERIALS AND METHODS

Study Design: This prospective cohort study was conducted at a tertiary care center in Puducherry, India, from July 2021 to December 2022. Ethical approval was obtained from the Institutional Ethics Committee Board (Approval No. MGMCRI/Res/01/2020/23/IHEC/252), and informed consent was obtained from all participants.

Sample Size Estimation: The sample size was determined using statistical procedures to calculate a proportion with a 1% absolute precision and a significance level of 5%. Qualtrics software was utilized for assistance, resulting in an all-inclusive sample size of 62 individuals.

Inclusion Criteria: The study included patients of both genders aged above 18 years who tested positive for SARS-CoV-2 by RT-PCR.

Exclusion Criteria: Patients with other systemic infections, inflammatory disorders, autoimmune

disorders, and those on long-term steroid or cytotoxic drug therapy were excluded.

Study Procedure: Basic demographic data including age, gender, comorbidities (diabetes, hypertension, dyslipidemia), and personal history (smoking and alcohol intake) were collected. Venous blood samples were collected upon admission and again after 72 hours to assess complete blood count, D-dimer, serum ferritin, serum LDH, and CRP levels.

Patient Categorization: Patients were categorized as mild, moderate, or severe based on clinical and laboratory data as indicated by WHO guidelines:

- Mild: Absence of shortness of breath or hypoxia (normal oxygen saturation).
- Moderate: Clinical symptoms of dyspnea and/or hypoxia, fever, cough, and SpO₂ ≤ 94% in room air, with a respiratory rate ≥ 24/minute.
- Severe: Clinical indications of pneumonia along with either a breathing rate > 30 breaths/min, significant respiratory distress, or SpO₂ < 90% in room air.

Outcome Measures: Patient outcomes, including length of stay, complications (pulmonary embolism, ARDS, AKI, DIC), oxygen requirement, ventilator support, and mortality, were assessed throughout hospitalization.

RESULTS

The mean age across different grades of COVID-19 infection was 57.58 in the mild category, 59.22 in moderate, and 65.27 in severe, with no statistically significant difference observed ($p = 0.30$, One-way ANOVA). Similarly, the gender distribution did not show a significant trend across mild, moderate, and severe grades ($p > 0.05$, chi-square test for trends).

Comorbidities included 34 patients with diabetes mellitus (DM), 23 with systemic hypertension, 6 with hypothyroidism, and coronary artery disease (CAD), as depicted in TABLE-1. Notably, 14% of diabetic patients and 17.34% of hypothyroid patients had severe grades of infection.

The median time from symptom onset to hospital admission was 4.5 days for mild, 5 days for moderate, and 7 days for severe infection, with no

Table 1 Distribution of Co-Morbidities among study participants

Variables	GRADING OF SEVERITY			TOTAL
	MILD	MODERATE	SEVERE	
DM	16	13	5	34
	47.06%	38.24%	14.71%	100 %
SHT	13	10	0	23
	56.52%	43.48%	0%	100 %
HYPOTHYROID	2	3	1	6
	33.33%	50.00%	17.34%	100 %
CAD	3	3	0	6
	50.00%	50.00%	0%	100 %

Table 2 Association between severity of COVID infection and various outcome

VARIABLES (OUT COME)	GRADING OF SEVERITY			P Value
	MILD Mean ± SD N=24	MODERATE Mean ± SD N=27	SEVERE Mean ± SD N=11	
AGE	57.58 ± 14.03	59.22 ± 12.58	65.27 ± 16.05	0.30
ARDS	0	21	11	0.001
	0.0%	77.8%	100.0%	
O2 REQUIREMENT	0	21	11	0.001
	0.0%	77.8%	100.0%	
VENTILATOR ASSISTANCE	0	0	11	0.001
	0.0%	0.0%	100.0%	
PULMONARY EMBOLISM	0	0	3	0.001
	0.0%	0.0%	27.3%	
AKI	3	7	7	0.007
	12.5%	25.9%	63.6%	
DIC	0	0	3	0.001
	0.0%	0.0%	27.3%	
IN HOSPITAL MORTALITY	0	0	6	
	0.0%	0.0%	54.5%	0.001

statistically significant difference observed ($p = 0.177$). However, the median hospital stay significantly increased with infection severity ($p = 0.001$, Kruskal-Wallis test).

All subjects with severe COVID-19 and 77.8% of those with moderate infection developed acute respiratory distress syndrome (ARDS), whereas none in the mild category had this condition ($p = 0.001$, Pearson chi-square test). Similarly, oxygen supplementation was required by all severe cases and 77.8% of moderate cases, but none in the mild category ($p = 0.001$, Pearson chi-square test).

All severe cases required ventilator assistance, contrasting with none in the mild or moderate categories ($p = 0.001$, Pearson chi-square test). Pulmonary embolism, acute kidney injury (AKI),

and disseminated intravascular coagulation (DIC) were significantly more prevalent in severe cases compared to mild and moderate cases ($p < 0.05$, Pearson chi-square test).

Mortality was observed in 54.5% of severe cases, while none occurred in the mild or moderate categories ($p = 0.001$, Pearson chi-square test).

CRP levels were elevated in 81.8% of severe cases on day 1, decreasing to 74.1% on day 3, compared to 96.3% and 74.1% in moderate cases and 50% and 16.7% in mild cases, respectively ($p = 0.001$, Pearson chi-square test).

Inflammatory markers, including D-dimer, ferritin, and LDH, increased with infection severity at both day 1 and day 3 ($p < 0.05$, Kruskal-Wallis test).

Table 3 Association between severity of COVID infection and CRP on DAY 1 and after 72 hours

CRP	GRADING OF SEVERITY			P Value
	MILD	MODERATE	SEVERE	
Positive on DAY 1	12	26	9	0.001
	50.0%	96.3%	81.8%	
Positive after 72 hours	4	20	8	0.001
	16.7%	74.1%	72.7%	

Table 4 Comparison of various blood parameters (D dimer, Serum ferritin, Serum LDH) with severity of COVID infection

Blood parameters	Mild Median (IQR) N=24	Moderate Median (IQR) N=27	Sever Median (IQR) N=11	P value (One-way ANOVA)
D-dimer				
Day 1	492.34 (324.25 - 831.54)	734.73 (555.02 - 1022.9)	844.05 (511.8 - 10000)	0.01
@ 72 hrs	462.53 (349.40 - 686.24)	509.31 (360.71- 652.68)	1013.87 (555.21 - 3790)	0.02
Ferritin				
Day 1	145.98 (44.93 - 348.51)	446.96 (269 - 595.06)	362.7 (173 - 881)	0.001
@ 72 hrs	143.74 (57.02 - 318.79)	293.6 (220.8 - 703.01)	406.57 (213.5 - 804.58)	0.003
LDH				
Day 1	242.5 (176.75 - 315.25)	391 (288 - 542)	519 (462 - 704)	0.001
@ 72 hrs	254.5 (213.25 - 342.25)	398 (366 - 549)	600 (484 - 822)	0.001

DISCUSSION

This prospective cohort study aimed to evaluate the prognostic significance of elevated inflammatory markers in COVID-19 patients admitted to a teaching medical college hospital in South India. Our findings reveal notable correlations between disease severity, clinical outcomes, and levels of inflammatory markers.

The median duration from symptom onset to hospital admission increased with disease severity, indicating potential delays in seeking medical care among patients with more severe illness. Consistent with previous studies, ARDS and the need for external oxygen support were predominant in patients with moderate and severe disease, with assisted mechanical ventilation required exclusively in severe cases. Additionally, severe disease was associated with higher rates of pulmonary embolism and disseminated intravascular coagulation (DIC), underscoring the systemic impact of COVID-19.

Mortality outcomes were significantly linked to disease severity, with all fatalities occurring in patients with severe disease. Elevated levels of inflammatory markers, including CRP, D-dimer, ferritin, and LDH, were consistently observed in patients with severe illness, aligning with previous research highlighting their prognostic value in COVID-19. Our findings corroborate existing literature demonstrating the utility of these markers in predicting disease severity and mortality.

Comparison with previous studies further supports our observations, with similar proportions of disease severity categories reported across different cohorts. Consistent trends in inflammatory marker levels were noted, with CRP, ferritin, D-dimer, and LDH showing associations with disease severity and mortality. These findings emphasize the importance of routine monitoring of inflammatory markers in

COVID-19 patients to guide clinical management and prognostication[5].

Sakthivadivel V et al⁶ reported in their study findings that CRP levels increased with increasing disease severity. Furthermore, in addition to CRP (sensitivity – 68% and specificity-64.8%), ferritin (sensitivity – 75% and specificity-71%), D-dimer (sensitivity – 71% and specificity-65%) and LDH levels (sensitivity – 68% and specificity-67%) also had good accuracy in predicting death among sufferers of Covid-19 infection. Though, in the present research work the severity of the disease was correlated as against mortality in the above discussed studies, the results of the above study are comparable to that of the associations observed in the present research work.

Huang et al⁷ study reported a significant positive correlation between severity of Covid-19 disease and D dimer, CRP, Ferritin, and IL-6 levels

Paixao et al⁸ observed in their research findings that CRP, D-dimer, ferritin and LDH levels were significantly high amongst patients who had a mortal outcome as compared to those patients who survived.

Parimoo A et al⁹ in their study results also documented that higher ferritin or CRP levels at baseline and before the terminal event (survival or death) were linked to a higher likelihood of a negative outcome ($p < 0.001$ and $p < 0.001$, respectively). It was also found that higher levels of LDH were associated with poor outcomes (p value -0.004). These findings were in agreement with that of the finding observed in the present study.

CONCLUSION

A significant proportion of COVID-19 patients with concomitant illnesses develop moderate to severe disease, necessitating intensive care. ARDS symptoms were observed in the majority of patients with severe illness and in all COVID-19 patients. CRP, D-dimer, ferritin, and LDH levels were all considerably higher in patients with severe illness. Acute Kidney Injury was also present in a significantly larger proportion of patients with moderate and severe illness.

Ethical Approval

This research was conducted in accordance with guidelines established by the Institutional Ethical Committee (IEC). Approval number:

MGMCRI/Res/01/2020/23/IHEC/252 Dated: 20-01-2020 was obtained from the IAEC prior to the commencement of the study. All procedures involving animals were carried out with care and consideration for their welfare, in compliance with ethical standards and regulations.

Author Contribution

All authors made substantial contributions to the conception, design, acquisition, analysis, or interpretation of data for the work. They were involved in drafting the manuscript or revising it critically for important intellectual content. All authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work, ensuring its accuracy and integrity.

Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

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