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Original Article

Role of Inflammatory Markers in the Severity and Outcome in Patients with COVID-19 Infection

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Abstract

Introduction: Inflammatory responses triggered by active viral replication of severe acute respiratory syndrome coronavirus 2 plays a critical role in the pathogenesis of COVID-19 pneumonia. It induces the release of cytokines and chemokines. This study was undertaken to assess the role of inflammatory markers in COVID-19 infection.

Materials and Methods: This is a retrospective cohort study which included 200 patients with COVID-19 diagnosed by RTPCR positivity who were classified as severe and non-severe based on oxygen saturation levels.

Results: Among 200 patients who had COVID-19 infection, 56% were male and 44% were female with mean age group of 18–89 years. Among them, 58% had non-severe disease and 42% had severe disease. Out of 200 patients, 71% of them survived and 29% of them were non-survivors. In the present study, inflammatory markers were elevated among patients with severe disease than among patients with non-severe disease. The mean value of inflammatory markers among non-survivors was as follows NLR being 16.85, D-dimer 20.47, C reactive protein 13.49, lactate dehydrogenase 614.48, and ferritin 1182.51 showing statistically significant association with $P < 0.001$ among non-survivors when compared to survivors.

Conclusion: Our study showed that inflammatory markers were raised predominantly among patients who were classified as having severe pneumonia, which shows prognostic significance in the treatment of the disease.

Key words: Corona virus disease, Severe acute respiratory syndrome, Neutrophil lymphocyte ratio, D-dimer, C reactive protein, Lactate dehydrogenase, Ferritin

INTRODUCTION

The ongoing pandemic of COVID-19 has posed a huge threat to public health. Globally as of December 13, 2021, there have been 269,468,311 confirmed cases of COVID-19, including 5,304,248 deaths, reported to the World Health Organization (WHO).[1]

The pathogen has been identified as novel single-stranded ribonucleic acid beta coronavirus named as severe acute respiratory syndrome coronavirus 2 (SARS COV-2).[2]

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The clinical severity of COVID-19 ranged from asymptomatic to severe pneumonia, acute respiratory distress syndrome, and even death. Hence, monitoring and early intervention are the fundamental measures for favorable clinical outcome.[3]

Inflammatory responses triggered by rapid viral replication of SARS COV-2 play an important role in the progression of COVID-19. Cellular destruction recruits' macrophages and monocytes which in turn induces the release of cytokines and chemokines. In most cases, this process is capable of resolving the infection. However, in some cases, a dysfunctional immune response occurs, which can cause severe lung and even systemic pathology.[4] These cytokines and chemokines attract immune cells and activate them. Thus, the activated immune response leads to cytokine storm and progression of the disease, which can be monitored by measuring inflammatory markers.[5]

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Inflammatory markers such as procalcitonin, serum ferritin, ESR, C-reactive protein, and IL-6 have reported significant association with the severity of disease.[2]

Our study highlights the role of inflammatory markers in COVID-19 disease and further can assist in monitoring and prognosis of disease.

MATERIALS AND METHODS

This is a retrospective cohort study which included 200 patients with COVID-19 infection diagnosed by RTPCR positivity age >18 years at Kempegowda Institute of Medical Sciences, Bangalore.

In the present study, severe and non-severe disease was classified based on oxygen saturation levels: Non-severe disease with oxygen saturation >90% and severe disease with oxygen saturation <90% (based on the WHO criteria).

Data based on medical records of the hospital.

Statistical Analysis

Descriptive analysis was done using frequency and proportions for categorical variables, whereas mean and standard deviation for continuous variables.

Mann–Whitney test was used to compare the mean values of diagnostic markers based on the clinical severity and outcome.

ROC curve analysis was performed for diagnostic parameters for determining the cutoff between severe and non-severe and also between survivors and non-survivors of COVID-19 patients.

The level of significance was set at $P < 0.05$.

RESULTS

Among 200 patients who had COVID-19 infection, 56% were male and 44% were female with mean age group of 18–89 year. The demographic characteristics are as shown in Table 1.

In the study, out of 200 cases, 58% had non-severe disease and 42% had severe disease. Among 200, 71% survived and 29% died because of disease, as described in Table 2.

Inflammatory markers such as NLR, D-dimer, CRP, lactate dehydrogenase (LDH), and Ferritin showed significant association among patients with severe disease as described in Table 3.

Table 1: Demographic characteristics of patients

Age and Gender distribution among study patients			
Variable	**Category**	***n***	**%**
Age	≤ 20 years	4	2.0
	21–40 years	41	20.5
	41–60 years	88	44.0
	61–80 years	60	30.0
	>80 years	7	3.5
		Mean	**Standard deviation**
Gender	Mean	53.2	16.1
	Range	18–89	
	Male	112	56.0
	Female	88	44.0

Table 2: Distribution of patients based on the clinical severity and outcome

Variable	Category	*N*	%
Severity	Severe	84	42.0
	Non-severe	116	58.0
Survival	Survivor	142	71.0
	Non-survivor	58	29.0

Table 3: Comparison of mean values of diagnostic markers based on the clinical severity

Parameters	Severity	*n*	Mean	Standard deviation	Mean Diff	*P*-value
NLR	Severe	83	11.10	10.72	6.39	<0.001*
	Non-severe	115	4.71	7.68		
D-DIMER	Severe	84	14.27	91.89	13.42	<0.001*
	Non-severe	116	0.85	1.96		
CRP	Severe	84	10.12	16.32	5.77	<0.001*
	Non-severe	116	4.35	6.50		
LDH	Severe	55	576.59	364.36	233.98	<0.001*
	Non-severe	41	342.61	209.73		
FERRITIN	Severe	51	1051.80	1208.77	614.79	<0.001*
	Non-severe	62	437.01	424.55		

*p <0.05, LDH: Lactate dehydrogenase

Table 4: Comparison of mean values of diagnostic markers based on the outcome

Parameters	Outcome	*n*	Mean	Standard deviation	Mean Diff	*P*-value
Age	Survivor	140	49.96	16.26	−11.02	<0.001*
	Non-survivor	58	60.98	12.70		
NLR	Survivor	140	3.48	3.30	−13.37	<0.001*
	Non-survivor	58	16.85	12.76		
D-DIMER	Survivor	142	0.78	1.85	−19.69	<0.001*
	Non-survivor	58	20.47	110.31		
CRP	Survivor	142	4.03	5.74	−9.46	<0.001*
	Non-survivor	58	13.49	18.85		
LDH	Survivor	45	320.47	138.01	−294.01	<0.001*
	Non-survivor	51	614.48	382.36		
FERRITIN	Survivor	70	426.98	406.57	−755.53	<0.001*
	Non-survivor	43	1182.51	1272.57		

*p <0.05, LDH: Lactate dehydrogenase

Our study showed significant association of NLR, D-dimer, CRP, LDH, and Ferritin mean values with non-survivors with $P < 0.001$. This is described in Table 4.

ROC curve analysis showed that D-dimer, NLR, CRP, Ferritin, and LDH are fair enough test to detect inflammatory marker among severe and non-severe patients, as described in Table 5 and Figure 1.

DISCUSSION

Host cell exhibits different immunological reaction against various infectious agents. An effective immune response is essential to control viral infection; an exaggerated or prolonged response will result in immunopathogenesis.

Table 5: ROC curve analysis for diagnostic parameters for determining the cutoff between severe and non-severe COVID-19 patients

Variable	AUC	Std. Error	95% Conf. Interval		*P*-value	Cutoff	Sn (%)	Sp (%)
			Lower	Upper				
D-Dimer	0.76	0.04	0.70	0.82	<0.001*	>0.43	75.00	70.69
NLR	0.78	0.03	0.72	0.84	<0.001*	>3.77	75.90	71.30
CRP	0.72	0.04	0.65	0.78	<0.001*	>5.93	58.33	79.31
Ferritin	0.73	0.05	0.64	0.81	<0.001*	>879.5	50.98	90.32
	0.79	0.05	0.70	0.87	<0.001*	>323.0	85.45	70.73

*p <0.05, LDH: Lactate dehydrogenase

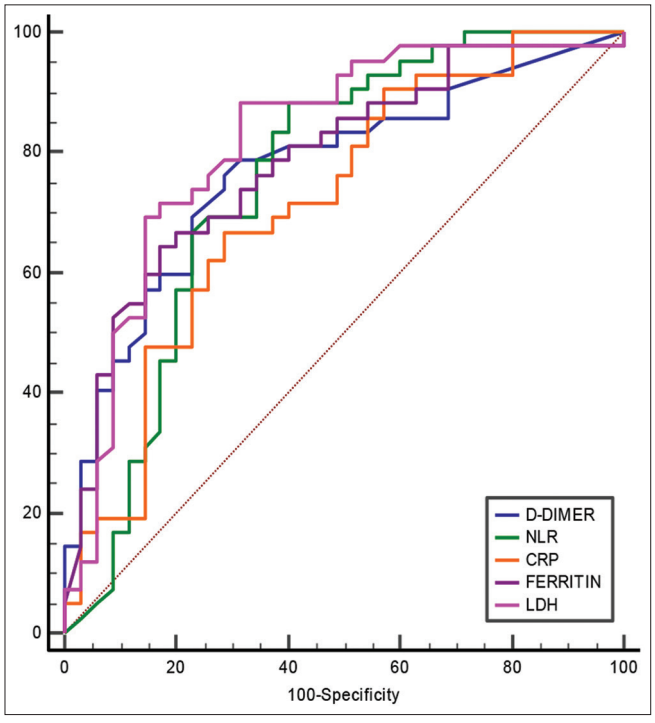

Figure 1: Comparison of ROC curves for different diagnostic parameters based on the severity

Excessive production of inflammatory mediators is involved in the pathogenesis of development of organ dysfunction. Hence, it is necessary to identify the rise in the level of inflammatory markers to monitor the progression of disease and to treat the patients at the earliest.[6]

Activation of neutrophils releases large amount of reactive oxygen species that causes DNA damage and further produces cytokines. Neutrophil releases are triggered by various inflammatory factors such as IL-6, IL-8, TNF-alpha, and granulocyte colony stimulating factors. Interferon-gamma produced by lymphocyte and endothelial cells.

Immune responses triggered by viral infection mainly depend on lymphocytes whereas systemic inflammation significantly depresses cellular immunity which decreases CD4+ lymphocyte and increases CD8+ suppressor lymphocyte. Thus, virus triggered inflammation increases NLR, which promotes COVID-19 progression.[7] Our study showed significant association between NLR and severe disease with mean being 11.10. The study done by Al-Ping Yang concluded that NLR is an independent prognostic biomarker for COVID-19 patients.[7]

CRP concentration is a very useful biochemical marker of inflammation, measurement of which contributes to monitoring of the response to treatment of inflammation and infection [8]. Ali et al. concluded that elevated level of CRP maybe a valuable early marker in predicting the severity of COVID 19 infection [9].Our study showed association between severe disease and C-reactive protein with mean being 10.12 and 4.35 among non-severe. A study done by Nurshad Ali showed that elevated levels of CRP may be valuable early marker in predicting the possibility of disease progression in non-severe patients with COVID-19 so that the treatment can be initiated at an early stage.[10]

D-dimer is also a marker of inflammation in addition to being a measure of hypercoagubility. In our study, mean value of D-dimer among severe disease was 14.27 and 0.85 among non-severe disease, which shows significant association among severe disease. Yumeng Yao *et al.* concluded that D-dimer is commonly elevated in patients with COVID-19 and it correlates with disease severity and is a reliable prognostic marker for in-hospital mortality in COVID-19 patients.[10]

LDH is an enzyme involved in energy production by interconversion of lactate and pyruvate. It is present in almost all body cells with the highest levels in heart, liver, lungs, muscles, kidney, and blood cells. LDH is released following acute or chronic tissue damage and is considered as an inflammatory marker. In COVID-19 patients, LDH

might represent as an expression of lung damage and might reflect the respiratory distress secondary to abnormal inflammatory status.[11] In a study done by Henry *et al*., they concluded that elevated LDH levels were associated with six fold increase in odds of developing severe disease and sixteen fold increase in odds of mortality in patients with COVID-19.[12] In our study, LDH has a significant association with severe disease with $P < 0.001$, mean being 576.59 among severe and 342.61 among non-severe COVID-19 patients.

Ferritin is an acute phase reactant elevated in inflammatory responses of any type. Study done by Katia Lino concluded that the magnitude of inflammation present at admission in COVID-19 patients represented by the high ferritin levels is an independent predictor of in hospital mortality.[13] In our study, mean serum ferritin was high among patients with severe disease with value around 1051.80 and 437 among non-severe COVID-19 patients.

In this study, we conclude that neutrophil lymphocyte ratio, D-dimer, C-reactive protein, LDH, and ferritin were positively correlated with severity of COVID-19 disease.

CONCLUSION

SARS COV-2 infection results in elevated levels of inflammatory markers, which may be associated with severity of the disease and the outcome. Hence, by monitoring the levels of inflammatory markers, one can predict the severity of the disease and its prognosis.

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