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Association Of Inflammatory Markers With Severity And Outcome Of Covid-19 Infection - A Retrospective Hospital Based Study

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Abstract

Aim: To study the association of inflammatory markers with severity and outcome of covid-19 infection

Materials and Methods: This retrospective study included 671 COVID-19 patients admitted in a Bengaluru tertiary care hospital during the third wave of Covid-19. The patient's data including medical history, laboratory findings including LDH, D-dimer and CRP, severity and outcome of infection was extracted for subsequent evaluation and association.

Results

The study included 671 patients, 59.3% of them males and 40.7% females. The mean age was 52.22 (± 18.55) years. Overall, 14.9% (100/671) had severe infection, 29.1% (195/671) had moderate infection, 53.1% (356/671) had mild illness, while 3.0% (20/671) were asymptomatic. 87.2% (585/671) of them got discharged and 12.8% (86/671) died.

Serum LDH and CRP levels were elevated in 57.2% (384/671) of the patients and were significantly higher in severe infection (p value < 0.05). CRP levels were also significantly elevated in patients with adverse outcome (p value 0.001).

Conclusion

Levels of serum LDH and CRP in COVID-19 patients were significantly elevated in severe SARS-COV-2 infection. This highlights the role of immune response in pathophysiology and inflammatory markers in the prognosis of Covid-19 infection.

Keywords: NIL

Introduction

The novel coronavirus disease 2019, a viral infection caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), emerged in Wuhan city of China towards the end of 2019.[1] Over the next few months, the virus spread all across the world and with the emergence of new variants, it posed a huge threat to global public health.[2] A lot still remains to be unveiled and understood about this growing pandemic.[3]

Accumulating evidence has suggested that inflammatory responses play a critical role in the progression of COVID-19. While most of the cases have an asymptomatic or mild course, a significant number of patients develop severe disease, often associated with a hyperinflammatory state called a

cytokine storm.[4] Cytokine release syndrome is characterized by extensive tissue damage and end-organ dysfunction due to ineffective control of inflammatory cytokines released due to immune dysregulation.[5] This leads to a cytokine storm and a sudden rise in pro-inflammatory cytokines. Monitoring the severity of COVID-19 and effective early intervention are the fundamental measures for reducing mortality.[6]

Clinical assessment is indispensable, but laboratory markers, or biomarkers, can provide additional, objective information which can significantly impact many components of patient care.[7] The early identification of patients who are likely to deteriorate will help in effective utilization of the limited medical resources we have at present.[8] This study aims to find out the correlation between inflammatory markers and the severity of covid-19 infection.

Materials And Methods

This was an observational cross sectional study conducted among patients admitted under General Medicine department between December 2021 to February 2022 at a tertiary care hospital in Bangalore, Karnataka, India. Approval and clearance were obtained from the institutional ethics committee. The study included patients aged ≥ 18 years of either sex, diagnosed with COVID-19 infection by RT-PCR technique and willing to give informed consent. The study excluded patients <18 years and those not willing to provide signed informed consent prior to the study.

Case record form with follow-up chart was used to record the demographic data, and duration and clinical features of the disease. Patients data like clinical symptoms and prevalence and duration of co-morbidities were collected. All the selected participants were followed up until discharge or death. Blood samples were collected from all the patients and sent for laboratory investigations, which included inflammatory markers like C-Reactive Protein, LDH and D-dimer. Patients were divided into 4 groups (Asymptomatic, mild, moderate, severe) based on clinical severity using SpO2 and respiratory rate on admission. CRP, LDH and D-dimer were compared among these groups to co-relate the levels with severity of the disease. The demographics and clinical outcome were further correlated.

Statistical Analysis

SPSS (Statistical Package For Social Sciences) version 20. (IBM SPASS statistics [IBM corp. released 2011] was used to perform the statistical analysis

1. Data was entered in the excel spread sheet.
2. Descriptive statistics of the explanatory and outcome variables were calculated by mean, standard deviation for quantitative variables, frequency and proportions for qualitative variables.
3. Inferential statistics like

a. Chi-square test was applied to associate the inflammatory markers with severity and outcome.

4. The level of significance is set at 0.05.

Results

Demographics

The study included 671 patients admitted to Bowring and Lady Curzon Hospital, Bangalore under General Medicine department who were diagnosed positive for SARS-COV-2 infection.

Age And Sex Distribution

Among the 671 patients, 398 (59.3%) were males and 273 (40.7%) were females.

The mean age of all patients was 52.22 years

Table 1: Age distribution

Age groups	Frequency	Percent
13 to 30	109	16.2
31 to 40	82	12.2

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41 to 50	107	15.9
51 to 60	128	19.1
61 to 70	130	19.4
> 70	115	17.1
Total	671	100.0

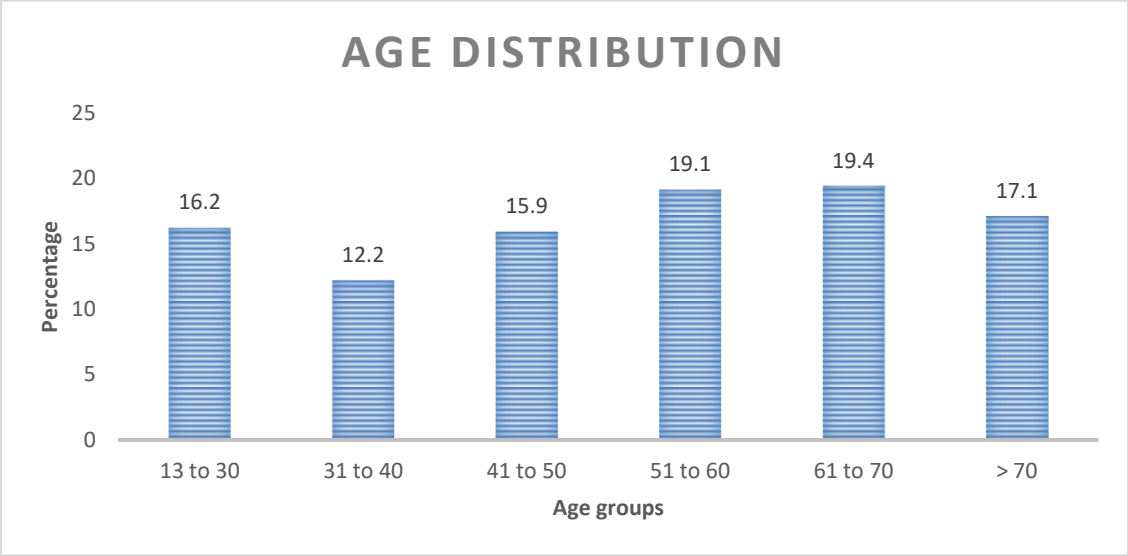

Table 2: Gender distribution

Gender	Frequency	Percent
Females	273	40.7
Males	398	59.3
Total	671	100.0

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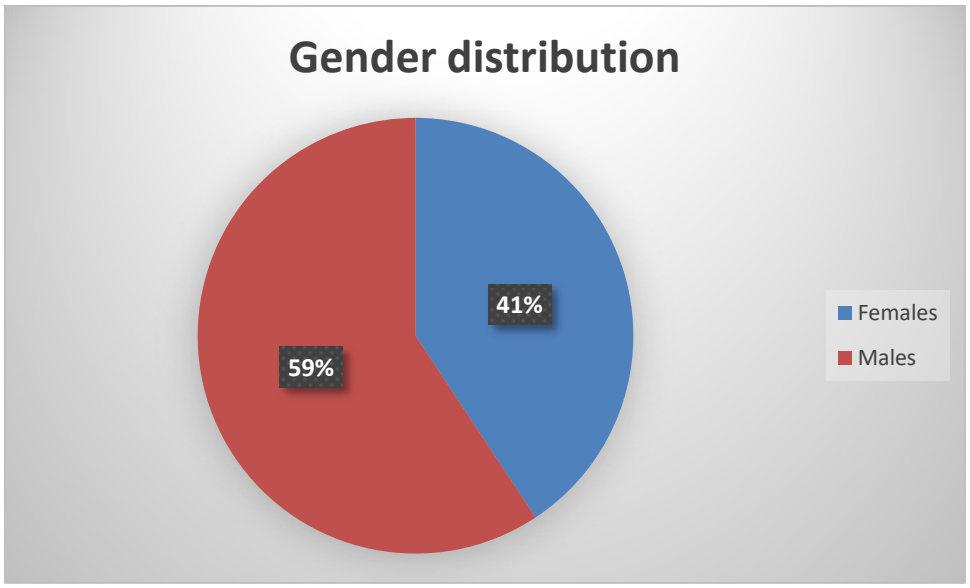
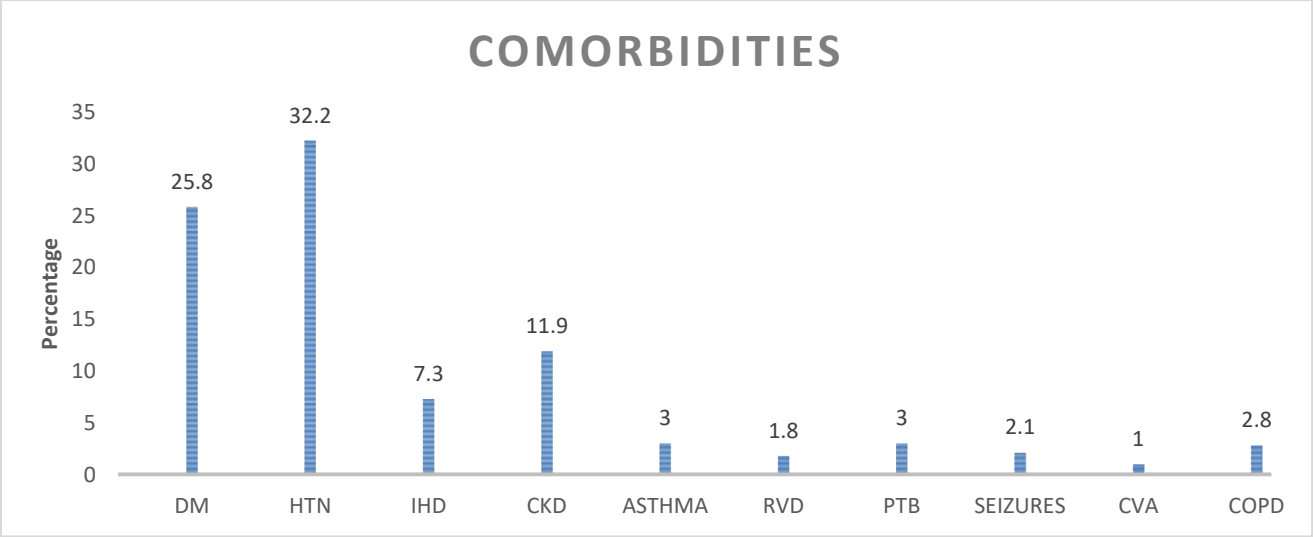


Associated Conditions And Comorbidities

Hypertension (32.2%) and Diabetes Mellitus (25.8%) were the most prevalent co-morbidities. Others included Chronic Kidney Disease (11.9 %), Ischemic Heart Disease (7.3%), Bronchial Asthma (3%), Pulmonary TB (3%), Cerebro Vascular Accident and COPD.

Table 3: Comorbidities distribution



Severity

671 patients were categorized into 4 Groups based on clinical severity -

Asymptomatic - 20 (3%)

Mild infection - 356 (53.1%)

Moderate infection - 195 (29.1%)

Severe infection - 100 (14.9%)

Majority (53.1%) of the patients had mild infection.

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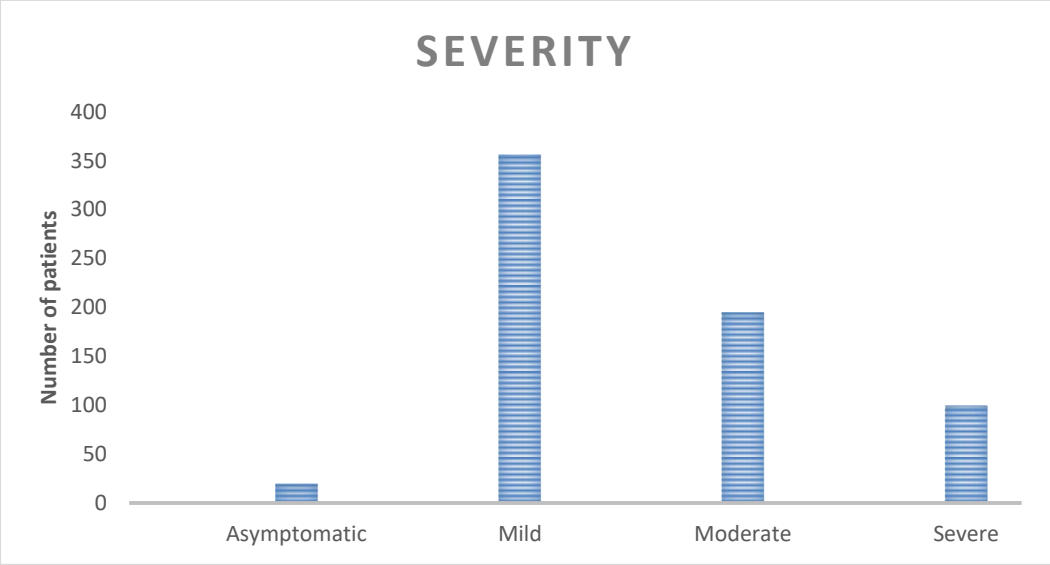
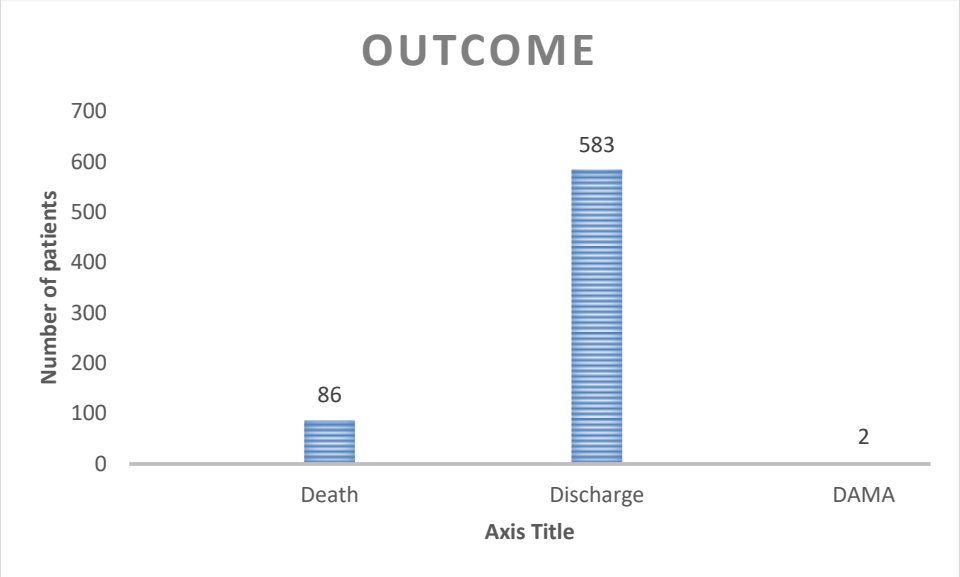


Outcome

Out of 671 patients, 86 patients (12.8 %) died and 583 patients (86.9 %) got discharged. 2(0.3%) patients were discharged against medical advice.



Inflammatory Markers And Severity

LDH - LDH was elevated in 67% patients with severe infection (mean - 344.74) as compared to 50% patients with mild infection (mean - 295.81) - which was **statistically significant**

CRP - CRP was elevated in 88% patients with severe infection (mean - 71.7) as compared to 33.1% patients with mild infection (mean - 6.99) - which was **statistically significant**

D-dimer - D-dimer was elevated in 68% patients with severe infection (mean - 741) as compared to 67.7% patients with mild infection (mean 396) - not statistically significant.

Table 4: Association Of Inflammatory Markers With Severity

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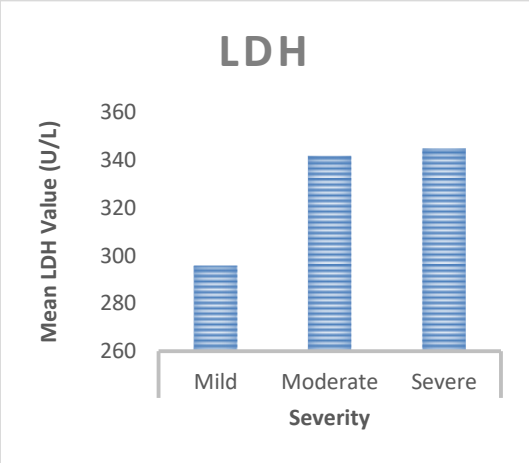
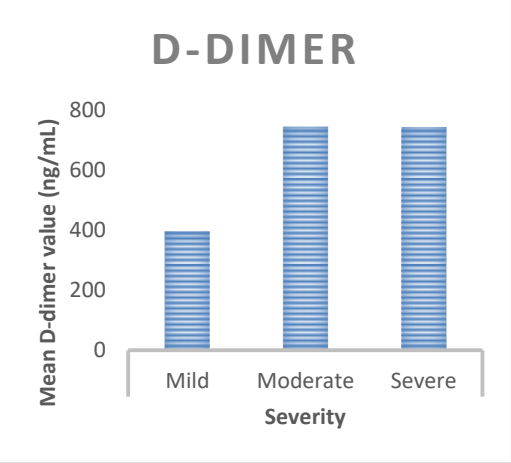
			SEVERITY				Total	Chi-square value	p value
			Asymptomatic	Mild	Moderate	Severe			
LDH	< 140	Count	2	41	15	9	67	17.12	0.009*
		%	10.0%	11.5%	7.7%	9.0%	10.0%		
	140 to 248	Count	3	136	57	24	220		
		%	15.0%	38.2%	29.2%	24.0%	32.8%		
	> 248	Count	15	179	123	67	384		
		%	75.0%	50.3%	63.1%	67.0%	57.2%		
CRP	0 to 5	Count	16	238	21	12	287	215.94	0.001*
		%	80.0%	66.9%	10.8%	12.0%	42.8%		
	> 5	Count	4	118	174	88	384		
		%	20.0%	33.1%	89.2%	88.0%	57.2%		
D-Dimer	≤ 255	Count	9	115	70	32	226	2.005	0.571
		%	45.0%	32.3%	35.9%	32.0%	33.7%		
	> 255	Count	11	241	125	68≤	445		
		%	55.0%	67.7%	64.1%	68.0%	66.3%		
	Total	Count	20	356	195	100	671		
		%	100.0%	100.0%	100.0%	100.0%	100.0%		





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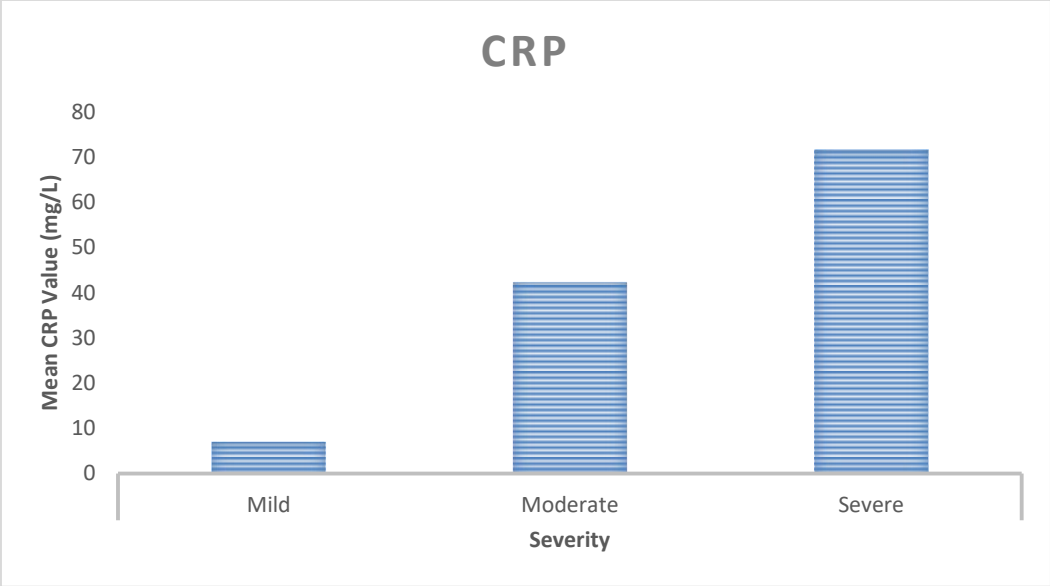

Inflammatory Markers And Outcome

LDH - LDH was elevated in 69.8% patients who died (mean - 356) as compared to 55.2% patients with got discharged (mean - 312) - not statistically significant

CRP - CRP was elevated in 87.2% patients who died (mean - 72) as compared to 52.8% patients who got discharged (mean - 20.04) which was **statistically significant**

Ddimer - D-dimer was elevated in 67.4% patients who died (mean - 698) as compared to 66.2% patients who got discharged (mean 524) - not statistically significant.

Table 5: Association Of Inflammatory Markers With Outcome

			OUTCOME			Total	Chi-square value	p value
			DAMA	DEATH	DISCHARGE			
LDH	< 140	Count	0	6	61	67	7.96	0.093
		%	0.0%	7.0%	10.5%	10.0%		
	140 to 248	Count	0	20	200	220		
		%	0.0%	23.3%	34.3%	32.8%		
	> 248	Count	2	60	322	384		
		%	100.0%	69.8%	55.2%	57.2%		
CRP	0 to 5	Count	1	11	275	287	36.23	0.001*
		%	50.0%	12.8%	47.2%	42.8%		
	> 5	Count	1	75	308	384		
		%	50.0%	87.2%	52.8%	57.2%		
D-Dimer	≤ 255	Count	1	28	197	226	0.29	0.86

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		%	50.0%	32.6%	33.8%	33.7%		
	> 255	Count	1	58	386	445		
		%	50.0%	67.4%	66.2%	66.3%		
	Total	Count	2	86	583	671		
		%	100.0%	100.0%	100.0%	100.0%		

Discussion

The rapidly spreading pandemic, COVID-19 caused by the SARS-CoV-2, has put an enormous burden on health-care systems, globally. Clinically, COVID-19 encompasses broad spectrum of symptoms ranging from mild ILI (influenza-like illness) to severe acute respiratory distress syndrome with multisystem involvement.[9] Framing effective testing strategies which would enable physicians to triage patients accordingly and initiate treatment and monitoring is the need of the hour. Biomarkers are quantitative indicators which reflect the underlying pathological processes, and seem to be valuable, cost-effective tools to guide treatment as compared to imaging procedures such as CT chest.[10] There are many biomarkers related to COVID-19 infection such as N: L ratio, ferritin, CRP, D-dimer, LDH, and Procalcitonin, to name a few. This retrospective study was conducted to understand the use of these COVID-19 biomarkers - CRP, D-dimer, LDH in disease prognostication and correlation between these markers and clinical severity of the disease and outcomes.

SARS-CoV-2 binds to the cell surface receptor of ACE-2 by the spike glycoprotein and enters the cell cytoplasm and replicates, resulting in the formation of new viral particles.[11] The cell then disintegrates and the virus spreads to other cells. The immune dysregulation initiated by pyroptosis (pro-inflammatory form of apoptosis) with rapid viral replication leads to massive release of inflammatory mediators.[12] The disease which starts as a simple viral infection could rapidly progress to development of the cytokine storm and serious organ damage.

CRP is an exquisitely sensitive systemic marker of acute-phase response in inflammation, infection, and tissue damage, which could be used as indicator of inflammation.[13] In a study by Guan et al, CRP was elevated in 60.7% of patients and lactate dehydrogenase (LDH) in 41% of patients.[14] In the study by Chen et al., although no statistically significant difference was found in the level of CRP between the nonsevere and the severe group, the mean level of CRP was higher in the severe group than in the nonsevere group.[15] Our study also showed CRP (>5mg/L) was elevated in 57.2% of all patients and in 88% of the patients who had severe infection which was statistically significant and co-related with severity. Higher values of CRP was seen in severely infected patients (mean - 71) as compared to mildly infected (mean - 6.99). Our study also showed CRP levels to be significantly higher in patients who died as compared to patients who got discharged

Lactate dehydrogenase (LDH) catalyses the last step of aerobic glycolysis, the pyruvate to lactate conversion. Elevated LDH signifies tissue hypoperfusion and indicates the extent of the disease, hence, may affect prognosis. A study by Martha et al concluded that LDH was elevated in 44% of the patients and associated with poor outcome and mortality.[16] Our study also showed that LDH (>248U/L) was elevated in 57.2% of the patients. LDH was significantly evelated in severe infection as compared to non severe infection. However, there was no significant difference in outcome of the disease in our study.

D-dimer may be an indirect manifestation of inflammatory reaction, as inflammatory cytokines could cause the imbalance of coagulation and fibrinolysis in the alveoli, which may activate the fibrinolysis system and then increase the level of D-dimer. A study by Yao et al concluded that D-dimer is commonly elevated in patients with COVID-19 and correlate with disease severity and are a reliable prognostic marker for in-hospital mortality.[17] Our study showed that D-dimer (>255 ng/ml) was elevated in 66.3% of the total patients. However,

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there was so significant difference when compared to severity of infection or outcome.

Conclusion

Levels of serum LDH and CRP in COVID-19 patients were significantly elevated in severe SARS-COV-2 infection. This highlights the role of immune response in pathophysiology and inflammatory markers in the prognosis of Covid-19 infection. Judicious use of these various markers is helpful in correctly identifying the severity of COVID-19 pneumonia and predicting the outcomes. This would thereby help in guiding appropriate treatment strategies.

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