Study of inflammatory markers in corona virus disease (COVID-19) patients

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ABSTRACT:

Background: Coronavirus disease (COVID-19) is caused by the Severe acute respiratory syndrome coronavirus 2 (SARS-COV2) which causes mainly pneumonia and other clinical signs due to inflammation and cytokine storm, which leads to rise in certain inflammatory markers. And studying these laboratory parameters with disease causation and progression would be beneficial for clinicians to predict prognosis of the disease. *Aim and objectives*: To study the relation of laboratory parameters (serum Ferritin, serum D-dimer, serum LDH, CRP, ESR) of Covid-19 positive patients with severity and outcome of Corona virus disease (Covid-19). *Material and methods:* This was a single centre, hospital-based prospective, observational study, conducted on patients admitted to COVID ward and intensive care unit of the tertiary care Hospital. This study was conducted over a period of 18 months from February 2021 to August 2022.A total 100 patients were included in this study satisfying the Inclusion criteria. All enrolled patients were tested for serum ferritin, serum D-dimer, serum LDH, CRP, ESR. The above data was collected and complied in Microsoft excel. Results of quantitative data measurement were presented on mean +/- SD (min-max) and qualitative data measurements were presented in percentage and proportions (%). Comparison of qualitative variable was analysed by chi-square test. A p value of <0.05 was considered statistically significant. Data analysis was done using open epi version 2.3.1. *Results*: A total of 100 patients were enrolled in the study, 67% were males and 33% were females, predominated by the male gender with a male to female ratio of 2:1. It was observed that there was association between positive inflammatory markers (i.e. D-Dimer, Ferritin, LDH, ESR, CRP) with the severity of COVID-19 disease and was statistically significant .

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Conclusion: Present study concluded that the inflammatory markers like ESR, C-reactive protein, Lactate dehydrogenase, serum Ferritin and D-Dimer were elevated in severe cases and had adverse outcomes. Thus, these inflammatory markers can be used to risk stratify prognosis of COVID-19.
Keywords: COVID-19, Inflammatory markers, Serum Ferritin, Serum D-dimer, Serum Lactate dehydrogenase, C-reactive protein, Erythrocyte sedimentation rate

INTRODUCTION:

The novel coronavirus was discovered as the causative pathogen of pneumonia in Wuhan city, Hubei province in China in December 2019[1]. Severe acute respiratory syndrome coronavirus 2 (SARS-COV2) was name as Covid-19 pneumonia by the World Health Organization [2]. World health organization on 30th January 2020, declared the Chinese outbreak of covid-19, as a pandemic posing a high risk to countries with vulnerable health systems [3]. Till date, many countries in the world in different continents were involved in covid-19. Patients suffering with covid-19 pneumonitis mostly presented with mild symptoms like fever, sore throat, fatigue, dry cough and majority of them recovered spontaneously. However, some of them developed fatal complications like multiple organ failure, acute infarcts, myocarditis, sepsis and acute respiratory distress syndrome (ARDS) [4]. Inflammatory responses play a critical role in the pathogenesis and progression of covid-19 [5]. Inflammatory responses triggered by rapid viral replication of sars-cov-2 and cellular destruction can recruit macrophages and monocytes and induce the release of cytokines and chemokines [6,7,8]. These cytokines and chemokines then attracted immune cells, activated immune responses and release of pro-inflammatory cytokines, leading to cytokine storm causing a systemic inflammation [9,10,11]. Neutrophilia with lymphopenia is a response of the innate immune system to systemic inflammation. Hence neutrophil-to-lymphocyte ratio (NLR) is another inflammatory marker, which is the ratio of absolute neutrophil count to lymphocytes on routine complete blood counts. An elevated NLR is associated with the prognosis of systemic inflammatory diseases, especially infectious diseases. C reactive protein is one of the acute phase reactants, which is elevated in many viral respiratory infections. CRP testing is used at the forefront for evaluation of infection and is important for covid-19 management and prognosis. Two inflammatory markers such as c-reactive protein (CRP), erythrocyte sedimentation rate (ESR), d-dimer, procalcitonin (PCT), lactate dehydrogenase [LDH], serum ferritin and interleukin-6 (il-6) have been reported to be significantly associated with severity and outcome of covid-19[12,13]. Thus present study was carried out to find the association of inflammatory markers with the severity of covid-19.

Aim and objectives

To study the inflammatory markers in Corona virus disease (Covid-19) patients.

Objectives: to study the relation of laboratory parameters (serum Ferritin, serum D-dimer, serum LDH, CRP, ESR) of Covid-19 positive (by RT-PCR) patients with severity and outcome of Corona virus disease (Covid-19)

Material and methods

Study type: this was a single centre, hospital-based prospective, observational study.

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Study area: The study was conducted on patients admitted to COVID ward and intensive care unit of the tertiary care institute, Krishna Hospital, Karad.

Study duration: This study was conducted over a period of 18 months from February 2021 to August 2022.

Sample Size:

A total 100 patients were included in this study satisfying the Inclusion criteria. All enrolled patients were tested for serum ferritin, serum D-dimer, serum LDH, CRP, ESR.

Inclusion criteria: All patients aged more than 18 years, tested positive for COVID-19 RTPCR swab were included in the study

Exclusion criteria:

Patients aged <18years

Patients who have refused to give consent to the study.

Statistical analysis:

All data was collected and complied in Microsoft excel. Results of quantitative data measurement were presented on mean +/- SD (min-max) and qualitative data measurements were presented in percentage and proportions (%). Comparison of qualitative variable was analysed by chi-square test. Wherever necessary between groups, comparison of quantitative variables was analysed by independent student t test according to distribution. A p value of <0.05 was taken as level of significance and was considered statistically significant. Data analysis was done using open epi version 2.3.1.

OBSERVATION AND RESULTS:

A total of 100 patients with diagnosis of COVID-19 positive cases were enrolled in present observational study which yielded the following results. Of them, 67 (67%) were males and 33 (33%) were females. This study was predominated by the male gender with a male to female ratio of 2:1.

Among the males (67%), 23(52.27%) were mild cases, 32(80%) were moderate cases,12(80%) were severe cases. And among the females (33%), 21(47.72%) were mild cases, 8(20%) were moderate cases, 3(20%) severe, and 1(100%) very severe cases. Male preponderance was observed. In present study, mild and moderate group patients were significantly more compared to severe and very severe group ('p'= 0.014 Chi square (χ2) =10.55 DF: 3

Table 1: Distribution of COVID-19 patients according to the severity of illness in study population

Severity of COVID-19	Male		Female		Total	
	n=67	%	n=33	%	n=100	%
Mild	23	52.27	21	47.72	44	44
Moderate	32	80	8	20	40	40
Severe	12	80	3	20	15	15
Very severe	0	0	1	100	1	1

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Total	67		33		100	

[Chi square value(χ^2) = 10.55DF:3 'p'= 0.014]

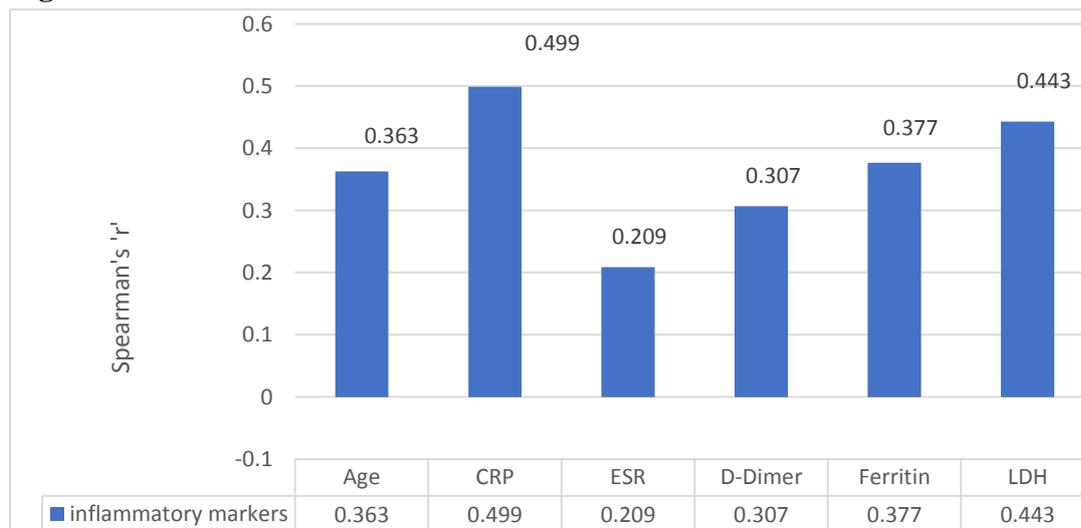**Table 2: Mean and standard deviation of various parameters and inflammatory markers in the study population**

Parameter	Male		Female		T value	'p' value
	Mean	SD (±)	Mean	SD (±)		
PF ratio	318.9	143.7	350.1	113.3	1.09	0.2
HRCT score	6.9	7	3.1	6.6	2.6	0.01
ESR	50.4	29.9	48.4	5.5	0.38	0.7
CRP	2.2	1.99	3.4	7.1	1.2	0.1
Ferritin	417.2	475	248.2	346.1	1.8	0.07
D dimer	3.4	9.6	2.1	5.4	0.7	0.47
LDH	653.1	301.5	468.2	194.5	3.2	0.001

It was observed that as the level of CRP increased, it was associated with more severe form of illness (Spearman's rho correlation coefficient=0.499,p value <0.001) followed by LDH (Spearman's rho correlation coefficient=0.443,p value <0.001), Ferritin (Spearman's rho correlation coefficient=0.377,p value <0.001) as compared to the increasing age and severity of illness (Spearman's rho correlation coefficient=0.363,p value <0.001) , D-dimer (Spearman's rho correlation coefficient=0.307, p value 0.002) and ESR (Spearman's rho correlation coefficient=0.209, p value 0.037).

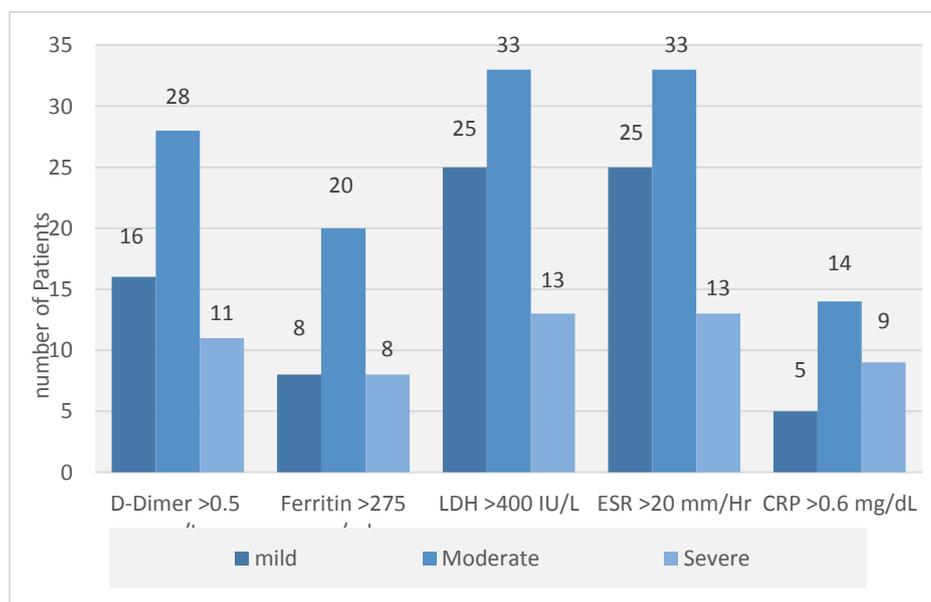**Table 3: Relation between inflammatory markers and age with the severity of COVID-19 disease**

Severity of COVID-19 disease		
Parameters	Correlation 'r' (Spearman's rho)	'p' value
Age	0.363	<0.001
CRP	0.499	<0.001
ESR	0.209	0.037
D-Dimer	0.307	0.002
Ferritin	0.377	<0.001
LDH	0.443	<0.001

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Figure1:

Of total 100 patients in the study population, 55(55%) patients had positive D-dimer (>0.5 mg/L), of which 16(29%) were mild cases ,28(50%) were moderate cases, 11 (20%) were severe cases.36(36%) patients had positive Ferritin (>275 ng/ml), of which 8(22%) were mild cases ,20(55%) were moderate cases, 8 (22%) were severe cases.71(71%) patients had positive LDH (>400 IU/L) of which 25(35%) were mild cases ,33(46%) were moderate cases, 13 (18%) were severe cases.71(71%) patients had positive ESR (>20 mm/Hr) of which 25(35%) were mild cases ,33(46%) were moderate cases, 13 (18%) were severe cases.28(28%) patients had positive CRP (>0.6 mg/dL) of which 5(17%) were mild cases ,14(50%) were moderate cases, 9 (32%) were severe cases.The association between positive inflammatory markers (i.e. D-Dimer, Ferritin, LDH, ESR, CRP) with the severity of COVID-19 disease was statistically significant with p values <0.05.

Figure2: Association of positive inflammatory markers with the severity of COVID-19 disease

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DISCUSSION:

Age distribution: In present study, the mean age of the study population was 51.62 (±18.8) years. The mean age of males was 58(±16.8) years and of females was 45(±20.1) years. Most of the patients belonged to 61 to 70years (21%). Majority of the patients were elderly, similar to studies by Marimuthu K et al(60 years) Parimoo A et al(55.6+17 years), Lee et al (55.2+19.7 years), Kate et al reported that the mean age among discharged patients was 62 years and among the patients who died was 66years[14,15,16].**Outcome of disease:** In the present study, 83% of them were discharged and 17% of them died. Of the 83% of patients who were discharged home, 44% were mild cases,37%were moderate and 2 % were severe cases. Of the 17% patients who died,7.5% were moderate,86.6% severe and 100% very severe cases, similar to the studies by Marimuthu et al and Lee et al where it was noted that the mortality rate was 15.8% and 13.3% respectively[14,17]. **Gender distribution:** In present study,67%were males and 33% were females. It was predominated by male gender with a male to female ratio of 2:1, similarly in studies by Marimuthu et al (70.1% were males), Parimoo A et al (60% males), Lee et al (59%), Sudhir Bhandari et al (66.6%males) and Kate et al (78%) [14,72]. **Severity of disease:** 44% were mild cases,40% moderate,15%severe and 1% very severe case. Mild cases were mostly found in 21 to 30years of age (83.3%), whereas moderate cases were mostly seen 51 to 60 years of age (64.7%) and severe, very severe cases in >70years of age (35.7%) and (7.14%) respectively. Mild cases were seen in younger age groups and severe cases were found in elderly. In present study, significant association was found between increasing age and severity of the disease ('p'= 0.02; rho=0.363), as compared to the study by Marimuthu et al which reported that 35.7% had mild disease,24.9% had moderate disease and 39.4% had severe disease [14].

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Author name	Type of study	Sample size	Interpretation
Marimuthu et al. (2021)	Retrospective cross-sectional	221	N: L ratio,CRP levels, IL-6 and D-dimer had good correlation with in-hospital mortality
Zeng et al. (2020)	Meta-analysis	3962	Non-severe group had lower levels of CRP, procalcitonin, ESR, serum ferritin compared to severe group. There was an association of inflammatory markers with the severity of COVID-19.
Zhe-Feng Zhong (2020)	Cross-sectional Observational	48	The levels of CRP, fibrinogen, blood glucose,LDH,D-Dimer,SGOT, SGPT, and creatinine kinase(CK) were increased in severe COVID-19 disease.
Jain et al. (2021)	Retrospective observational cohort study	735	CRP and D-Dimer on admission positively predicts final outcome of in hospital mortality. Whereas, CT severity score had AUROC 0.73 (p= 0.014)
Ignatius Bima Prasetya(2021)	Retrospective observational cohort study	391	Increasing CRP, NLR, and d-dimer at hospital admission was an an important marker for early identification of COVID-19 patients with poor disease prognosis.
Solangel Ortega-Rojas(2020)	secondary analysis of data from a retrospective cohort	263	The NLR and PLR are predictors of higher risk of mortality, however, by themselves, they are weak prognostic markers.
Linlin Cheng(2019)	systematic review and meta-analysis	52 records involving 10 614 patients	The ferritin level was significantly increased in severe patients compared with the level in non-severe patients.
Ghahraman et al. (2020)	Meta-analysis	3396	There was an increase in ESR, C-reactive protein (CRP), D-dimer and neutrophil to lymphocyte ratio (NLR) in the severe group.
Zhu et al. (2021)	Retrospective cross-sectional	163	Significant association was found between WBC count and death (p<0.001). WBC count at admission was correlated with death in COVID-19.
Ahmed N. Kaftan (2021)	retrospective cohort study	938	Combination of routine laboratory biomarkers (CRP, LDH and ferritin ±D dimer) can be used to predict the diagnosis of COVID-19
Ian Huang (2020)	Meta-analysis	25 studies with 5350 patients	elevated serum CRP, PCT, D-dimer, and ferritin were associated with a poor outcome in COVID-19.
Laguna Goya et al. (2020)	Prospective cohort study	611	High IL-6 level, CRP level, LDH level, ferritin level, d-dimer level, neutrophil

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			count, and NLR were predictive of mortality.
Present study	observational study	100	inflammatory markers like ESR, C reactive protein, Lactate dehydrogenase, serum Ferritin and D Dimer were elevated in severe cases with higher HRCT scores and had adverse outcomes

Table: Comparison between different studies with present study

CONCLUSION:

Present study concluded that the inflammatory markers like ESR, C-reactive protein, Lactate dehydrogenase, serum Ferritin and D-Dimer were elevated in severe cases and had adverse outcomes. In present study, elderly population (>60years) were often affected and had severe illness with high mortality. As in line with the high prevalence of multiorgan failure, high D-dimer levels, Ferritin levels, IL-6 levels etc. were found in severe COVID-19 disease. Thus, these inflammatory markers can be used to risk stratify prognosis of COVID-19, hence can be a helpful tool to initiate appropriate treatment and assist in timely management, and predict complications. Thus, we strongly suggest to consider these inflammatory markers for the patients with COVID19 disease requiring oxygen supplementation with features of acute respiratory distress syndrome.

Conflict of interest: None
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REFERENCES:

1.Lu H, Stratton CW, Tang YW. Outbreak of pneumonia of unknown etiology in Wuhan, China: The mystery and the miracle. Journal of medical virology. 2020 Apr;92(4):401.

2. World Health Organization 2. WHO Director-General's remarks at the media briefing on 2019-nCoV on 11 February 2020.

3. World Health Organization, Coronavirus WN. situation report-12 [Internet]. Geneva: World Health Organization; 2020 [cited 2020 Nov 12].

4. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Yu T. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. The lancet. 2020 Feb 15;395(10223):507-13.

5. Wang Y, Wang Y, Chen Y, Qin Q. Unique epidemiological and clinical features of the emerging 2019 novel coronavirus pneumonia (COVID-19) implicate special control measures. Journal of medical virology. 2020 Jun;92(6):568-76.

6. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The lancet. 2020 Feb 15;395(10223):497-506.

7. Conti P, Ronconi G, Caraffa AL, Gallenga CE, Ross R, Frydas I, Kritas SK. Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by Coronavirus-19 (COVI-19 or SARS-CoV-2): anti-inflammatory strategies. J Biol Regul Homeost Agents. 2020 Mar 1;34(2):327-31.

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8. Liu X, Shen Y, Wang H, Ge Q, Fei A, Pan S. Prognostic significance of neutrophil-to-lymphocyte ratio in patients with sepsis: a prospective observational study. Mediators of inflammation. 2016 Oct;2016..

9. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. The lancet. 2020 Mar 28;395(10229):1033-4.

10. Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LF. The trinity of COVID-19: immunity, inflammation and intervention. Nature Reviews Immunology. 2020 Jun;20(6):363-74.

11. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, Liu S, Zhao P, Liu H, Zhu L, Tai Y. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. The Lancet respiratory medicine. 2020 Apr 1;8(4):420-2.

13. Cheng KB, Wei M, Shen H, Wu C, Chen D, Xiong W. Clinical characteristics of 463 patients with common and severe type coronavirus disease 2019. Shanghai Medical Journal. 2020 Mar;1:1-5.

14. Marimuthu AK, Anandhan M, Sundararajan L, Chandrasekaran J, Ramakrishnan B. Utility of various inflammatory markers in predicting outcomes of hospitalized patients with COVID-19 pneumonia: A single-center experience. Lung India: Official Organ of Indian Chest Society. 2021 Sep;38(5):448.15. Parimoo A, Biswas A, Baitha U, et al. (October 27, 2021) Dynamics of Inflammatory Markers in Predicting Mortality in COVID-19. Cureus 13(10): e19080.

16. Stoeckle K, Witting B, Kapadia S, An A, Marks K. Elevated inflammatory markers are associated with poor outcomes in COVID-19 patients treated with remdesivir. Journal of Medical Virology. 2022 Jan;94(1):384-7.

17. Lee EE, Song KH, Hwang W, Ham SY, Jeong H, Kim JH, Oh HS, Kang YM, Lee EB, Kim NJ, Chin BS. Pattern of inflammatory immune response determines the clinical course and outcome of COVID-19: unbiased clustering analysis. Scientific reports. 2021 Apr 13;11(1):1-8.

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