



Original Article

Utility of D-dimer and other biomarkers in COVID-19 patients: A prospective study in a tertiary care center

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ABSTRACT

Background: Clinical status and concurrent comorbidities of COVID-19 patients largely determine the need for their admittance to ICUs, similarly several laboratory parameters like D-dimer, LDH, serum ferritin, CRP, and IL-6 may facilitate the assessment of disease severity and rational triaging. Therefore, their role in the management of COVID-19 patients has to be assessed.

Materials and methods: Prospective study was done on patients who were tested positive for COVID-19 infection and admitted to various centers under the Vijayanagara Institute of Medical Sciences, India. Patients were divided into mild, moderate, and severe cases. Demographic data and serum levels of biomarkers like D-dimer, LDH, ferritin, CRP, and IL-6 were collected in these patients, and data were statistically analyzed.

Results: A total of 164 cases were included in this study, of which, 62 were mild, 47 moderate, and 55 were severely infected COVID-19 patients. There was male predominance in patients infected with COVID-19. The median age of presentation was 53, 60, and 57 years in mild, moderate, and severe cases respectively. Median was also derived for D-dimer, LDH, serum ferritin, CRP, and IL-6 in mild, moderate, and severe cases. Changes in D-dimer, LDH, and serum ferritin levels in mild, moderate, and severe cases showed statistical significance ($p < 0.05$).

Conclusions: D-dimer helps in the early identification of mild, moderate, and severe cases and can be used for the vigilant monitoring of patients. LDH and serum ferritin helps in the identification of oxygen-dependent and oxygen-independent patients. The role of CRP and IL-6 in the management of COVID-19 patients has to be further investigated.

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INTRODUCTION

In December 2019, an outbreak of coronavirus disease (COVID-19) occurred in Wuhan, China, and SARS-CoV-2 had been designated as the pathogen. COVID-19 has inflicted millions of people worldwide, but definite prognostic factors and treatment regimens could not be adequately defined.¹ While the clinical status [in particular, oxygen saturation (SpO₂) levels] and concurrent comorbidities of COVID-19 patients largely determine the need for their admittance to ICUs, several laboratory parameters may facilitate the assessment of disease severity and rational

triaging. It is more likely that the course of the disease will be unfavourable if some or all of the parameters like serum levels of D-dimers, lactate dehydrogenase(LDH), ferritin, C-reactive protein(CRP), and interleukin-6(IL-6) are altered.² Though, chest CT has been preferentially used as a stable marker of COVID-19 patient triaging, its availability for critical cases (i.e., within ICU) is less.³ The real challenge for clinicians is to quickly identify COVID-19 patients at high risk for acute respiratory distress syndrome.⁴ As the evaluation of biomarker levels can be for all COVID-19 patients, their utilization in assessing the severity helps in better management.

Of the various biomarkers participating in cytokine storm and hypercoagulability seen as events leading to complications in severe cases, D-dimer, which is the degradation product of fibrin and reflects the activation of both thrombotic and fibrinolytic pathways, has been abnormal in patients with poor prognosis.^{5,6} SARS-CoV-2 induces, in severe cases, a cytokine storm that triggers the coagulation cascade, causing thrombotic complications which have become major causes of morbidity and mortality.⁷ Serum LDH levels serve as a non-specific indicator of cellular death which occur in hyperinflammatory syndromes and also in many other diseases such as hemolysis, cancer, severe infections and sepsis, liver diseases, hematologic malignancies, and many others.³ Mehta P et al⁸ have proposed that COVID-19 can be characterized by hyperferritinemia, and high levels of cytokines like IL-6 and others.⁹ CRP, which is an acute reactant protein, was also extensively studied and used in the management of COVID-19 patients.

In the present study, we analyzed commonly used laboratory markers like D-dimer, LDH, serum ferritin, CRP, and IL-6, detected during coagulopathies, tissue damage, and inflammation to know their usefulness in predicting the severity of respiratory failure in COVID-19 patients.

MATERIALS AND METHODS

A prospective study was done at the Vijayanagara Institute of Medical Sciences on patients who tested positive for COVID-19 infection. The diagnosis of COVID-19 was according to the Ministry of Health and Family Welfare Government of India(MOHFWGOI) guidelines¹⁰ i.e., confirmed by RT-PCR/RAT testing performed on nasopharyngeal and throat swab samples. Patients with SpO₂>94%, normal RR, and no pneumonia were taken as mild cases and were admitted to COVID care centers. The patients with SpO₂ between 90%-94%, RR 24 bpm, and pneumonia with no signs of severe disease were taken as moderate cases and managed in a dedicated COVID health care center. Patients with SpO₂<90%, RR >30 bpm, and severe pneumonia were taken as severe cases and managed in dedicated COVID Hospitals with ICU facilities.

The demographic data, clinical status, laboratory parameters, and other relevant investigation findings were recorded from case sheets in the respective COVID wards. Blood

sample for D-Dimer was collected in citrate vacutainers, centrifuged, and processed in ERBA ECL 760.0 automated coagulation analyzer. Blood samples for serum ferritin, LDH, IL-6, and CRP were collected in plain vacutainers, centrifuged, and processed in automated analyzers ERBA XL 640 for LDH, serum ferritin, and CRP; and in HITACHI ROCHE COBASe411 analyser for IL-6. COVID-19-positive patients who were kept under home isolation and/or did not get institutional admission for treatment were excluded from the study. The following normal range values were used in the present study: D-dimer: ~500ng/mL, LDH: 0-250 U/L, serum ferritin: 30-400µg/L(males), and 20-160µg/L(females), CRP: ~7mg/L and IL6: 0-7pg/mL.

Statistical Package for Social Sciences (SPSS)version 20. [IBM SPSS statistics (IBM corp. Armonk, NY, USA released 2011)] was used to perform the statistical analysis. The median was calculated for quantitative variables. Kruskal-Wallis test was applied to check the statistical difference of D-dimer, LDH, serum ferritin, CRP, and IL-6 with posthoc Mann-Whitney for pair-wise comparison. The chi-square test was used to calculate statistical significance. The level of significance was set at 5 percent.

RESULTS

A total of 164 patients were included in the study, of which, 62 were mildly infected COVID-19 patients, 47 were moderately, and 55 were severely infected cases. COVID-19-infected patients presented commonly with respiratory symptoms like dry cough, breathlessness, and cold along with generalized symptoms like fever, generalized body ache, generalized weakness, etc. Mildly infected patients commonly presented with symptoms of fever (64.5%), dry cough(50%), and breathlessness(51.6%). In moderate COVID-19 patients, breathlessness was the most common symptom seen in about 80.9% of patients along with fever(70.2%) and dry cough (48.9%) as other common symptoms at presentation. Severely infected patients also showed breathlessness(85.5%) as the most common presentation similar to moderately infected patients. Other common presenting symptoms were fever(50.9%) and dry cough(47.3%). (Table 1).

Table 1: Clinical presentation in COVID-19 patients

Symptoms	Mild 62 cases	Moderate 47 cases	Severe 55 cases
Asymptomatic	5(8%)	-	-
Fever	40(64.5%)	32(68.1%)	28(50.9%)
Dry cough	37(59.7%)	23(48.9%)	26(47.3%)
Breathlessness	32(51.6%)	38(80.9%)	47(85.5%)
Cold	6(9.7%)	7(14.9%)	3(5.5%)
Generalized body ache	5(8%)	4(8.5%)	5(9.1%)
Generalized weakness	4(6.5%)	3(6.4%)	1(1.8%)
Headache	2(3.2%)	-	1(1.8%)
Loss of appetite	1(1.6%)	-	-
Loss of taste	1(1.6%)	-	-
Loss of smell	1(1.6%)	-	-
Nausea	-	1(2.1%)	-
Loose stools	-	1(2.1%)	-

Patients with co-morbidities were in higher numbers than severely infected patients(43.6%). The most common co-morbidities in these patients were hypertension(25.5%), diabetes mellitus(20%), hypothyroidism(3.6%), and asthma(3.6%). A few other less common co-morbidities were Wilson's disease, cerebrovascular accident, chronic kidney disease, ischemic heart disease, and HIV infection(1.8% each). In mildly infected patients with co-morbidities(total-30.6%), hypertension(24.2%), diabetes mellitus(19.4%), ischemic heart disease(3.2%) and congenital heart disease(1.6%) were seen. Moderately infected patients had co-morbidities(total-38.3%) like diabetes mellitus(25.5%), hypertension(19.1%), asthma(2.1%), deep vein thrombosis(2.1%), leukemia(2.1%) and cellulitis(2.1%).

Of 164 COVID-19 patients, the cases were distributed between the age range of 8 years to 85 years. In the age-wise distribution of cases in mild patients, the highest number of cases were seen in the age group of 31-45 years(30.6%) and the least number of cases were seen in the pediatric (<15 years) patients(1.6%). In these patients, the median age of presentation was 53 years(Interquartile range(IQR)-22 years). In moderate and severely infected COVID-19 patients, the median age of presentation was 60 years (IQR 23 years) and 57 years (IQR-17 years) respectively. The highest number of cases was seen in the age group of 46-60 years (36.2% & 45.5%) in both moderate(36.2%) and severe(45.5%) cases. No COVID-19 patients were seen in the pediatric age group in moderately infected patients, whereas early adults(16-30 years) were not affected severely (0%) in the present study. (Table 2)

Table 2: Age-wise distribution of COVID-19 patients

Age		Groups			Total
		Mild n(%)	Moderate n(%)	Severe n(%)	
< 15 yrs	Count	1 (1.6)	0 (0.0)	1 (1.8)	2 (1.2)
16 to 30 yrs	Count	2 (3.2)	2 (4.3)	0 (0.0)	4 (2.4)
31 to 45 yrs	Count	19 (30.6)	7 (14.9)	10 (18.2)	36 (22.0)
46 to 60 yrs	Count	18 (29.0)	17 (36.2)	25 (45.5)	60 (36.6)
61 to 75 yrs	Count	18 (29.0)	15 (31.9)	17 (30.9)	50 (30.5)
> 75 yrs	Count	4 (6.5)	6 (12.8)	2 (3.6)	12 (7.3)
Total	Count	62 (100.0)	47(100.0)	55(100.0)	164(100.0)

p-value: 0.304

The gender-wise distribution of cases showed that the males were infected commonly with male-to-female ratios(M: F) of 2.6:1, 3.3:1 & 2.1:1 in mild, moderate, and severe COVID-19 patients.

Among the various biomarkers included in the study, D-dimer showed a median of 367.5ng/mL(IQR-471.9), 656ng/mL(IQR-1027), and 1400ng/mL(IQR-5426.7) in mild, moderate, and severe cases respectively. This finding was statistically significant(p-value= 0.00). Similarly, when variations in D-dimer values were compared between mild-moderate, mild-severe and moderate-severe cases, there was statistical significance(p-value=0.025, 0.000, and 0.08 respectively). (Table 3,4)

Table 3: Distribution of cases in mild, moderate, and severe

	Severity	No. of cases	Least value	Highest value	Median	IQR	p-value
D-dimer	Mild	62	86.19	7670	367.5	471.9	<0.001*
	Moderate	47	110	9360	656	1027	
	Severe	55	100	14919	1400	5426.7	
LDH	Mild	62	169	932	436.65	345.6	<0.05*
	Moderate	47	114.5	1993	567	321	
	Severe	55	200	2265	593.8	364	
S.ferritin	Mild	31	16	910	254	208	<0.01*
	Moderate	29	17	1650	400	599	
	Severe	28	72	1053	379.8	273	
CRP	Mild	30	2	251	7.57	29	>0.05
	Moderate	18	3	600	17.24	82	
	Severe	44	1	318	21.9	70	
IL-6	Mild	1	14.77	14.77	14.8	-	>0.05
	Moderate	1	5	5	5	-	
	Severe	15	11	445	24.4	134	

*Statistically significant

Table 4: Comparison between mild, moderate, and severe cases

		D-DIMER	LDH	S.f ferritin	CRP	IL-6
Mild v/s Moderate	U value	1089.5	1103.5	292.0	221.0	0.0
	p-value	<0.05*	<0.05*	<0.05*	>0.05	>0.05
Mild v/s Severe	U value	870.0	1223.5	243.0	489.5	3.0
	p-value	<0.001*	<0.05*	<0.05*	>0.05	>0.05
Moderate v/s Severe	U value	900.5	1259.0	403.0	379.0	0.0
	p-value	<0.05*	>0.05	>0.05	>0.05	>0.05

*Statistically significant

The medians for LDH were 436.6 IU/L(IQR=345.6), 567 IU/L(IQR=321), and 593.8IU/L(IQR= 364) in mild, moderate, and severe cases respectively. These findings were statistically significant(p-value=0.017). Values of LDH were compared between mild-moderate, mild-severe, and moderate-to-severe patient groups and showed statistical significance for variations between mild-moderate(p-value=0.031) and mild-severe(p-value= 0.009), and no statistical significance was found when LDH values were compared between moderate and severe cases(p-value=0.822). (Table 3,4)

Medians for serum ferritin levels were calculated for mild, moderate, and severe cases and were 254µg/L(IQR=208),400µg/L(IQR=599), and 379.8 µg/L(IQR=273) respectively. This finding showed statistical significance(p-value=0.01). Serum ferritin levels were compared between mild-moderate, mild-severe and moderate-severe patients. There was statistical significance when serum ferritin levels of mild were compared to moderate(p-value=0.02) and severe(p-value=0.004) cases similar to LDH and there was no statistical significance when patients of moderate and severe(p-value= 0.962) groups were compared. (Table 3,4)

Medians for CRP levels were calculated and were 7.57mg/L(IQR=29), 17.24mg/L(IQR=82), and 21.9 mg/L(IQR=70) in mild, moderate, and severe COVID-19 patients respectively. IL-6 levels showed medians of 14.8pg/mL, 5pg/mL, and 24.4pg/mL(IQR=134) in mild, moderate, and severe cases respectively. The variation of CRP & IL-6 showed no statistical significance (p-value>0.05) in mild, moderate, and severe cases (Table 3). Similarly, upon comparing the CRP and IL-6 levels between mild-moderate, mild-severe, and moderate-severe patient groups there was no statistical significance p-value>0.05). (Table 4)

DISCUSSION

Various complications seen during the COVID-19 infection were attributed to coagulation dysregulation and systemic hyperinflammation contributing to prolonged hospital stay and mortality. Measuring serum concentration of biomarkers involved in coagulation and inflammation helps in the early controlling of complications to prevent deterioration of COVID-19 patients. In the present study, we divided total patients(n=164) into mild(n=62), moderate(n=47),

and severe(n=55) cases infected with COVID-19 based on clinical presentation and analyzed the demographic presentation and role of biomarkers like D-dimer, LDH, serum ferritin, CRP and IL-6 in these patients.

These patients commonly presented with respiratory symptoms like dry cough, breathlessness, cold, etc along with systemic symptoms like fever, generalized body ache, and generalized weakness, etc. Fever was the common presenting symptom in mildly infected patients whereas breathlessness was the most common presenting symptom as the severity of the COVID-19 infection increased (i.e., in moderate and severe cases). Poggiali E et al¹¹ also showed that their patients commonly presented with flu-like symptoms and dyspnoea was seen in patients who had respiratory failure. Knowledge of the clinical presentation helps in the identification of suspected cases and early isolation and institution of treatment.

As the severity of the disease increased, the patients with co-morbidities were more, present in 30.6% of patients in mild, 38.3% in moderate, and 43.6% in severe cases. The most common co-morbidities were hypertension and diabetes mellitus. The study done by Porcheddu R et al¹² mentioned that co-morbidities have been shown to be important contributors to death.

The medians for age at presentation were 53, 60, and 57 years in mild, moderate, and severe cases respectively. In mild cases, the most common age group to be affected was 31-45 years(30.6%). Whereas, moderate and severe cases are most commonly presented in the later age group of 46-60 years(36.2% & 45.5% respectively). COVID-19 infection caused serious complications in elderly patients. This finding was similar to that seen in the study done by Fan BE et al¹³ where the ICU patients were about a decade older than the non-ICU patients and the median age of ICU patients was 54 years while the median age of non-ICU patients was 42 years. This may be implicated in low immunity in the older age groups and association with the co-morbidities.

Overall, males were predominantly affected compared to females with M: F ratios of 2.6:1, 3.3:1 & 2.1:1 in mild, moderate, and severe cases respectively. This finding was similar to various studies conducted by Guan WJ et al⁷ and Chen N et al¹⁴(M: F ratios 1.4:1 and 2.1:1 respectively). However, the study done by Zeng Z et al¹⁵ showed that

males(51.1%) and females (48.9%) were affected almost equally. The predominance of COVID-19 infection in males could be attributed to lifestyle in our country where most male population is involved in outdoor activities leading to higher chances of exposure.

The median D-dimer levels in mild, moderate, and severe cases were 367.5, 656, and 1400 ng/mL respectively showing an increasing trend with increasing severity of COVID-19 infection and there was statistical significance for this finding(p-value= 0.00). These findings were similar to the meta-analysis of 12 studies done by Paliogiannis P et al¹⁶, where the serum D-dimer concentration in patients with severe forms of the disease was significantly higher than those with milder forms(mean difference range, 0.62-3.15 mg/L). Similarly, Wang D et al¹⁷ showed that the levels of D-dimer were higher in ICU patients(median= 414mg/L) than in non-ICU patients(median=166mg/L).

Human ACE2 has been confirmed as the receptor for SARS-CoV-2 in the lower respiratory tract epithelium. The physiological balance between ACE and ACE2 is likely disrupted by SARS-CoV-2 infection, which results in the activation of RAS and abnormal functions of vascular endothelial cells and the coagulation system.¹⁸In severe cases, SARS-CoV-2also induces a cytokine storm that triggers the coagulation cascade causing thrombotic complications⁷ and activation of the coagulation cascade is a common feature of disseminated intravascular coagulation (DIC) and adverse clinical outcomes in COVID-19 patients.¹⁹ D-dimer elevation (>1000ng/mL) was the strongest independent predictor of mortality.²⁰

The median of LDH in mild(436.6 IU/L), moderate(567 IU/L), and severe cases (593.8 IU/L) also showed an increasing trend and statistical significance(p-value=0.017). These findings were similar to those seen in the study done by Asghar MS et al²¹where a total of 364 COVID-19-positive patients were included in the study and mean LDH in survivors was significantly lower when compared to non-survivors. Elevated serum LDH serves as a non-specific indicator of cell-death²² and in the study done by Wu Met al³, serum LDH was validated for its potential usefulness in monitoring treatment response in COVID-19 pneumonia and normalization of serum LDH titer was consistently accurate in predicting treatment success in the patients.

Though the median of serum ferritin was within the normal range i.e., 254, 400, and 379.8 µg/L in mild, moderate, and severe cases respectively, there was statistical significance(p value= 0.01) in this finding. A retrospective study done by Ruan Q et al²³ on 150 COVID-19 patients showed that there was elevated ferritin (1297.6 ng/mL in non-survivors 614.0 ng/mL in survivors; p<0.001) and mortality was due to virally driven hyperinflammation; and similarlyVelavan TP et al² stated that serum levels of ferritin were taken as a predictor of poor outcome. However, a study done by Asghar MS et al²¹ showed that the significance of ferritin

as a biomarker to monitor and predict disease severity as compared to CRP and LDH was much lower.

In the present study, the median for serum CRP was higher in mild, moderate, and severe cases i.e., 7.57, 17.24, and 21.9 mg/L respectively, and in severe COVID-19 patients there was an almost 3 times increase in values. In the study done by Asghar MS et al²¹, CRP at a cut-off of 108.30mg/dL has not shown death predictability with good sensitivity as compared to other parameters like D-dimer, neutrophil count, LDH serum urea, and creatinine. In another study by Ruan Q et al²³, it was shown that survivors had median CRP values of approximately 40 mg/L, while non-survivors had median values of 125 mg/L. These values were much higher when compared to those of our study indicating that there is a need for further research with a larger sample size.

Coming to the median of IL-6, there was an increase in mild and severe cases(14.8 and 24.35pg/mL respectively), and levels were within the normal limit in moderate cases(5 pg/mL). However, a study done by Zeng Z et al¹⁵showed that compared to moderate and severe patients, critically ill patients showed a significant increase in serum concentrations of IL-6 and Zhou F et al²⁰ mentioned that IL-6 was elevated in non-survivors(median=11 pg/mL) compared to survivors(median=6.3 pg/mL) and increased with illness deterioration in COVID-19 patients.

The limitation of the study was that serum levels of CRP and IL-6 were not investigated in all the patients included in the study. Therefore, there is a need for further studies with a larger sample size to know the applicability of CRP and IL-6 in the management of COVID-19 infection.

CONCLUSIONS

COVID-19 infection may result in complications due to coagulopathy and hyper-inflammation leading to elevated levels of coagulation and inflammatory parameters, of which, D-dimer showed significant changes in mild, moderate, and severe cases. This biomarker can be used for risk stratification, vigilant monitoring, and early treatment institution for coagulopathy and inflammation. LDH and serum ferritin helps in identifying patients who are oxygen-dependent and oxygen-independent but failed to identify patients who need ICU admission among oxygen-dependent patients. Therefore, these biomarkers can be used as supportive investigations. CRP and IL-6 did not show significant changes in mild, moderate, and severe cases and there is a need for further research to substantiate their use in the management of COVID-19 patients.

Conflict of interest: None

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