Section: Medicine

Original Research Article

OBSERVATIONAL STUDY OF PATIENTS INFECTED WITH SARS-COV-2 AND ITS CORRELATION WITH CLINICAL AND LABORATORY PARAMETERS (CRP AND D- DIMER)

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Abstract

Background: To correlate clinical findings, and role of laboratory parameters CRP and D dimer in severity of COVID 19 induced morbidity and mortality and clinical outcome. **Materials and Methods:** Patients confirmed by Covid-19 RTPCR, Covid RAT Ag positivity, CT CORADS Scoring, Chest X Ray along with other parameter studies. The demographic variables. Authors computed the proportion and 95% CI form ask compliance by age group, gender, and regions. Compared the biochemical parameters like CBC, LDH, D- dimer, CRP, S Ferritin tests with prognosis of patients. Receiver operating characteristics curve was employed to know the relevance between survivability of the COVID19 admitted cases, using the chi-square for trend test. A p-value less than 0.05 was considered significant. **Result:** The males were predominant, comorbidity was more common, majority of the patients infected the aged 41-50 years followed by 31-40 years 51-60 years respectively. CRP and D-dimer are significantly associated with the severity of the disease. **Conclusion:** In conclusion, the severity of covid 19 increases with rise in serum CRP and D-dimer values. Patients with high D-dimer and high CRP value have the greatest risk of adverse outcome.

INTRODUCTION

SARS-CoV-2 reported from Wuhan, China, on 31 December 2019, has spread across theglobe, affectingover 120 million individuals, and causing over 2-2.50 million deaths by March 2022. India reported its first case on 30 January 2020, with over 11 million confirmed (43060086) cases and 522223 deaths as of April 2022. Major cities have been major hubs for outbreaks worldwide which have posed challenges in controlling transmission and mitigating economic and social hardship. In the second week of April Early in the pandemic, metropolitan areas reported the highest incidence of SARS-CoV-2. Six months after the start of the pandemic, nearly 95% of SARS-CoV-2cases reported globally were from urban areas.

In the Indian context, almost all states were affected by the pandemic virus; 3-4 mutant viruses have spread the disease. Delta plus mutant virus deliriously destroys the human quality of life to the maximum extent. The concerned state and UTs health departments had to overcome several challenges, including a lack of adequate human resources for public health activities, a large population in Delhi that had lack of awareness about disease symptoms, and fear of being isolated and self quarantined. Unlike other states, the surge of the second wave drastically hit the infection and public care health system with an extensive loss.

The urban health care system is more fragmented with many people seeking care in private facilities, closure of most private clinics and hospitals made passive surveillance difficult and led to overcrowding of patients at government tertiary care referral centers, and medical laboratories were overloaded increasing the turnaround time of test results. The movement of people after the relaxation of restrictions posed challenges in contact tracing. Like metropolitan Delhi, cities across the globe have been facing the problem of compacting the SARS-Cov-2.Understanding this health crisis several health

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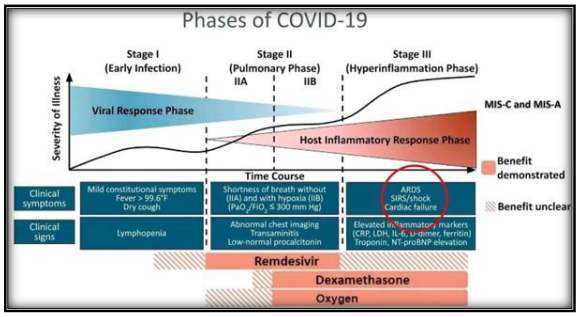
organizations have paid additional attention and issued separate guidelines for mitigating the transmission rate. Besides all epidemiological changes, clinical correlation is very important to implement a policy intervention and draw clinical decisions based on the observed data sets.

This present study will help the researcher to address public health interventions undertaken to control the COVID-19 epidemic in India and examine the relationship between these interventions (CRP and D-dimer) and the spread of COVID-19. In this study our aim is to see that CRP and D-dimer values can be a potential predictors of adverse outcomes in the patients.

Pathophysiologyand Transmission



In the systemic hyper inflammation phase of COVID-19 proposed by Siddiqi and Mehra, there is a significant elevation of inflammatory cytokines and biomarkers, such as interleukin (IL)-2, IL-6, IL-7, granulocyte-colony stimulating factor, macrophage inflammatory protein1-α, tumor necrosis factor-α (TNF-α), CRP, ferritin, PCT, and D-dimer. This stage consists of the most severe manifestation of the cytokine storm, in which excessive hyper inflammation may lead to cardiopulmonary collapse and multi-organ failure.

CRP is an acute phase inflammatory protein produced by the liver that may be elevated in several conditions, such as inflammation, cardiovascular, and infection. CRP levels are elevated in patients with COVID-19 and may correlate with severity of disease and disease progression. The time period for serum CRP measurement was critical considering the timely manner of serum CRP increment, which culminates 72 h after the initial insults. Despite its value in predicting outcome in COVID-19, it should be noted that various factors could affect serum CRP levels, including age, gender, smoking status, weight, lipid levels, blood pressure, and liver injury. Elevated CRP levels not only suggest a Pro-inflammatory state but also can be used as a prognostic marker for the underlying disease processes.[1] D-dimers are multiple peptide fragments produced as a result of degradation of crosslinked fibrin, mediated by plasmin.[2] The presence of D-dimers indicates the production and degradation of crosslinked fibrin, reflecting the coagulation and fibrinolysis processes occurring concomitantly

An elevated D-dimer was associated with an increased composite poor outcome, especially mortality and severe COVID-19.This finding supports the hypothesis that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection could induce the dysfunction of the hemostatic system, leading to a hypercoagulable state, a condition which we commonly encounter in sepsis. Recent evidence of lung pathology dissection has shown occlusion and micro-thrombosis formation in pulmonary small vessels of patients critically ill with COVID-19. However, the etiology of elevated serum D-dimer level is multifactorial and the optimal cut off value of elevated D-dimer in patients with COVID-19 remains to be established.

Bio marker Typical Reference Range Units:

CRP

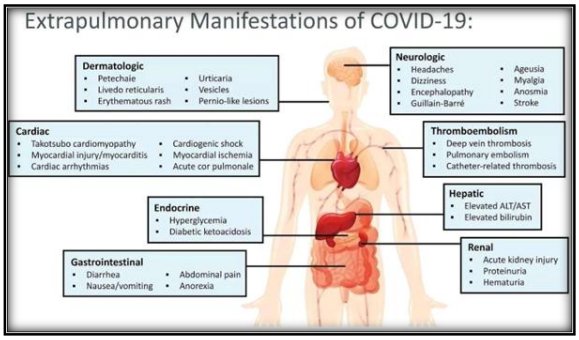
Normal: < 5 mg/L

D-dimer

Normal: < 0.5 µg/mL

Manifestation of Severe COVID-19

- Hyperinflammation
- Respiratory
  - Pneumonia, Acute Respiratory Distress Syndrome (ARDS)
- Cardiac
- Cardiomyopathy, arrythmias, acute cardiac injury, myocarditis
- Hypercoagulability → thromboembolic complications:
  - Pulmonary embolism, acute stroke, venous/ arterial thrombosis
- Acute Kidney Injury
- Neurological disorders
- Multisystem Inflammatory Syndrome in Children (MIS-C) and Adults (MIS-A)



Long COVID, also known as post-COVID syndrome or long-haul COVID, refers to a condition where individuals continue to experience symptoms and health issues for weeks or months after their initial recovery from COVID-19, the disease caused by the SARS-CoV-2 virus. While most people with COVID-19 recover within a few weeks, some individuals, even those with mild or asymptomatic initial infections, may go on to experience lingering symptoms and complications.

CO-RADS, the COVID-19 Reporting and Data System

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CO-RADS provides a level of suspicion for pulmonary involvement of COVID-19 based on the features seen at unenhanced chest CT. The level of suspicion increases from very low (CO-RADS category 1) to very high (CO-RADS category 5). Two additional categories encode a technically insufficient examination (CO-RADS category 0) and RT-PCR–proven severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) infection at the time of examination (CO-RADS category 6). It should be noted that CO-RADS is a CT-based system that is used to assess the suspicion of pulmonary involvement in COVID-19.

An overview of CO-RADS is given in [Table 1].

MATERIALS AND METHODS

Design: A retrospective observational study was conducted at the Department of Medicine Swami Dayanand Hospital, Delhi.

Participants

Patients screened as per ICMR guidelines, Clinical evaluation, Laboratory investigation (CBC, CRP, serum ferritin and D-dimer) and confirmed by Covid-19 RTPCR, Covid RAT Ag positivity, CT CORADS Scoring, Chest X Ray. SARS –CoV-2 infected Patients considered with age of 18 years and older were included in study with mild and moderate disease.

Inclusion Criteria

Over 18 years and older with or without comorbidity. All confirmed observed (mild to moderate) COVID 19 admitted cases at Department of General Medicine in Swami Dayanand hospital Delhi (Secondary Centre Hospital without ICU facilities.)

- The mild type was defined as patients with mild clinical symptoms and normal imaging on CT.
- The moderate type was defined as patients with fever, respiratory symptoms, or other symptoms, and altered imaging evidence with pneumonia.
- The severe type was defined as patients with atleast one of the following symptoms : shortness of breath (breathing rate≥30/min), SaO2 at rest≤90%,partial pressure of oxygen in arterial blood (PaO2) / inspired oxygen fraction (FiO2) ≤300 mmHg, or lung infiltrates > 50% within 24 to 48 h.
- The critical type was defined as patients with any of the following symptoms : respiratory failure requiring mechanical ventilation , shock ,or a combination of other organ failures requiring ICU monitoring treatment.

Exclusion Criteria

Pediatric age, patients with severe Covid and requiring ICU facilities.

Data Source and Data Collection: The data were collected from the Covid wards of Department of General Medicine, Swami Dayanand Hospital, Delhi. Total patients screened were 300 (Observed in Day Care 17, admitted 283, Discharged 177, Referred 24, LAMA 09, Deaths 73.) Sample size was 100 patients, chosen for the study from the admitted patients.

Duration of study: APRIL 2021 TO JULY 2021 (3 Months).

Ethical Consideration

All patients attended were provided information regarding treatment available in the hospital (Mild to Moderate Cases were only admitted excluding Severe and critical patient requiring ICU facilities). Treatment was followed as per MOHFW / ICMR guidelines. Informed written consent was taken by each patient/ attendant/ Relative before admission.

RESULTS

Statistical analysis

We analyzed the data using SPSS-16 statistical software. The demographic variables were summarized first as the frequency with proportions. We estimated the odd ratio and confidence intervals by binary logistic regression and descriptive statistics. We computed the proportion and 95% CI for mask compliance by age group, gender, and regions. We also compared the biochemical parameters like CBC, LDH, D- dimer, CRP, S Ferritin tests with the prognosis of the patients. Receiver operating chi square curve was employed to know the relevance between survivability of the COVID admitted cases, using the chi-square for trend test. A p-value less than 0.05 was considered significant.

Table 1: Overview of CO-RADS categories and the corresponding level of Suspicion for Pulmonary involvement in COVID-19

CO-RADS Category	Level of Suspicion for pulmonary involvement of COVID-19	Summary
0	Not interpretable	Scan technically insufficient for assigning a score
1	Very low	Normal or noninfectious
2	Low	Typical for other infection but not COVID-19
3	Equivocal / unsure	Features compatible with COVID-19 but also other diseases
4	High	Suspicious for COVID-19
5	Very high	Typical for COVID-19
6	Proven	RT-PCR positive for SARS-CoV-2

Table 2: Descriptive statistics and correlation of age and sex of SARS-COV-2 infected patients.

Variables (Gender)	NO.	%	ODDS	P-Value
Male	62	62%	6.5	≤0.001Sig
Female	38	38%	2.85	≤0.001Sig

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Age class	No.	%	ODDS	P-Value
20-30	16	16%	5.88	≤0.001Sig
31-40	26	26%	3.58	≤0.001Sig
41-50	27	27%	4.21	≤0.001Sig
51-60	18	18%	2.22	≤0.001Sig
61-70	11	11%	3.14	≤0.001Sig
>71	2	2%	2.87	≤0.001Sig
Mean age ±SD	40.75±8.56		5.08	≤0.001Sig

Table 3: Descriptive statistics and correlation of hospital stay of SARS-COV-2 infected patients.

Hospital Stay	No.	%	odds	P-value
< 5 Days	11	11%	3.19	≤0.001Sig
5-10 days	14	14%	2.77	≤0.001Sig
11-15Days	30	30%	5.55	≤0.001Sig
15-20 Days	14	14%	2.14	≤0.001Sig
21-25 Days	17	17%	1.42	≤0.001Sig
26-30 Days	8	8%	1.22	≤0.001Sig
>30 Days	6	6%	1.87	≤0.001Sig
Mean Hospital stay ±SD	14.02±2.33			≤0.001Sig

Table 4: Clinical symptoms of COVID 19 infected patients

Variables	No.	%	Odds	P-value
Fatigue	34	34%	2.55	≤0.001sig
Fever	67	67%	3.62	≤0.001sig
Cough	42	42%	4.55	≤0.001sig
Expectoration	22	22%	5.68	≤0.001sig
Shortness of breath	45	45%	1.89	≤0.001sig
Diarrhea	18	18%	3.21	≤0.001sig
Myalgia	36	36%	2.55	≤0.001sig

Table 5: Degree of severity of COVID19 with SPo2

Variables (Spo2)	Before	After	Odds	P-Value
Mild (>93%)	43	76	5.78	≤0.001Sig
Moderate (90-93%)	57	24	3.87	≤0.001Sig

Table 6: Comorbidities associated with COVID-19 infected patients

Comorbidity	No	%	P-value
HTN	6	6%	≤0.001Sig
COPD/ Asthma	12	12%	≤0.001Sig
DM	10	10%	≤0.001Sig
CAD	2	2%	>0.001 Not Sig
CVA	1	1%	>0.001 Not Sig
CLD	1	1%	>0.001 Not Sig
RENAL DESEASE	1	1%	>0.001 Not Sig
Obesity	2	2%	>0.001 Not Sig
Thyroid Disorder	1	1%	>0.001 Not Sig

Comorbidity was defined as having at least one of the following diseases: Diabetes, hypertension, cardiovascular disease, cancer and chronic liver, renal, respiratory disease, obesity, thyroid disorder.

Table 7: Descriptive statistics and correlation of CRP of SARS-COV-2 infected patients.

Age group	No. of patients	Before	After	Association with comorbidity
20-30	16	96.54±6.33	10.54±0.8	-
31-40	26	92.23±0.98	9.98±2.3	-
41-50	27	99.98±6.33	6.25±.07	+
51-60	18	86.25±8.07	12.88±.22	+
61-70	11	122.88±2.22	14±0.5	++
>71	2	118±0.25	20.56±8.07	+++

Table 8: Descriptive statistics and correlation of D-Dimer of SARS-COV-2 infected patients.

Age group	No. of patients	Before	After	Association with comorbidity
20-30	16	1.02±0.22	0.38±0.5	-
31-40	26	1.23±0.98	0.24±0.2	-
41-50	27	0.98±0.33	0.38±0.6	+
51-60	18	1.25±0.07	0.28±0.8	+
61-70	11	1.88±0.22	1.08±0.2	++
>71	2	118±0.25	1.12±0.4	+++

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Table 9: Descriptive statistics and correlation of lab parameters of SARS-COV-2 infected patients.

LAB Parameters	Before	After	odds	P-value
HB(%)Mean±SD	11.23±0.98	12.23±0.8	2.55	≤0.001Sig
LDH Mean±SD	369.98±6.33	129.98±2.3	3.62	≤0.001Sig
Ferritin	436.25±8.07	236.25±8.07	4.55	≤0.001Sig
CRP Mean±SD	122.88±2.22	12.88±.22	5.68	≤0.001Sig
D-Dimer Mean±SD	1.78±0.25	0.48±0.5	1.89	≤0.001Sig
Neutrophil count	4.88±1.74	2.88±1.4	3.21	≤0.001Sig

DISCUSSION

Health care workers have had a challenging task since the COVID-19 outbreak. Prompt and effective predictors of clinical outcomes are crucial to recognize potentially critically ill patients and improve the management of COVID-19 patients. The aim of this study was to identify potential predictors of clinical outcomes in critically ill COVID-19 patients. The present study reported 100 cases of SARS-Cov-2. Males are more predominant (62%) compared with females (38%). The medium young aged population was more common for the infection. Most of the patients infected were between 41-50 years (27%) followed by 31-40 years (26%) and 51-60 years (18%) respectively in the surge of the second wave of SARS-CoV-2. No proven medication to treatSARS-CoV-2 infection has been identified at this time, the mainstay of treatment has been supportive care and also curbing the spread of the disease at the population level. Fever was the most common complaint (67%) f/b shortness of breath (45%), cough was the 3rd most common (42%) symptom. Patients are being treated in separate isolation COVID19 centers and they are closely monitored and quarantined, the mean duration of hospital stay was 14.02 days and SD 2.33 days, and the median hospital discharge was 5.11-6.89 days. Total 36 cases (36%) had one or more comorbidity and significantly associated with outcome or result of the treatment odds 3.69($p<0.001$).[1-5]

As the clinical capacity to treat patients improves, the mortality of critically ill patients with SARS-CoV-2 pneumonia is expected to decrease. As mentioned in previous studies, nearly 70% of patients infected by SARS-CoV-2 were men. The patients are younger in our study than in previous studies. We observed that non-survivors were older than survivors. Based on previous studies, evidence suggests that older, male patients are the most susceptible to SARS-CoV-2 infection which is supported by our data. The median duration from onset of symptoms to radiological confirmation of pneumonia was 5 (3–7) days, meaning that early or repeated radiological examinations are useful in screening patients with SARS-CoV-2 pneumonia.[4,6,7]

The mean Hb was 11.23 with SD odds 2.55, LDH mean was 369.98 with SD 6.33, odds 3.62, Ferritin 436.25with SD 8.07 odds 4.56; CRP mean was 122.88 with SD 2.22 odds 5.68; D-dimer mean was 1.78 with SD 0.25 and neutrophil count mean was 4.88 with SD 1.74 odds 3.21. For critically ill patients, however, aggressive treatments and intensive care are needed. To our knowledge and experience comorbidity was more common than was seen in the follow-up period. As per the literature and published article on SARS-CoV-2 covid19 induced mortality was less as compared to other pandemic diseases. The fundamental pathophysiology of severe viral pneumonia is severe ARDS. Men and people of older age (>60-65 years) are more likely to develop ARDS than women or those of a younger age. Therefore, it is reasonable that the mortality at 28 days of severe SARS-CoV-2 pneumonia is like the mortality of severe ARDS, which is near 50%.[8-14]

Similar to our study, Ullah W et al studied predictability of CRP and D-Dimer levels for in-hospital outcomes and mortality of COVID-19. This study aims to assess the clinical utility of the C-reactive protein (CRP) and D-Dimer levels for predicting in-hospital outcomes in COVID-19. Both high D-Dimer (>501 ng/ml) and high CRP (>101 mg/dl) were associated with increased need for upgrade to the ICU and higher requirement for IMV on day-7 of hospitalization. Authors concluded that CRP value greater than 100 mg/dL and D-dimer levels higher than 500 ng/ml during hospitalization might predict higher odds of in-hospital mortality. Higher levels at presentation might indicate impending clinical deterioration and the need for IMV.[15]

Debi H et al did a systematic review and meta-analysis association of serum C-reactive protein (CRP) and D-dimer concentration on the severity of COVID-19 cases with or without diabetes. The prevalence of COVID-19 infection was comparatively higher in male diabetic patients. There was no publication bias. CRP and D-dimer rose with age in COVID-19 diabetic and non-diabetic patient. Overall, the serum CRP and D-dimer concentration in COVID-19 diabetic patients was significantly higher than non-diabetic patients indicating severe illness. Ali AM et al studied serum troponin, D-dimer, and CRP level in severe coronavirus (COVID- 19) patients. In the first week of hospitalization, there were significant differences in D-dimer, CRP and troponin level between survived and deceased patient groups. In the second week of the admission, both groups had significant differences in the level of all studied parameters. It was concluded that troponin, D-dimer, CRP, and WBCs level were significantly higher in COVID-19 patients who died than in COVID-19 survivors. High troponin and WBC levels, were considerably associated with families that lost more than one

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member, when compared with the unrelated COVID-19 patient control.[12,16,17]

Milenkovic M et al did study on D-dimer, CRP, PCT, and IL-6 levels at admission and in ICU and postulated that it can predict in-hospital mortality in patients with COVID-19 pneumonia. The study was designed as a retrospective cohort study, which included 318 patients treated from June 2020 to January 2021 in the Intensive Care Unit (ICU) of the Clinical Hospital Center. During the treatment, 195 (61.3%) patients died, thereof 130 male (66.7%) and 65 female (33.3%). 123 (38.7%) patients were discharged from hospital treatment. Cutoff value of CRP was 81 mg/L (Sn 60.7%, Sp 60%) and cutoff value of D-dimer was 760 ng/mL Ali AH et al did a meta-analysis on the association of lymphocyte count, CRP, D-dimer, and LDH with severe coronavirus disease. The analysis revealed that low lymphocyte count and high levels of CRP, LDH, and D-Dimer are associated with severe COVID-19. These laboratory markers could be used as clinical indicators of worsening illness and poor prognosis of COVID-19.[18]

Gonçalves FA et al did a post-hoc analysis of a prospective cohort study on use and misuse of biomarkers and the role of D-dimer and C-reactive protein in the management of COVID-19: A. Severe acute respiratory syndrome coronavirus 2 infection can trigger both inflammatory and thrombotic processes, and these complications can lead to a poorer prognosis. This study aimed to evaluate the association and temporal trends of D-dimer and C-reactive protein (CRP) levels with the incidence of venous thromboembolism (VTE), hospital mortality, and costs among inpatients with COVID-19.[19,20]

Valerio Let al did a retrospective analysis of 577 patients and studied course of D-dimer and C-reactive protein levels in survivors and nonsurvivors with COVID-19 pneumonia. D-Dimer and inflammatory parameters are frequently used as a marker of COVID-19 severity, driving decisions such as the use and dosage of anticoagulation and anti-inflammatory drugs. In the present retrospective analysis, authors studied the dynamic changes in D-dimer and C-reactive protein (CRP) levels in survivors versus nonsurvivors admitted with laboratory- and imaging-confirmed COVID-19 pneumonia at a single high-volume center since the start of the outbreak and followed until discharge or death. For both markers, authors first identified the highest value measured over the entire hospitalization. Both were expressed as a continuous variable (unit increase/day). Total 36 cases (36%) had one or more comorbidity and significantly associated with outcome or result of the treatment odds 3.69($p<0.001$), status was assessed based on the receiver operating characteristic analysis .50 patients were given trial by the Jak inhibitor Tofacitinib along with steroids and were also studied to have responsive outcome in CRP and D-dimer.[21-24]

CONCLUSION

All laboratory parameters were assessed on sample-based data, further study can explore the clinical and diagnostic route map of the diseases. The rapid progression of Coronavirus disease 2019 (COVID-19) and its increasing burden on health systems necessitate the identification of parameters of severe infection to help in monitoring, prognoses and development of treatment algorithms. D-dimer and CRP levels were associated with higher hospital mortality and a higher incidence of VTE. D-dimer was more strongly associated with VTE, although its discriminative ability was poor, while CRP was a stronger predictor of hospital mortality.

Limitations of the Study

This study has several limitations. First, only sample-based and no critically ill patients were included. However, the population from which they were sampled was much larger than that of the studies previously published. The data in this study permit a preliminary assessment of the clinical course and outcomes of semi-critically ill patients with SARS-CoV-2 pneumonia. Other specific markers such as cytokines IL6 might improve the performance of our study.

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