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ORIGINAL RESEARCH

To identify rising level of CRP and D-Dimer as a predictor of increased morbidity and mortality in COVID -19 patient- A retrospective study

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ABSTRACT

Aim and objectives: The present study assessed the correlation between rising levels of CRP and D-dimer with morbidity and mortality in adult Covid -19 patients.

Materials and method: This retrospective observational study was conducted at Max Super speciality Hospital I.P. Extension, Delhi a tertiary care centre in North India. CRP and D-Dimer values were collected at the time of admission and within 15 days after admission. The statistical analysis was done by independent t-test.

Results: The study population consisted of 194 (64.7%) males and 106 (35.3%) females. The mean age of the study population was 56.78±15.42 (28-94) years. The mean age of the non-survivors (58.83±15.64 years) was significantly more than survivors (54.43±14.85 years). The mean CRP and D-DIMER at the time of admission and within 15 days after admission was significantly more among non-survivors compared to survivors.

Conclusion: A high CRP and elevated D-Dimer levels among COVID-19 patients predict higher odds of mortality; however, large scale and longer-term studies are needed to validate our findings. The predictive model based upon CRP and D-DIMER levels can help the clinicians to improve individual treatment, make timely clinical decisions, and make optimal use of limited clinical resources.

Keywords: COVID-19, CRP, D-DIMER, Mortality

INTRODUCTION

Currently, the novel coronavirus disease 2019 (COVID-19) has become one of the deadliest pandemics that has ravaged the world and carries a high mortality rate. Due to a higher volume of patients, it is imperative to look for predictors that can guide us in allocating resources for these patients and be prepared in advance as presently our health systems have been stretched to their limits. In the multitude of blood tests and imaging conducted on these patients, CRP and D-Dimer levels are measured in many health-care settings.[1]

SARS COV-2 has caused unprecedented morbidity and mortality over last one year. Cytokine storm caused by release of pro-inflammatory mediators e.g., IL-6, TNF-α etc. is the hallmark of COVID-19 disease. This cytokine storm results in severe systemic inflammation in Covid 19 disease which is characterised by immune-thrombomodulation.[2]

The rapid spread of the SARS-CoV2, rapid changes in clinical features, and increased mortality have become the world's biggest concern. The reported overall case-fatality rate (CFR) for COVID-19 by now was 2.3%, but cases in those aged 70 to 79 years had an 8.0% CFR and cases in those aged 80 years and older had a 14.8% CFR.[3] In some patients, severe pulmonary and extra-pulmonary complications may lead to respiratory failure and life-threatening events.[4]

One of the most routinely used biomarkers for infection and inflammation is C-reactive protein (CRP), an acute-phase protein that is synthesized by the liver.[5] CRP analysis is cheap and readily available in most hospitals. Furthermore, the CRP level is frequently measured in both ICU and non-ICU patients with suspected or verified infection.[6]

C-Reactive Protein (CRP) is a pentameric protein synthesized by the liver under the action of cytokine interleukin 6 (IL-6). Raised levels of CRP are seen in various inflammatory conditions vis a vis bacterial infection, trauma, acute cardiovascular disease. Elevated CRP levels suggest a pro-inflammatory state and can also be used as a prognostic marker for the underlying disease processes.[2]

D-dimer is a peptide produced by plasmin mediated degradation of fibrin.[7] D-dimer is raised in many disease states like venous thromboembolism (VTE), cancer, pregnancy, infections and other pro inflammatory states where coagulation and fibrinolysis occur simultaneously.[8]Though it is nonspecific but can be used to rule out acute thrombosis. D-dimer values are differing by patient to patient and it depends on clot burden, measurement timing, and initiation of treatment.[9] It has been reported that about 50% of the patients had increased D-dimer levels, and abnormal D-dimer levels are associated with poor prognosis. [10-11,4]

Covid -19 is new disease and current pandemic has put enormous disease burden on healthcare institutions around the globe. There is a pressing need to identify a method for monitoring and prognosticating which is cheap, easy and fast yet reliable. So, we are conducting this study to see the correlation between rising levels of CRP and D-dimer with morbidity and mortality in adult Covid -19 patients.

MATERIALS AND METHOD

This retrospective observational study was conducted at Max Super speciality Hospital I.P. Extension, Delhi a tertiary care centre in North India. Adult(age>18 years) patients with confirmed diagnosis of COVID-19 admitted to COVID-ICU between 1st April 2021 to 30th June 2021(3-month period) were included and checked for CRP and D-Dimer values retrospectively. CRP and D-Dimer values were collected at the time of admission and within 15 days after admission.

ETHICAL CLEARANCE

This protocol and/or any subsequent modification were reviewed and approved by the ethics committee responsible for the oversight of the study.

SAMPLE SIZE

At least 300 adult's patient age >18 years suffering from covid 19 disease and admitted in ICU from 1st April 2021 to 30th June 2021 were included for study. The sample size was calculated by taking the prevalence of high levels (CRP >100, D-Dimer >500) of CRP and D-Dimer among those who survived versus those who died from the paper by Ullah et al.

For CRP,

$\pi 1' = 0.55$ (died) and $\pi 0' = 0.56$ (survived)

For D-Dimer

$\pi 1' = 0.55$ and $\pi 0' = 0.56$

The following formula was used for calculation for estimating the odds ratio where:

$z1-\alpha/2$ = 1.96 for 95% level of confidence

$\pi 1'$ = anticipated probability of disease among the cases

$\pi 0'$ = anticipated probability of disease among the controls

ε = relative precision in terms of proportion of OR

ε is the relative precision. Generally, $\varepsilon = 0.1$ is used for good precision but that was giving a sample size of more than 3000.

STUDY POPULATION

The study population was chosen based on the inclusion and exclusion criteria. The study population included All adults > 18 years admitted in ICU with confirmed diagnosis of COVID-19 disease either by RT-PCR, CBNAAT or Rapid Antigen test. The study excluded those patients admitted to ICU on clinical and radiological suspicion (Ground Glass Opacities) but negative on Laboratory confirmation.

STUDY METHOD

All CRP and D-dimer values were recorded on admission and thereafter till 15th day of admission. Rising trend of CRP and D-dimer levels were correlated with need for invasive mechanical ventilation, average length of ICU stayand 28-day mortality. Statistical analysis was done by independent t-test.

RESULTS

Table 1: Distribution of study population according to age and gender

	Frequency	Percent
Male	194	64.7%
Female	106	35.3%
Total	300	100.0%
Age in years	56.78±15.42 (28-94)	

The study population consisted of 194 (64.7%) males and 106 (35.3%) females. The mean age of the study population was 56.78±15.42 (28-94) years. The mean age of the non-survivors (58.83±15.64 years) was significantly more than survivors (54.43±14.85 years). (Table 1)

Table 2: Comparison of CRP levels at the time of admission and within 15 days after admission between survivors and non-survivors

	Survivors		Non-survivors			
CRP	**Mean**	**Std. Deviation**	**Mean**	**Std. Deviation**	**t-test value**	**p-value**
At the time of admission	119.09	97.88	155.55	85.95	-3.434	0.001*
Within 15 days after admission	49.06	49.87	248.35	133.00	-16.961	0.001*

The mean CRP at the time of admission and within 15 days after admission was significantly more among non-survivors (155.55±85.95 and 248.35±133.00 respectively) compared to survivors (119.09±97.88 and 49.06±49.87 respectively).

Table 3: Comparison of D-DIMER at the time of admission and within 15 days after admission between survivors and non-survivors

D-DIMER	Survivors		Non-survivors			
	Mean	Std. Deviation	Mean	Std. Deviation	t-test value	p-value
At the time of admission	617.93	965.77	988.89	898.30	3.152	0.045*
Within 15 days after admission	1374.40	4062.62	3509.10	3971.90	-8.532	0.001*

The mean D-DIMER at the time of admission and within 15 days after admission was significantly more among non-survivors (988.89±898.30 and 3509.10±3971.90 respectively) compared to survivors (988.89±898.30 and 3509.10±3971.90 respectively).

Table 4: Length of mechanical ventilation and Average length of ICU stay among survivors and non-survivors

	Death	Mean	Std. Deviation	t-test value	p-value
Length of mechanical ventilation	No	1.48	5.45	-10.084	0.001*
	Yes	8.70	6.82		
Average length of ICU stay	No	13.55	11.46	-0.155	0.877
	Yes	13.75	10.48		

The mean Length of mechanical ventilation was significantly more among non-survivors compared to survivors.

DISCUSSION

The number of patients with COVID-19 is currently rapidly increasing globally, and asymptomatic patients are also the source of infection.[12] COVID-19-related case fatality is also rapidly increasing. COVID-19 is a new threat for populations, [13-15] and treatment options need to be evaluated.[16] Early monitoring of key indicators was an important basis to guide treatment strategies, and early assessment of the severity of patients' condition was of great value.[17] The main pathological changes of COVID-19 are lung and immune system damage. Serous, fibrin exudates and clear membrane form in the alveolar cavity and congestion and oedema appear in the lung.[18]

Several recent studies have investigated the serum markers to be closely associated with the severity of COVID-19 patients, such as neutrophil-to-lymphocyte ratio, D-Dimer, procalcitonin, IL-6, and lactate dehydrogenase. [19-21] However, only a few studies focused on the prognostic role of laboratory findings for mortality in these patients so far.

Male patients in present study were more inclined to occurred ARDS and death events. In present study, the mean age of the non-survivors (58.83±15.64 years) was significantly more than survivors (54.43±14.85 years). This is in agreement with a retrospective report with a cohort of 44,672 patients where male patients over 60 years of age with comorbidities had a higher death risk.[22] Corresponding to the previous reports, old patients with a median age of 68 years (IQR 61-75 years) presenting more coexisting illnesses such as hypertension and CVD were more likely to develop severe COVID-19.[23-25]

CRP

CRP levels are correlated with the level of inflammation, and itsconcentration level is not affected by factors such as age, sex, andphysical condition.[26] CRP levels can activate the complementand enhance phagocytosis, thus clearing the pathogenic microorganisms invading the body. CRP levels can be used for early diagnosis of pneumonia, and patients with severe pneumonia had high CRP levels. It is an important index for the diagnosis and assessment of

severe pulmonary infectious diseases.[27] Matsumoto.[28] showed that CRP levels and the diameter of the largest lung lesion increased as the disease progressed. CRP levels were positively correlated with lung lesion and disease severity. This suggests that in the early stage of COVID-19, CRP levels could reflect lung lesions and disease severity.

In present study, the mean CRP at the time of admission and within 15 days after admission was significantly more among non-survivors (155.55±85.95 and 248.35±133.00 respectively) compared to survivors (119.09±97.88 and 49.06±49.87 respectively). Our data on CRP are also in line with literature seen on ICU admissions and mortality pertaining to sepsis syndromes, where a higher CRP was associated with longer length of stays and worse prognosis in terms of mortality. [6,29]

Zavareh et al. [30] found that revealed significantly higher CRP-levels in severe cases than in non severe patients suggesting that the CRP level may be a biomarker of diseases verity and progression in patients with COVID-19. Liuet al. [31] reported that more severe cases infected with COVID-19 expressed significantly higher CRP-levels than non-severe patients. Qinet al. [32] observed higher CRP levels in severe COVID-19 patients than in non-severe cases, suggesting that this biomarker can be monitored to evaluate progress of the disease. Sahuetal. [33] in their meta-analysis analysed that CRP-levels are apotential biomarker of the COVID-19 prognosis which indicated that CRP-concentrations remain high in expired patients and could be a promising biomarker for assessing mortality. Some studies have showed that some frequent complications in severe and expired COVID-19 patients, such as shock, ARDS, acute kidney injury and acute cardiac injury, were correlated with higher CRP-levels.[34]

Ullah et al. [1] stated that a high C-reactive protein(CRP) (>101 mg/dl) on admission predicts not only a greater need for IMV but also for an upgrade toa higher level of care. After completion of therapy forCOVID-19, both a high CRP (>101 mg/dl) and elevated D-Dimer levels (>501 ng/ml) were associated with higher odds of in-hospital mortality, need for IMV and upgrade to ICU. When adjusted for baseline comorbidities and medications, patients with CRP level (>101 mg/dl) on presentation have 2-fold higher odds of requiring IMV and 3 times higher odds to be upgraded to the intensive care units (ICU).

Ullah et al. [1] reported that CRP at presentation could serve as a reliable early predictor for in-hospital complications in terms of both the need for IMV and upgrade to ICU, while elevated D-Dimer (>501 ng/ml) could predict only the need for IMV (Invasive mechanical ventilation). Lobo et al. [35] showed that ICU patients with higher CRP levels on ICU admission had significantly higher mortality and risk of organ failure with no difference in APACHE II scores between the different CRP groups. Wang et al.[36] found that CRP predicted ICU mortality independent of APACHE II in a medical ICU setting with 576 patients and suggested the addition of CRP to APACHE for improved prognostication.

D-DIMER

In current study, the mean D-DIMER at the time of admission and within 15 days after admission was significantly more among non-survivors (988.89±898.30 and 3509.10±3971.90 respectively) compared to survivors (988.89±898.30 and 3509.10±3971.90 respectively).

Hu et al.[37] found thatD-dimer was found to be very significantly different according to the disease-severity status, and a higher proportion of patients with severe (50.7%) andcritical (57.1%) disease had D-dimer levels >0.5 mg/L, which is consistent with other studies.[23,25] However, in terms of clinical outcomes, even though the patients with unfavourable outcomes had higher percentage (51.9%) of D-dimer >0.5 mg/L than patients (40.4%) with favourable outcomes with non-significant difference.

Ullah et al. [1] showed that patients on the 7thday of admission with D-dimer levels morethan 500 ng/mL are 10 times more likely to die than patients with D-dimer levels less than 500

ng/mL. Bycontrast, the odds of mortality in the higher CRP(>101 mg/dl) were 3 times compared to patients with lower CRP (<100 mg/dl). Even at presentation, elevated D-Dimer (>501 ng/ml) and raised CRP levels (>101 mg/dl) were associated with higher odds of mortality; however, these values did not reach the level of statistical significance. These results contrast the recent findings of a study from Wuhan, China reporting a four-fold increase in in-hospital mortality with a higher D-Dimer level.[38]Previous studies have shown that in medically ill patients, D-dimer levels twice the upper limit of normal were found to have a high risk of developing VTE. [39-43]

Guan and colleagues.[25]analysed 1099 patients with laboratory-confirmed Covid-19 from over 550 hospitals in China, and found the non-survivors had a significantly higher D-dimer (median: 2.12 μg/ml) than that of survivors (median: 0.61 μg/ml). Similarly, Tanget al. [44] also observed abnormal coagulation results, especially markedly elevated D-dimer in deaths with Covid-19.

Zhou et al. [45] conducted a retrospective study involved 191 patients with Covid-19 and found that d-dimer greater than 1 μg/mL on admission was associated with in-hospital death. Huang and colleagues showed D-dimer levels on admission were higher in patients needing critical care support than those who did not require it (median: 0.5 μg/ml.[24] However, these previous studies did not provide well evaluated cut-off for D-dimer. Therefore, a recent guidance on recognition and management of coagulopathy in Covid-19 from International Society of Thrombosis and Haemostasis (ISTH) "arbitrarily defined markedly raised D-dimers on admission as three-four folds increase".[46]

Zhang et al. [47] stated that a cut-off value (2.0 μg/ml, 4-fold increase) for D-dimer was well established by ROC curve. Notably, of 12 non-survivors with D-dimers ≥2.0 μg/ml, 7 of whom had no severity symptoms on admission. Thus, for patients who have markedly raised D-dimers (cut-off: 2.0 μg/ml, four-fold increase), admission to hospital and closely monitoring should be considered even in the absence of other severity symptoms.

Recently, D-Dimer was reported to be closely related to the severity of the COVID-19 patients, and when combined with IL-6 detection, it had the highest specificity and sensitivity for its early prediction.[48] The elevated level of D-Dimer was also associated with ICU admission and lower survival in CAP patients.[49] The D-Dimer levels were lower in the survivors compared with the non-survivors at admission, with AUC 0.88 for predicting in-hospital mortality.

This is also in line with a smaller retrospective study from Suzhou, China which showed elevated D-Dimer levels in severe COVID-19 patients on day 1, 7 and 14 of hospitalization when compared to mild/ moderate COVID-19 patients during the same time period.[50]

Elevation of D-dimer indicated a hyper coagulable state in patient with Covid-19, which might be attributed to several reasons as follows. First, virus infections are usually accompanied by an aggressive pro-inflammatory response and insufficient control of an anti-inflammatory response. It might induce the dysfunction of endothelial cells, resulting in excess thrombin generation. Second, the hypoxia found in severe Covid-19 can stimulate thrombosis through not only increasing blood viscosity, but also a hypoxia-inducible transcription factor-dependent signalling pathway. Third, hospitalized patients, especially severe patients with Covid-19, were more intend to have elder ages, underlying conditions, long-term bed rest and invasive treatment, which were all risk factors of hyper coagulation or thrombosis.[47]

There were some limitations in our study. Incomplete laboratory tests results in some patient records may have caused deviations in statistical analysis.

CONCLUSION

A high CRP and elevated D-Dimer levels among COVID-19 patients predict higher odds of mortality; however, large scale and longer-term studies are needed to validate our findings. The predictive model based upon CRP and D-DIMER levels can help the clinicians to improve individual treatment, make timely clinical decisions, and make optimal use of limited clinical resources.

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