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General Medicine

ROLE OF INFLAMMATORY MARKERS IN PREDICTING SEVERITY IN SARS-COV-2 INFECTION: A PROSPECTIVE OBSERVATIONAL STUDY.

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ABSTRACT **Background:** Coronavirus disease 2019 (COVID-19) exhibits wide variability in clinical severity. Hyperinflammation and COVID-associated coagulopathy appear central to disease progression. Simple, widely available inflammatory biomarkers such as C-reactive protein (CRP) and D-dimer may serve as early predictors of severity and clinical outcomes. **Objectives:** To evaluate serial changes in CRP and D-dimer levels on days 1, 3, and 5 of admission in RT-PCR-confirmed COVID-19 patients and determine their correlation with disease severity. **Methods:** A hospital-based prospective observational study was conducted in a tertiary care centre in Manipur, India, from August 2020 to January 2022. One hundred patients aged >12 years with confirmed SARS-CoV-2 infection were enrolled. CRP and D-dimer levels were measured on days 1, 3, and 5 after diagnosis. Disease severity was categorized as mild, moderate, or severe based on SpO_2, respiratory rate, and ventilatory requirement. Statistical analyses included descriptive statistics and one-way ANOVA. **Results:** Mean CRP levels significantly decreased from day 1 (102.18 ± 62.37 mg/dL) to day 5 (27.28 ± 25.92 mg/dL) ($p < 0.001$). Mean D-dimer levels also reduced significantly from day 1 (2368.67 ± 2567.08 ng/mL) to day 5 (751.66 ± 985.92 ng/mL) ($p < 0.001$). Both biomarkers were consistently higher in patients with severe disease across all time points ($p < 0.001$). CRP and D-dimer levels demonstrated strong correlation with clinical severity and disease progression. **Conclusion:** Elevated CRP and D-dimer levels are strongly associated with COVID-19 severity. Serial measurements offer valuable prognostic information and may help guide clinical monitoring and therapeutic decision making in hospitalised patients.

KEYWORDS : COVID-19, SARS-CoV-2, C-reactive Protein, D-Dimer, Inflammatory Markers, Disease Severity, Prognosis.

INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), emerged in late 2019 and rapidly evolved into a global pandemic, posing a major public health challenge worldwide.[1-3] The disease demonstrates a broad range of clinical manifestations, from asymptomatic or mild upper-respiratory symptoms to severe viral pneumonia, acute respiratory distress syndrome (ARDS), multi-organ dysfunction, and death.[4]

Common presenting symptoms include fever, cough, dyspnoea, anosmia, headache, and fatigue, although gastrointestinal manifestations such as nausea, vomiting, and diarrhoea are also reported.[5] SARS-CoV-2 RNA has been detected not only in respiratory secretions but also in saliva, tears, breast milk, urine, and semen, highlighting its multi-systemic involvement.[5] Disease burden varies across age groups, with older individuals demonstrating higher susceptibility and worse outcomes.[6]

Emerging evidence suggests that dysregulated host immune response, hyper-inflammation, and COVIDassociated coagulopathy play key roles in disease severity and clinical deterioration.[7] Several laboratory markers—including lymphopenia, elevated neutrophil count, high lactate dehydrogenase (LDH), ferritin, procalcitonin, C-reactive protein (CRP) and D-dimerhave been associated with severe disease and poor outcomes.[8] Among these, C-reactive proteinand D-dimer are of particular interest due to their accessibility, rapid turnaround time, and prognostic relevance.

CRP is an acute-phase reactant synthesised by hepatocytes in response to interleukin-6 (IL-6). Elevated CRP reflects systemic inflammation and has been linked to pneumonia severity and lung involvement on imaging.[9] D-dimer, a fibrin degradation product, serves as an index of ongoing coagulation and fibrinolysis. Its elevation in COVID-19 is believed to reflect endothelial injury, activation of coagulation pathways, and micro-thrombotic complications.[10]

Severity of COVID-19 has been stratified based on respiratory parameters including oxygen saturation (SpO_2), respiratory rate, and need for ventilatory support, as outlined by the Ministry of Health and Family Welfare, Government of India.[11] Early identification of patients at risk of severe disease is essential for timely escalation of care, appropriate allocation of resources, and reduction of morbidity and mortality.

Given the critical role of inflammation and coagulopathy in determining disease progression, serial monitoring of CRP and D-dimer may provide valuable prognostic information. However, limited data are available from the northeastern region of India regarding the temporal trends of these biomarkers and their association with clinical severity.

Therefore, this study aimed to evaluate the levels of CRP and D-dimer on days 1, 3, and 5 following confirmed SARS-CoV-2 infection and to assess their correlation with disease severity in hospitalised patients.

MATERIALS AND METHODS

Study Design and Setting

A hospital-based prospective observational study was conducted at Shija Hospitals and Research Institute, Imphal, Manipur, over a period of 18 months (August 2020 to January 2022). The study evaluated serial inflammatory markers in hospitalised patients diagnosed with SARS-CoV-2 infection.

Study Population

All patients admitted with confirmed COVID-19 during the study period were screened. Eligible participants were enrolled after obtaining informed written consent.

Inclusion Criteria

- RT-PCR or RAT-confirmed SARS-CoV-2 infection
- Age >12 years
- Patients willing to give informed consent

Exclusion Criteria

- Immunocompromised conditions
- Pregnant women
- Chronically immobilised patients
- Use of systemic or inhaled corticosteroids in the last one month
- Poorly controlled diabetes (based on HbA1c)
- Failure to provide consent

Sample Size
Based on an assumed prevalence of elevated inflammatory markers of 62% in severe COVID-19 cases, with 10% absolute precision and 95% confidence interval, the minimum sample size was calculated as 91. Accounting for a 10% non-response rate, the final sample size was set at 100 patients, all of whom were included.

Data Collection Procedure
After enrolment, detailed demographic data, clinical history, comorbidities, vital signs, and physical examination findings were recorded using a structured proforma.

Diagnosis was based on:
- Clinical evaluation
- Rapid Antigen Test (RAT), where applicable
- Real-time PCR for SARS-CoV-2
- Radiological imaging (Chest X-ray or HRCT thorax)

Assessment of COVID-19 Severity
Severity classification followed the Ministry of Health and Family Welfare (MoHFW), Government of India guidelines:

Severity Level	Criteria
Mild	SpO_2 >94%,no dyspnoea
Moderate	SpO_2 90–94% and/or, respiratory rate ≥24/min
Severe	SpO_2 <90%, respiratory rate >30/min, or need for ventilatory support

Patients were re-assessed on Days 1, 3, and 5 of confirmed infection.

Laboratory Investigations
1. C-reactive Protein (CRP)
CRP was measured using a latex-enhanced nephelometry method (Behring Nephelometer). The assay quantifies CRP concentration based on antigen–antibody reactions causing light scattering.
Reference Range:<6 mg/dL.
2. D-dimer
D-dimer levels were measured using Enzyme-Linked Fluorescent Assay (ELFA) technology. Test reactions were performed automatically by the instrument using anti-FbDP monoclonal antibodies.
Reference Range:<500 ng/mL.

Both biomarkers were measured on Day 1, Day 3, and Day 5 after confirmation of SARS-CoV-2 infection.

Additional Clinical Parameters
The following were monitored on Days 1, 3, and 5:
- Oxygen saturation (SpO_2)
- Respiratory rate
- Oxygen requirement
- Need for ventilatory support
- HRCT chest severity score
- MMRC dyspnoea scale

Outcome Measures
Primary Outcome:
- Association between CRP/D-dimer levels and COVID-19 disease severity.

Secondary Outcomes:
- Temporal trends in CRP and D-dimer over the first 5 days.
- Correlation of biomarker levels with oxygenation status and HRCT severity.

Ethical Considerations
The study was conducted after obtaining approval from the Institutional Ethics Committee (IEC).

Statistical Analysis
Data were analysed using descriptive statistics (mean, standard deviation, frequencies, and percentages).

Comparisons of biomarker levels across days and severity categories were performed using:
- One-way ANOVA
- Post-hoc testing where required

A p-value <0.001 was considered statistically significant.

RESULTS
A total of 100 patients diagnosed with SARS-CoV-2 infection were included in the study. Laboratory parameters (CRP and D-dimer) and clinical parameters (SpO_2, respiratory rate, oxygen requirement) were recorded on Days 1, 3, and 5.

1. Demographic Characteristics:
1.1. Age Distribution
The most commonly affected age group was 41–50 years (25%), followed by 31–40 years (20%). Only 2% of patients were below 20 years of age.

Table No.1.1: Distribution of Age

AGE IN YEARS	NO OF PATIENTS	PERCENTAGE
<20	2	2%
21-30	7	7%
31-40	20	20%
41-50	25	25%
51-60	15	15%
61-70	16	16%
>70	15	15%

1.2.Sex Distribution
There was a slight male predominance (54%).

Table 1.2. Sex Distribution

SEX	NO OF PATIENTS	PERCENTAGE
MALE	54	54%
FEMALE	46	46%

2. CT Severity Scores:
CT thorax was performed for all patients.

Table 2.CT Severity Distribution

CT SEVERITY	NO OF PATIENTS	PERCENTAGE
MILD	41	41%
MODERATE	34	34%
SEVERE	25	25%

3. C-Reactive Protein (CRP) Levels:
3.1. CRP Elevation on Days 1, 3, and 5.
All patients had elevated CRP (>6 mg/dL) on Day 1. By Day 5, 9% had returned to normal values.

Table 3.1. CRP Levels (<6 mg/dL vs >6 mg/dL)

C-REACTIVE PROTEIN	LESS THAN 6	MORE THAN 6
DAY1 OF INFECTION	0	100
DAY3 OF INFECTION	3	97
DAY5 OF INFECTION	9	91

3.2.Mean CRP Levels
Mean CRP values decreased significantly over the three measurements (ANOVA $p < 0.001$).

Table 3.2. Mean CRP Levels (mg/dL)

C-REACTIVE PROTEIN	MEAN	SD
DAY1 OF INFECTION	102.18	62.37
DAY3 OF INFECTION	57.2	45.56
DAY5 OF INFECTION	27.28	25.92
ANOVA		
PVALUE <0.001		
SIGNIFICANT		

4. D-dimer Levels:
4.1. D-dimer Elevation
Most patients had D-dimer >500 ng/mL on Day 1, decreasing significantly by Day 5.

Table 4.1. D-dimer Levels (<500 vs >500 ng/mL)

D-DIMER	LESS THAN 500	MORE THAN 500
DAY1 OF INFECTION	6	94
DAY3 OF INFECTION	20	80
DAY5 OF INFECTION	48	52

4.2. Mean D-dimer Levels
A significant reduction was observed from Day 1 to Day 5 ($p < 0.001$).

Table 4.2. Mean D-dimer Levels (ng/mL)

D-DIMER	MEAN	SD
DAY1 OF INFECTION	2368.67	2567.08
DAY3 OF INFECTION	1464.46	1793.04

DAY5 OF INFECTION	751.66	985.92
ANOVA		
PVALUE <0.001		
SIGNIFICANT		

5. Respiratory Parameters:

Respiratory Rate

Most patients maintained a respiratory rate <24/min throughout the study period.

Table 5. Respiratory Rate

RESPIRATORY RATE	<24	24-30
DAY1 OF INFECTION	78	22
DAY3 OF INFECTION	86	14
DAY5 OF INFECTION	87	13

6. Disease Severity Categorization:

Severity on Days 1, 3, and 5.

There was progressive clinical improvement in most patients by Day 5.

Table 6. Severity of Disease

SEVERITY	MILD	MODERATE	SEVERE
DAY 1 OF INFECTION	51	24	25
DAY 3 OF INFECTION	60	15	25
DAY 5 OF INFECTION	69	5	26

7. Relationship Between CRP and Disease Severity:

CRP was significantly higher in severe cases at all time points ($p < 0.001$)

Table7.1. C Reactive Protein–day 1 of Infection – Vs Severity

C REACTIVE PROTEIN-DAY1 OF INFECTION		
SEVERITY	MEAN	SD
MILD	73.62	42.31
MODERATE	88.79	56.32
SEVERE	173.28	86.95
ANOVA		
PVALUE <0.001		
SIGNIFICANT		

Table7.2. C Reactive Protein–day 3 of Infection – Vs Severity

C REACTIVE PROTEIN-DAY 3 OF INFECTION		
SEVERITY	MEAN	SD
MILD	39.71	25.63
MODERATE	49.73	32.56
SEVERE	103.64	69.56
ANOVA		
PVALUE <0.001		
SIGNIFICANT		

Table7.3. C Reactive Protein–day 5 of Infection – Vs Severity

C REACTIVE PROTEIN-DAY 5 OF INFECTION		
SEVERITY	MEAN	SD
MILD	18.05	12.32
MODERATE	22.04	13.26
SEVERE	54.84	32.16
ANOVA		
PVALUE <0.001		
SIGNIFICANT		

8. Relationship Between D-dimer and Disease Severity:

D-dimer demonstrated the same pattern as CRP, with consistently higher levels in severe cases ($p < 0.001$).

Table 8.1. D-dimer–day1 of Infection–Vs Severity

D-DIMER-DAY1 OF INFECTION		
SEVERITY	MEAN	SD
MILD	1679.96	1562.32
MODERATE	1756.33	1655.42
SEVERE	4361.58	3562.35
ANOVA		
PVALUE <0.001		
SIGNIFICANT		

Table 8.2. Mean D–dimer–day 3 of Infection Vs Severity

D-DIMER-DAY3 OF INFECTION		
SEVERITY	MEAN	SD
MILD	922.25	885.3
MODERATE	982.93	865.3

D-DIMER-DAY3 OF INFECTION		
SEVERITY	MEAN	SD
MILD	922.25	885.3
MODERATE	982.93	865.3

Table 8.3. Mean D-dimer Day 5 of Infection–Vs Severity

D-DIMER-DAY5 OF INFECTION		
SEVERITY	MEAN	SD
MILD	480.36	345.63
MODERATE	491.4	366.52
SEVERE	1540.92	1358.63
ANOVA		
PVALUE <0.001		
SIGNIFICANT		

DISCUSSION

This prospective observational study evaluated the temporal trends of C-reactive protein (CRP) and D-dimer levels in patients with confirmed SARS-CoV-2 infection and assessed their association with disease severity. The findings demonstrate that both inflammatory markers were significantly elevated in patients with moderate to severe disease and showed a consistent decreasing trend over the first five days of hospitalisation. These results reinforce the prognostic utility of these biomarkers in predicting disease progression and clinical outcomes.

Inflammatory Response and CRP Trends:

CRP is an acute-phase reactant produced by hepatocytes under the influence of interleukin-6 (IL-6) and other pro-inflammatory cytokines. Elevated CRP levels are strongly linked to systemic inflammation and have been widely reported in patients with severe COVID-19.[12] In the present study, mean CRP levels were markedly elevated on Day 1 (102.18 mg/dL), with significantly higher values observed in severe cases compared to mild or moderate disease ($p < 0.001$). A reduction in CRP levels on Days 3 and 5 corresponded with clinical improvement in the majority of patients, consistent with the findings of Luo et al., who reported that serial CRP measurements closely correlate with disease trajectory.[13]

Furthermore, CRP values >100 mg/dL on admission—seen predominantly in severe cases in this study—have been associated with extensive lung involvement and increased risk of respiratory failure.[14] The downward trend in CRP among survivors suggests that serial monitoring may guide clinicians in assessing therapeutic response, particularly when corticosteroids or immunomodulators such as tocilizumab are employed.

Coagulation Abnormalities and D-dimer Patterns:

Coagulation abnormalities are a hallmark of COVID-19, characterised by endothelial injury, platelet activation, and microthrombosis.[15] D-dimer, a fibrin degradation product, serves as a marker of thrombin formation and fibrinolysis. Elevated D-dimer has been strongly associated with poor prognosis, need for mechanical ventilation, and mortality.[16]

In this study, high D-dimer levels were observed in 94% of patients on Day 1, with severe cases demonstrating significantly higher values (mean 4361.58 ng/mL) than mild and moderate disease ($p < 0.001$). A reduction in D-dimer by Day 5 reflected clinical improvement in most patients. These findings align with studies by Zhou et al. and Yao et al., which documented markedly elevated D-dimer in severe COVID-19 and its strong predictive value for disease severity and mortality.[17,18]

Persistent elevation of D-dimer beyond Day 5 in a subset of severe cases in this study suggests ongoing thrombo-inflammatory processes, emphasising the need for close monitoring and potential initiation of enhanced anticoagulation protocols in high-risk patients.

Correlation with Clinical Severity:

Both CRP and D-dimer demonstrated robust correlation with disease severity across all time points. Severe cases had substantially higher baseline and serial measurements compared to mild and moderate cases, consistent with previous reports.[19,20] This supports the growing body of evidence that hyperinflammation and dysregulated coagulation pathways contribute significantly to the pathogenesis of severe COVID-19.

Moreover, the progressive improvement in clinical severity category

by Day 5 in most patients corresponded with declining inflammatory markers. This reinforces the utility of serial biomarker assessment not only in early risk stratification but also in monitoring disease trajectory.

Comparison with Global Literature:

The findings of this study align with international literature emphasising that CRP and D-dimer serve as reliable prognostic indicators:

- A meta-analysis by Li et al. reported that CRP levels are significantly higher in severe versus non-severe COVID-19.[21]
- Tang et al. found that elevated D-dimer and prolonged coagulation profiles are associated with higher mortality.[22]
- Huang et al. demonstrated that elevated inflammatory markers, including CRP, correlate with radiological severity and clinical outcomes.[23]

This consistency across different populations strengthens the generalisability of our results.

Implications for Clinical Practice:

The study findings highlight several important implications:

1. Early Risk Stratification:

CRP and D-dimer on admission may help identify high-risk patients who require closer monitoring or early initiation of aggressive therapy.

2. Monitoring Therapeutic Response:

Declining biomarker levels can serve as indicators of improving inflammation and coagulation status.

3. Resource Allocation:

In resource-limited settings, simple and widely available tests such as CRP and D-dimer can guide clinical decision-making and triage.

Strengths and Limitations:

Strengths:

- Prospective design with serial measurement of biomarkers
- Inclusion of clearly defined severity categories
- Use of standardised laboratory assays

Limitations:

- Single-centre study limits external generalisability
- Short duration of follow-up (only up to Day 5)
- Did not evaluate mortality or long-term outcomes
- Potential confounders such as treatment variations were not fully controlled

Despite these limitations, the study adds meaningful evidence regarding the dynamic behaviour of CRP and D-dimer in COVID-19 and their correlation with disease severity.

CONCLUSION

This prospective observational study demonstrated that C-reactive protein (CRP) and D-dimer are significantly elevated in patients with severe SARS-CoV-2 infection and correlate strongly with disease severity. Serial monitoring on Days 1, 3, and 5 showed a progressive decline in both markers among clinically improving patients. Severe cases consistently exhibited higher CRP and D-dimer levels at all time points.

These findings underscore the importance of simple, widely available inflammatory markers in early risk stratification, monitoring disease progression, and guiding clinical decision-making in COVID-19 management. CRP and D-dimer can serve as reliable, cost-effective prognostic indicators, especially in resource-limited settings.

Future studies with larger sample sizes, multi-centre data, and inclusion of mortality outcomes are warranted to further validate these biomarkers' predictive value.

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