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Prognostic Biomarkers For Mortality In Severe COVID-19 Patients : The Worth of C-reactive Protein, Serum Ferritin and D-dimer

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Abstract

Background: *Nealy 4.5 million deaths of Coronavirus disease- 19 (COVID-19) have been accounted for worldwide since December 2019. We plan to look through risk factors related to death in COVID-19 patients and determine the utility of the D-dimer, ferritin, and C-reactive protein(CRP) as biomarkers for disease severity and clinical outcome.*

Methods: *We retrospectively investigated the clinical characteristics, laboratory findings and mortality- related risk factors of 81 patients of COVID-19 in the High Dependency Unit(HDU) of Midnapore Medical College, West Bengal, India. The relationship of the D-dimer, ferritin and the CRP between patients with the survivor group and the death group was investigated. SPSS version 28 was employed for statistical analysis and a P-value < 0.05 was considered statistically significant.*

Results: *The mean age of the 38 discharged patients and 43 death patients were 40.35±12.98 and 56.34±13.91 years respectively, and the mean age was significantly increased with the death group(p<0.0001). The mean D-dimer of the survivor group and the death group was 1301.67 ± 1123.54 and 3839.03±1188.07 respectively and the mean D-dimer was significantly increased with the death group (p<0.0001). CRP and ferritin were likewise altogether significantly present in the death group (p< 0.0001).*

Conclusion: *D-dimer, ferritin, and CRP are usually raised in patients with COVID-19 and could be effectively accessible and cost-effective biomarkers of mortality in the serious COVID-19 patients of HDU.*

Keywords - *D-dimer, CRP, Ferritin, Corona virus disease-19, Biomarker, Mortality*

I. INTRODUCTION

Emerging and reemerging infectious diseases have plagued mankind and have been potential killers since historic times. The current pandemic caused by SARS-CoV-2 (COVID-19), a novel β coronavirus of group 2B[1], began in China and soon spread globally taking over millions of lives. Its manifestations range from mild symptoms to respiratory failure and multi-organ damage in those with risk factors. Presentations include coughing, fever, shortness of breath, diarrhea, muscle pain, lymphopenia, prolonged coagulation profiles, cardiac disease, and sudden death[2,3]. Coagulopathy was accounted for, and D-dimer rises were seen in 3.75–68.0% of the COVID-19 patients[4,5]. D-dimer > 1000ng/ml is one of the risk factors for mortality in adults inpatients with COVID-19[5]. In any case, the investigation has not completely been done on the role of D-dimer in the patients with Covid-19. Serum ferritin is an iron storage protein that is a reflection of iron status as well as a notable inflammatory marker. Serum ferritin levels can be increased significantly in response to the systemic and pulmonary inflammation[6], that's why hyperferritinemia is associated with disease severity in patients with COVID-19. Possible mechanisms of hyperferritinemia in patients with COVID-19 are 1) proinflammatory cytokines including tumor necrosis factor-α (TNF-α), and IL-6 may promote ferritin synthesis[7]. 2) The cellular damage due to inflammation causing leakage of intracellular ferritin[8]. CRP is a kind of protein produced by the liver .CRP an early marker of infection and inflammation[9] . The normal serum concentration of CRP is less than 10mg/L. It rises quickly within 6 to 8 hours and gives the highest peak in 48 hours from the disease onset[10]. When the inflammation is settled, CRP level falls, making it a helpful marker for monitoring disease severity[10]. Serum CRP level increases significantly in severe covid-19.

In our study, we need to investigate the risk factors related to death in COVID-19 patients and judge the utilization of D-dimer, ferritin and CRP as the prognostic biomarkers for disease severity and clinical outcome.

II. METHODOLOGY

This was a retrospective, single-centered and observational study conducted at HDU, Midnapore Medical College and Hospital, Paschim Medinipur, West Bengal, India from July 1, 2021 to July 21, 2021. Written informed consent was waived by the Institutional Research Committee of Midnapore Medical College and Hospital.

We included adult patients (>18 years old) with confirmed severe COVID-19 (diagnosed using RT-PCR assay) infection. Moderate, severe, and critically-ill COVID-19 were defined as patients that met any of the following criteria as per ICMR guidelines: (i)Respiratory rate more or equal to 24/min (ii) SpO2 90 to ≤93% on room air, (i)Respiratory rate > 30/min (ii) SpO2 < 90% on room air and presence of either Acute respiratory distress syndrome or acute life-threatening organ dysfunction or septic shock respectively. Patients who were referred for hematological ailments were excluded from the study. We screened a total of 90 patients, and 81 patients were found to be eligible and enrolled in the study and they were segregated into 2 groups based on the clinical outcome: Survivor group (n=38) and Death group (n=43). Clinical data includes demographic information (age, gender, time of admission, time of discharge, comorbidities), medical history, laboratory tests (routine blood tests), and outcome (survival or death at hospital discharge). D-dimer, CRP, and serum ferritin levels were tested in the state reference laboratory of our institution.

III. STATISTICAL ANALYSIS

Data were coded and analyzed using Statistical Package for Social Sciences (SPSS) version 28. Data were summarized using mean and standard deviation in quantitative data and using frequency for categorical data. Categorical variables were expressed as number (percentage) and compared by proportions . P-values of less than 0.05 were considered statistically significant.

IV. RESULT

All the patients admitted to the High Dependency Unit(HDU) of Midnapore Medical College were confirmed with RT-PCR. We included eighty-one (81) consecutive inpatients between July 1 and July 21, 2021. Among 81 covid-19 patients,38 patients were discharged, and the rest (43) died. The reason for high mortality was all the patients were serious and were referred from the peripheral hospital was delayed. The mean age of the 38 discharged patients and 43 death patients were 40.35±12.98 and 56.34±13.91 years respectively, and the mean age significantly increased with the death group($p<0.0001$).

Table 1 : Demographic and clinical characteristics between survivor group (n = 38) and death group (n = 43)

Variables	Discharged (survivor) covid -19 patients(n=38)	Death covid-19 patients (n=43)	p-value
Age (M ± SD)	40.35±12.98	56.34±13.91	P<0.0001
Male	26(68.4%)	20 (46.5%)	0.1005
Female	12 (31.6%)	23(53.5%)	0.0485
SOB	15(39.5%)	37(86%)	P<0.01
Fever	24(63%)	26(60.5%)	0.8185
Cough	12(31.5%)	14(32.5%)	0.9238
Chest pain	1(2.6%)	5(11.6%)	0.1244
GI symptoms including vomiting, pain abdomen and diarrhea	18 (47.4%)	15(34.9%)	0.2381
Mayalgia	23 (65.5%)	31(72%)	0.5306
Loss of taste or smell	6 (15.8%)	3(7%)	0.2117
Headache	12(31.6%)	17(39.5%)	0.4620
Temperature (°F)	99.2 ± 1.88	100.4±0.79	0.0003
Comorbidities :			
1.Hypertension	6(15.75%)	7(16.3%)	0.9467
2.Type 2 DM	1(2.6%)	3(7%)	0.3646
3.Combined Hypertension and Type 2 DM	3(7.9%)	10(23.25%)	0.0620
4. Chronic Kidney Ds	4(10.5%)	12(27.9%)	0.0510
Clinical staging at HDU			

1.Moderate covid patients	23(60.5%)	4(9.3%)	<0.0001
2.Severe covid patients	10(26.3%)	16(37.20%)	0.2973
3.Critically ill covid patients	5(13%)	23(53.5%)	0.0001

The comparison of demographic with clinical characteristics and laboratory findings between discharged(survivor) and death covid -19 patients are shown in table 1 and table 2 respectively. One-third of the patients had comorbidities, with combined hypertension and diabetes being the most common (23.25%) in the death group. Critically ill cases accounted for 53.5% of the death covid-19 patients. On admission, shortness of breath (SOB) was present in 86% in the death group in comparison with nearly 40% in the survivor group($p<0.01$). The mean temperature of the survivor group(n=38) and the death group (n=43) was 99.2±1.88 and 100.4±0.79 respectively and the mean temperature significantly increased with the death group($p=0.0003$).

Table 2 : Laboratory findings between survivor group (n = 38) and death group (n = 43)

WBCs(10^3/µl)>10	14(38.84%)	30(69.76%)	-
CRP(M ± SD)	**24.81 ± 22.09**	**78.53 ± 38.61**	**P < 0.0001**
Creatinine(mg/dl) >1	16(42%)	25(58%)	-
Urea(mg/dl) >45	9(23.7%)	23(53.5%)	-
ALT (U/L) > 45	17(44.7%)	34(79%)	-
AST(U/L) > 45	16(42%)	32(74.4%)	-
D-dimer(M ± SD)	**1301.67 ± 1123.54**	**3839.03 ± 1188.07**	**P < 0.0001**
Serum ferritin(M±SD)	**390.4±208.9**	**1006.4±608.9**	**P<0.0001**

The mean D-dimer of the survivor group and death group was 1301.67 ± 1123.54 and 3839.03±1188.07 respectively, and the mean D-dimer significantly increased with the death group ($p<0.0001$). C-reactive protein (CRP) and serum ferritin were also significantly present in the death group ($p< 0.0001$).

V. DISCUSSION

Our study showed that raised serum CRP, D-dimer, and serum ferritin levels were related with poor clinical outcome that involves mortality, severe COVID-19, ARDS, and the requirement for ICU care in patients with COVID-19. There is an elevation of pro-inflammatory mediators and biomarkers, like interleukin (IL)- 2, IL-6, IL-7, TNF-α, CRP, ferritin, D-dimer in the hyperinflammatory stage of COVID-19 . This stage consists of clinical manifestations of cytokine storm may lead to vascular collapse and multi-organ failure[11].

Few studies have shown that the severity and the clinical outcome of the pneumonia are straightforwardly connected with the D-dimer[12,13]. In any case, the D-dimer has not been focussed on as a biomarker for viral pneumonia[14,15]. However, the D-dimer elevation has been seen in articles describing the clinical of COVID-19, regardless of whether the level of the D-dimer is a marker of seriousness has not been analyzed. The current study shows a significant relationship between the D-dimer level and infection severity defined by the clinical stages as per recent protocol. This might be because of the greatest number of severe or critically ill patients referred to our hospital, which is one more show of the relationship between the D-dimer level and infection severity. In our study, a raised CRP was related to serious COVID-19, the requirement for ICU care, however not with mortality. When the inflammation is settled, CRP level falls, making it a helpful marker for monitoring disease severity[7]. Serum CRP level increases significantly in severe covid-19 is shown in table 3.

Table3: Level of CRP in patients with COVID-19 in different studies

Reference	Group	Patients (n)	CRP, mg/L	P value	N&% of patients with elevated CRP
Chen et al[16]	Death	113	113(69.1-168.4)	NA	59/68(60)
	Recovered	161	26.2(8.7-55.4)		21/45(14)
Gao et al[17]	Severe	15	39.4(27.7)	0.011	NA
	Mild	28	18.8 (22.2)		
Luo et al[18]	Died	84	100(60.7-179.4)	.000	NA
	Recovered	214	9.6(5-37.9)		

We tracked down that higher serum ferritin had the option to foresee an increased mortality of si patients with COVID-19. In-HDU death of patients with Covid-19 was additionally connected with elevated D-dimer, CRP, ferritin levels, suggesting that the examination could be a helpful biomarker for clinical outcome in patients with COVID-19.

We infer from the study results that there was a significant difference in the D-dimer, CRP and ferritin between the survivor group and the death group COVID-19 patients with the death group patients tending to have significantly higher these three biomarkers.

VI. CONCLUSION

In conclusion, D-dimer, Ferritin, CRP levels in patients infected with SARS-CoV-2 are often high, and significantly higher levels are found in those with critical illness. So, these three levels may be used the biomarkers for in-hospital mortality.

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CONFLICTS OF INTEREST

There are no conflicts of interest.

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