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Original Research Article

Correlation between Inflammatory Markers with Disease Severity of COVID 19 Infection

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Abstract

Background: Patients with COVID-19 have characteristic of hyper inflammation, so the associated inflammatory biomarkers may be helpful for forecast the severity. But data for predicting severity of patients with COVID-19 infection are sparse and still under investigation. We aimed to investigate the association between several biomarkers such as serum C-reactive protein (CRP), procalcitonin (PCT), D-dimer, and serum ferritin, with disease the severity.

Methods: In the present study 150 COVID-19 patients aging between 18 and 45 years and 150 age and sex matched apparently healthy people were included. Then case group participants are subdivided into three sub-groups according to disease severity. Thereafter, all of the patients and healthy persons were subjected to the estimation of serum IL-6, D-Dimer, (LDH), CRP, ferritin, and PCT.

Results: The result showed that among all inflammatory markers only IL6 and CRP are well correlated with disease severity but after multiple regression analysis it is found that the CRP concentration was not well correlation with other inflammatory markers in different severity.

Conclusion: Compared to other inflammatory markers, we found that only serum IL6 concentration was significantly associated withCOVID-19 severity.

Keywords: COVID-19, interleukin 6, C-reactive protein, D-dimer, ferritin, Procalcitonin.

Introduction

COVID-19 disease is caused by a RNA virus Coronavirus 2 (SARS-CoV-2), which was first detected in Wuhan, China in 2019. The disease has evolved into a pandemic that has been declared a global public health emergency by the World Health Organization, as of today greater than 300 million people have been infected and more than 0.2 million have died worldwide. [1]The spectrum of disease is variable. The majority of patients with COVID-19 may be asymptomatic or have a mild influenza-like illness, a small proportion of patients develop severe pneumonia, acute respiratory distress syndrome, multi-organ failure, and can even die.[2,3]

Inflammation plays a major role in development and progression of COVID-19. People infected with COVID-19 are known to have an immune system that is dysregulated and can cause abnormal immune response.[4]It has a role of pathophysiology of COVID 19 infection that is reflected by serum C-reactive protein (CRP), procalcitonin (PCT), D-dimer, and hyperferritinemia.[5,6]

It has been also reported that the mortality from COVID 19 is due to the severe multisystem end-organ failure as a result of cytokine storm. [7] Hence, correlation of the inflammatory markers with disease severity will have importance in prognosis and management aspect of disease.

So, present study was conducted to explore better inflammatory marker that correlate well with disease severity of COVID-19 infection.

Material and Methods

Study Area

This hospital based cross-sectional study was conducted in the Department of General Medicine with the collaboration of Department of Biochemistry of

Burdwan Medical College, Burdwan, West Bengal, India.

Ethics Statement

The study was approved and permitted by the institutional ethics committee for care and use of laboratory and started after obtaining the written consent from the concerned ethics committee.

Study population

The present study was conducted between March 2021 and August 2022. Sample size was calculated at 95% confidence interval, with a power of 80% [8] using the formula

$$N = 2\{(Z\alpha + Z\beta)^2\sigma^2\}/d^2$$

As shown in Figure 1, 150 COVID-19 patients aging between 18 and 45 years old and of both sexes were included in the study. SARS-CoV-2 infection was detected fulfilling the WHO case definition of COVID-19[9] and by confirmed by the RT-PCR assay. In addition, 150healthy persons with SARS-CoV-2RT-PCR negative of the same ages and sexes were included in this study as a control group from same region. Both the cases and controls were selected by a simple random method. Every patient was informed about the details of the study through individual interviews and all the provided written informed consent. Patients with cancer, history of pre-existing musculoskeletal disease, chronic disease of liver, kidney, and heart are not included in this study.Pregnant and lactating women, persons suffering from bacterial and non-covid viral infections and on immunosuppressive drugs for another disease were excluded from the study.

COVID-19 patients then were grouped into three groups according to Indian Council of Medical Research recommended case definitions[10]

Mild illness (n =50) - Fever with or without upper respiratory tract symptomatology barring breathing difficulty/decreased oxygen saturation.

Moderate illness (n =50) - Individuals having either features: tachypnoea (RR>24/min), breathing difficulty or SpO_2between 90-93 percent without any oxygen support.

Severe disease (n=50) - Patients having anyone of the following features, either respiratory rate >30/min, breathlessness or SpO_2< 90% on room air.

Thereafter, all of the patients and healthy persons were subjected to the estimation of serum IL-6, D-Dimer, lactate dehydrogenase (LDH), CRP, ferritin, PCT as well as the total count of lymphocyte and neutrophils.

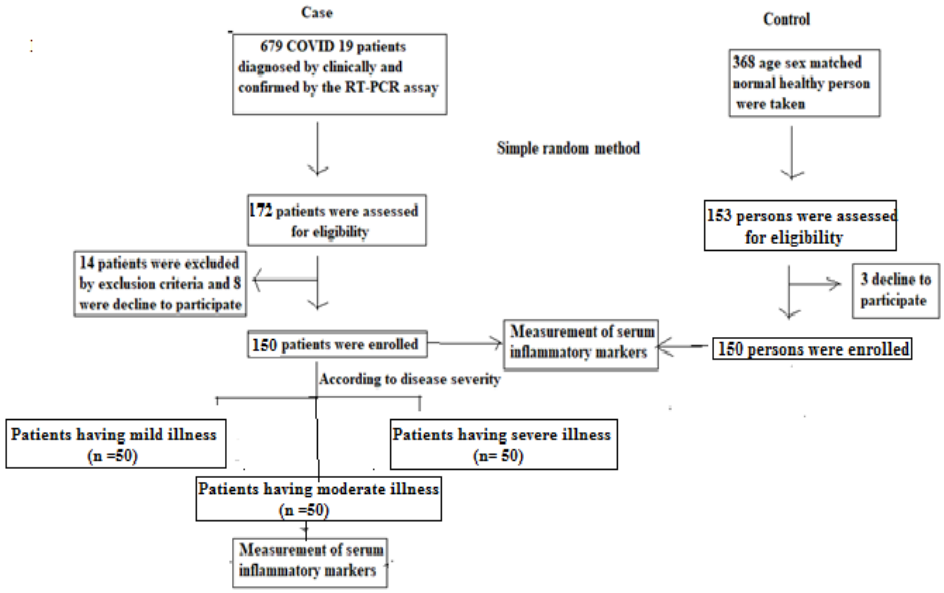

Figure 1: Study design of present study

Collection of samples

Peripheral venous blood was drawn under aseptic precautions from all participants and the samples were divided into two aliquots. The first one was collected in Ethylene diamine tetra acetic acid [EDTA] tubes for obtaining the hematology auto-analyzer (Pentra 80. manufactured by the ABX-Horiba group, Minami-Ku Kyoto Japan).

On the same day, the second part of the blood samples was collected and allowed to clot for 30 min at room temperature and then centrifuged at 2400×g for 10 min to separate serum. This serum is used for the determination of serum concentration of IL-6, D-Dimer, LDH, CRP, and ferritin. All serum samples were stored at (-70^{0}C) and kept under these conditions until chemical analysis was performed. All parameter assays should be done as soon as possible.

Parameters assay

Serum PCT was determined by an immunoluminometric assay (Sphere Light B.R.A.H.M.S PCT; Wako Diagnostics, Tokyo, Japan). The normal range of PCT is 0.5 ng/ml and the lower limit of detection is 0.1 ng/ml [13, 14]At a concentration between 0.1 and 0.3 ng/ml, an intra-assay CV of less than or equal to 7% and an inter-assay CV of less than or equal to 10%, and at concentrations greater than 0.3 ng/ml the intra-assay CV is less than or equal to 3% and the inter-assay CV is less than or equal to 6% Estimation of serum interleukin-6 Electrochemi-luminescence immunoassay technique and (Cobas) instrument are used for the detection of serum IL-6 in patients and the control group using a kit performed by Roche company (Roche Diagnostics GmbH, Sandhofer Strasse 116, D-68305 Mannheim. 2020). The assay has a claimed measuring range of 1.5−5000 pg/mL, a limit of quantitation (LOQ) of 2.5 pg/mL, an inter-assay precision (CV) of 17.4 % (at 1.82 pg/mL) and 2.0 % (at 4461 pg/mL). Determination of serum D-dimer and C-reactive protein Serum concentrations of D-Dimer and CRP were evaluated using a specific automated protein analyzer (PA120) provided by (Shenzhen Genius Electronics Co., Ltd. China 2019). Serum samples for each of the patients and healthy persons were applied to the instrument then the concentrations of D-dimer and CRP are calculated automatically. EDTA blood samples from both patients and the control group are applied to a hematology autoanalyzer (Pentra 80 manufactured by ABX-Horiba group, Minami-Ku Kyoto Japan) to estimate total counts of white blood cells (WBCs) and neutrophils. Samples are processed by the instrument then total WBCs and neutrophils are calculated automatically.

LDH was determined based on the principle of the enzymatic coupling reaction. LDH catalyzes the conversion of pyruvate and NADH to lactate and NAD+. Oxidation of NADH was monitored by reflectance spectrophotometry, which is used to measure the LDH activity.

The ferritin was measured using the principle of immunoturbidimetry. Agglutination formed due to the reaction between latex-bound ferritin antibodies and the antigen in the sample to form an antigen/antibody complex was measured turbidometrically.

Statistical analysis

Data were entered using Microsoft Excel 2007.Then the data for biochemical analysis was subjected to standard statistical analysis such as Student's t test using the Statistical Package for Social Science (SPSS) 20 software. For all tests 'p' value was considered to be significant if it was less than 0.05 at a confidence level of 95 %.

Correlations were evaluated with normal and Spearman correlation tests. The values are expressed as mean±SD.

Result

The characteristics and their comparison among different groups of study population – Unpaired t test

Baseline personal profile and clinical details of the study population are not statistically significant as shown in Table 1. It indicates that controls are baseline personal profile and clinical details matched with cases.

Table-1: Biochemical and anthropometric variables and their comparison between the controls, cases of Covid19 patients and with disease severity

Characteristics	Control (n)	Cases (n =150)		
		Mild illness	Moderate illness	Severe illness
Number of participants	150	50	50	50
Age (years)	32.96 ± 10.32	33.46 ± 9.29	33.12 ± 10.28	32.46 ± 11.02
Sex Male Female	 72 (48) 78 (52)	 26 (52) 24 (48)	 24 (48) 26 (52)	 25 (50) 25 (50)
Demographic data Urban background Rural background	 74 76	 25 (50) 25 (50)	 23 (46) 27 (54)	 24 (48) 26 (52)
BMI (Kg/m^2)	23.8±2.8	23.4±2.6	22.7 ± 2.2	22.3 ± 1.9
Fasting plasma glucose (mg/dl)	91.2 ± 10.5	93.35 ± 7.28	95.01 ± 10.45	100.38 ± 8.29
Serum urea (mg/dl)	29.79 ± 5.64	27.18 ± 6.88	30.98 ±4.11	29.25 ± 17.62
Serum creatinine (mg/dl)	1.06 ± 0.20	0.93 ± 0.18	0.99 ± 0.27	1.07 ± 0.32
Systolic blood pressure (mm Hg)	117.88 ± 5.62	121.38 ± 10.58	108.45 ± 07.38	115.27 ± 13.93
Diastolic blood pressure (mm Hg)	73.72 ± 5.71	76.29 ± 6.94	77.34 ± 4.96	80.12 ± 6.93

Data are expressed as numbers (group percentages in parentheses) for categorical variables and mean values ± SD for continuous variables.

Comparison of serum levels of interleukin-6, ferritin, lactate dehydrogenase, C-reactive protein and D-Dimer in COVID-19 patients and control group – Unpaired t test

The results of Table 2 are showing that the mean of the serum level of IL-6 was higher significantly in COVID-19 patients compared to the control group. Likewise, the mean of the serum levels of CRP, ferritin, LDH, and D-Dimer was also elevated significantly among COVID-19 patients compared to the control group.

Table 2: The differences in the serum levels of interleukin-6, ferritin, lactate dehydrogenase, C-reactive protein and D-Dimer in COVID-19 patients and control group

Parameters	Case	Control	p value
IL6 (pg/ml)	27.38 ± 14.83	5.21 ±0.72	0.000
Ferritin (µg/ml)	337.47 ± 117.62	73.56 ± 39.29	0.000
CRP (mg/ml)	109.37 ± 67.82	2.17 ± 0.63	0.000
LDH (IU/L) at 37^0C	424.38±105.51	131.44±21.14	0.000
D-Dimer (µg/ml)	0.73 ± 0.09	0.18±0.08	0.000
PCT (ng/ml)	10.47 ± 0.17	0.19 ± 0.04	0.000

Serum concentration of interleukin-6, ferritin, lactate dehydrogenase, C-reactive protein, and D-Dimer in COVID-19 patients according to the severity of infection.

The mean of interleukin-6, ferritin, lactate dehydrogenase, C-reactive protein and PCT are increased with disease severity. But the D-Dimer level was found to decreased with severity of infection [Table 3].

Table 3: Differences in the levels of interleukin-6, ferritin, lactate dehydrogenase, C-reactive protein, PCT and D-Dimer in COVID-19 patients according to the severity of infection

Parameters	Mild illness (Mean ± SD)	Moderate illness (Mean ± SD)	Severe illness (Mean ± SD)
IL6 (pg/ml)	9.29±0.17	19.46 ± 0.34	36.22 ±12.93
Ferritin (µg/ml)	287.75 ± 87.39	316.92 ± 111.24	338.60±174.17
CRP (mg/ml)	42.64±22.53	74.88 ± 43.82	129.98±68.54
LDH (IU/L) at 37^0C	349.80±83.18	389.47 ± 59.39	429.52±85.19
D-Dimer (µg/ml)	0.51±0.79	0.76 ± 0.31	0.82 ±0.30
PCT (ng/mL)	08.69 ± 1.05	10.22 ± 1.06	12.92 ± 0.12

Pairwise multiple comparison of different inflammatory markers within the case group - the post hoc ANOVA analysis with Bonferroni correction

Pairwise multiple comparison in the post hoc ANOVA analysis with Bonferroni correction within the case group was performed and it became evident that increase of IL6, ferritin, LDH, D-Dimer and CRP concentration was significantly increased compared to control as shown in Table 2. but only IL6 and CRP are well correlated with disease severity.

Table 4: ANOVA with Bonferroni correction showing multiple comparisons of different inflammatory markers in different severity of COVID 19 patients with significance of difference

Dependent variable	Factor (I)	Factor (J)	Mean difference (I-J)	Significance at 95% CI
IL6 (pg/ml)	1	2	-4.08	0.031*
		3	-14.25	0.003*
		4	-31.01	<0.001*
	2	1	4.08	0.031*
		3	-10.17	0.012*
		4	-26.93	<0.001*
	3	1	14.25	0.003*
		2	10.17	0.012*
		4	-16.76	<0.001*
	4	1	31.01	<0.001*
		2	26.93	<0.001*
		3	16.76	<0.001*
Ferritin (µg/ml)	1	2	-214.19	<0.001*
		3	-243.36	<0.001*

		4	-265.04	<0.001*
	2	1	214.19	<0.001*
		3	-29.17	0.161
		4	-50.85	0.092
	3	1	325.04	<0.001*
		2	50.85	0.061
		4	-21.68	0.094
	4	1	265.04	<0.001*
		2	50.85	0.061
		3	21.68	0.094
CRP (mg/ml)	1	2	-40.47	0.011*
		3	-72.71	<0.001*
		4	-127.81	<0.001*
	2	1	40.47	0.011*
		3	-36.24	0.036*
		4	-87.34	<0.001*
	3	1	72.71	<0.001*
		2	36.24	0.036*
		4	-55.1	0.015*
	4	1	127.81	<0.001*
		2	87.34	<0.001*
		3	55.1	0.015*
LDH (IU/L) at 37^0C	1	2	-218.36	<0.001*
		3	-258.03	<0.001*
		4	-298.08	<0.001*
	2	1	218.36	<0.001*
		3	-39.67	0.126
		4	-79.72	0.086
	3	1	258.03	<0.001*
		2	39.67	0.126
		4	-40.05	0.098
	4	1	298.08	<0.001*
		2	79.72	0.086
		3	40.05	0.098
D-Dimer (µg/ml)	1	2	-0.33	0.043*
		3	-0.58	0.024*
		4	-0.64	<0.001*
	2	1	0.33	0.043*
		3	-0.25	0.102
		4	-0.31	0.056
	3	1	0.58	0.024*
		2	0.25	0.102
		4	0.06	0.346
	4	1	0.64	<0.001*
		2	0.31	0.056
		3	0.06	0.346
PCT (ng/mL)	1	2	-8.5	<0.001*
		3	-10.03	<0.001*
		4	-12.73	<0.001*
	2	1	8.5	<0.001*
		3	-1.53	0.214
		4	-4.23	0.079
	3	1	10.03	<0.001*
		2	1.53	0.214
		4	-2.7	0.104
	4	1	12.73	<0.001*
		2	4.23	0.079
		3	2.7	0.104

*p value significant ($p < 0.05$) at 95% Confidence interval (CI); 1 = Baseline activity, 2 = Mild severity, 3 =Moderate severity, 4 = Severe infection

Correlation of CRP with other inflammatory markers - By multiple regression analysis

Among all inflammatory markers only IL6 and CRP are well correlated with disease severityas shown in Table 4 but after multiple regression analysis it is found that the CRP concentration wasnot well correlation with other inflammatory markersin different severity of COVID 19 infection as shown in Table 5.

Table 5: Multiple linear regression analysis showing significance of dependence of the CRP (mg/ml) on other inflammatory markers in different stages of COVID 19 patients.

Dependent factor	Predictor factors	Mild illness			Moderate illness			Severe illness		
		Standardized beta coefficients	T	Significance	Standardized beta coefficients	T	Significance	Standardized beta coefficients	T	Significance
CRP (mg/ml)	IL6 (pg/ml)	0.066	0.716	0.104	0.118	0.343	0.448	0.910	0.179	0.096
	Ferritin (µg/ml)	5.76	3.39	0.62	4.10	0.23	2.51	5.23	0.43	1.25
	LDH activity (IU/L) at 37^0C	4.72	0.01	0.749	3.65	0.053	0.552	0.003	0.822	0.056
	D-Dimer (µg/ml)	0.001	0.681	0.247	0.291	0.995	0.476	0.826	0.048	0.253
	PCT (ng/mL)	1.034	0.485	0.577	1.171	0.374	0.758	0.819	0.497	0.308

Discussion

The outbreak of COVID-19 disease is an emerging global health threat. The healthcare workers are facing challenges in reducing the severity and mortality of COVID-19 across the world. COVID-19 presents with a wide range of symptoms. The spectrum of disease is variable, with majority cases being mild and self-limiting. However, the disease can be fatal with development of severe pneumonia progressing to acute respiratory distress syndrome and multi-organ failure.[3] For the patients who develop these life threatening conditions, timely identification and intervention is necessary to reduce mortality and hospital stay. Circulatory biomarkers which depict inflammation can be used to assess the disease severity and a possible predictor of progression of disease. So, we conduct the study and Our result has demonstrated that IL-6 is significantly elevated in COVID-19 patients. Several previous studies have found that serum IL-6 concentration is increased in patients with SARS CoV2 infection.[11,12]

During viral infection, IL-6 secreted from local lesion and then induces the differentiation of native CD4 into Th17 cells, which are important for the defence against viruses. In addition, there is synergic interaction between IL-6 and IL-7 and IL-15 to induce the differentiation and catalytic ability of CD8 T cells which is important in the response against viral infections. [13] IL6 induces foam cell formation, the release of further inflammatory cytokines, and chemotaxis.[14]

The present study is also found that the activity of LDH is increased significantly in these patients. Other studies also suggest the similar finding.[15,16]LDH is an enzyme involved in anaerobic glycolysis found in cytoplasm and present almost all tissue and its elevation suggests tissue injury that occurs due to low oxygenation.

The ferritin level of present study in COVID-19 patients, is significantly increased than healthy persons. The finding is well corroborate with another study [17] and this is possibly due to secondary hemophagocytic lymphohistiocytosis and cytokine storm. [17,18]

Likewise, the serum level of CRP was also elevated significantly in patients when compared with the healthy group. A significant increase of CRP was found with levels on average 20 to 50 mg/L in patients with COVID-19 in several previous studies.[2,19,20] CRP is a type of protein produced

by the liver that serves as an early marker of infection and inflammation.[21]

Another inflammatory marker procalcitonin level is significantly increased in the patient. Practically, all the PCT formed in thyroid C cells that is formed under several non-inflammatory stimuli, are converted to calcitonin within the cell, so that no PCT is released into the circulation. Hence, the PCT level in healthy subjects is very low (0.05 ng/mL) but the inflammatory release of PCT from adipocyte is independent of the above regulations. During inflammation, PCT is produced mainly by two alternative mechanisms; direct pathway induced by lipopolysaccharide (LPS) or other toxic metabolite from microbes and indirect pathway induced by various inflammatory mediators like IL-6, TNF-α, etc. [22]

Significantly elevated D-dimer levels are seen in patients with COVID-19 patients and this finding is well corroborated with several previous findings.[23,24] Elevated levels of D-dimer indicate increased risk of abnormal blood clotting, and D-dimer assays are commonly used in clinical practice to exclude a diagnosis of venous thromboembolism. Elevated levels of D-dimer were also found to be related with higher mortality rate of community-acquired pneumonia.[25] Patients with severe community-acquired pneumonia had significantly higher D-dimer levels, and D-dimer within normal range indicated low risk for complications.[26] In a mouse model of SARS-CoV disease, it was shown that augmented activity of urokinase could cause hyperfibrinolysis, by increasing cleavage of plasminogen into the active plasmin and finally lead to diffuse alveolar damage and acute lung injury.[27] A virus infection may develop into sepsis and induce coagulation dysfunction. Hence, in addition to venous thromboembolism, D-dimer might be a manifestation of severe virus infection. Moreover, the increase of 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.[18,19] Our study also reflected similar finding showing D-dimer to be a sensitive predictor of mortality next to IL-6.

Then we performed Pair wise multiple comparison within the case group according to severity and it became evident that though IL6, ferritin, LDH, D-Dimer and CRP concentration was significantly increased in cases compared to control but only IL6 and CRP are well correlated with disease severity. Then after multiple regression analysis, it is found that the CRP concentration was not well correlation with other inflammatory markers in different severity of COVID 19 infection.

Conclusion

Compared to other inflammatory markers, we found that only serum IL6concentration was significantly associated withCOVID-19 severity. Therefore, IL6 on admission represents a simple and independent factor that can be useful for early detectionofCOVID-19 severity and thereby facilitates the guidance of treatment decisions

References

1. World Health Organization. (2020). Coronavirus disease 201 (COVID-19): situation report, 106. World Health Organization. https://apps.who.int/iris/handle/10665/33206
2. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020; 395: 507–513.
3. Ciccullo A, Borghetti A, Dal Verme LZ, Tosoni A, Lombardi F, Garcovich M, et al. Neutrophil-to-lymphocyte ratio and clinical outcome in COVID-19: A report from the Italian front line. Int J Antimicrob Agents. 2020;56(2):106017.
4. Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. Clin Infect Dis. 2020;71(15):762- 768.
5. Huang I, Pranata R, Lim MA, Oehadian A, Alisjahbana B. C-reactive protein, procalcitonin, D-dimer, and ferritin in severe coronavirus disease-2019: A meta-analysis. Ther Adv Respir Dis 2020; 14:1-14.
6. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID19: consider cytokine storm syndromes and immunosuppression. Lancet 2020; 395: 1033– 1034.
7. Devang N, Sreelatha S, Mamatha B. V. Assessment of inflammatory markers and their association with disease mortality in severe COVID-19 patients of tertiary care hospital in South India. The Egyptian Journal of Bronchology. 2022; 16:55
8. Szarpak L, Ruetzler K, Safejko K, Hampel M, Pruc M, Kanczuga-Koda L Krzysztof Jerzy Filipiak KJ, Jaguszewski MJ. Lactate dehydrogenase level as a COVID-19 severity marker. Am J Emerg Med. 2021; 45:638–639.
9. WHO COVID-19: Case Definitions Updated in Public health surveillance for COVID-19, published 16 December 2020 WHO reference number: WHO/2019-nCoV/Surveillance_Case_Definition/2020.2. https://apps.who.int/iris/rest/bitstreams/1322790/retrieve.
10. AIIMS/ ICMR-COVID-19 National Task Force/ Joint Monitoring Group (Dte.GHS) Ministry of Health & Family Welfare, Government of India. Clinical guidance for management of adult covid-19 patients Revised on 14/01/2022 https://www.icmr.gov.in/pdf/covid/techdoc/COVID Clinical Management 14012022.pdr

11. Zhu Z, Cai T, Fan L, Lou K, Hua X, Huang Z, Gao G. Clinical value of immune-inflammatory parameters to assess the severity of coronavirus disease 2019. Int J Infect Dis. 2020; 95:332-9
12. Huang L, Zhao X, Qi Y, Li H, Ye G, Liu Y, Zhang Y, Gou J. Sepsis-associated severe interleukin-6 storm in critical coronavirus disease 2019. Cellular Molecular Immunol 2020; 17:1092–1094.
13. Velazquez-Salinas L, Verdugo-Rodriguez A, Rodriguez LL, Borca MV. The role of interleukin 6 during viral infections. Front Microbiol 2019; 10:1057.
14. Hashizume, M. Outlook of IL-6 signaling blockade for COVID-19 pneumonia. Inflamm. Regen. 2020; 40:24.
15. Al Ghamdi M, Alghamdi KM, Ghandoora Y, Alzahrani A, Salah F, Alsulami A, Bawayan MF, Vaidya D, Perl TM, Sood G. Treatment outcomes for patients with Middle Eastern respiratory syndrome coronavirus (MERS CoV) infection at a coronavirus referral center in the Kingdom of Saudi Arabia. BMC Infect Dis. 2016; 16:1-7.
16. Choi KW, Chau TN, Tsang O, Tso E, Chiu MC, Tong WL, et al. Outcomes and prognostic factors in 267 patients with severe acute respiratory syndrome in Hong Kong. Ann Int Med 2003; 139:715-23.
17. Kadhim AS, Abdullah YJ. Serum Levels of Interleukin-6, Ferritin, C-Reactive Protein, Lactate Dehydrogenase, D-Dimer, and Count of Lymphocytes and Neutrophils in COVID-19 Patients: Its Correlation to the Disease Severity. Biomedical and Biotechnology Research Journal 2021;5(1) 69-73.
18. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, HLH Across Speciality Collaboration. COVID-19: Consider cytokine storm syndromes and immunosuppression. Lancet (London, England) 2020;395:1033.
19. Gao Y, Li T, Han M, Li X, Wu D, Xu Y, Zhu Y, Liu Y, Wang X, Wang L. Diagnostic utility of clinical laboratory data determinations for patients with the severe COVID-19. J Med Virol. 2020.
20. Mo P, Xing Y, Xiao Y, Deng L, Zhao Q, Wang H, Xiong Y, Cheng Z, Gao S, Liang K, Luo M, Chen T, Song s, Ma Z, Chen X, Zheng R, Cao Q, Wang F, ZhangY. Clinical characteristics of refractory COVID-19 pneumonia in Wuhan, China. Clin Infect Dis. 2020.
21. Marnell L, Mold C, Du Clos TW. C-reactive protein: ligands, receptors, and role in inflammation. Clin Immunol. 2005;117(2):104-111.
22. Vijayan AL, Vanimaya, Ravindran SS, R. Saikant, S. Lakshmi, R. Kartik and Manoj. G. Procalcitonin: a promising diagnostic marker for sepsis and antibiotic therapy. Journal of Intensive Care 2017; 5:51.
23. Zhang L, Yan X, Fan Q, Liu H, Liu X, Liu Z, Zhang Z. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. J Thromb Haemost. 2020; 18:1324–9.
24. Yao Y, Cao J, Wang Q, Shi Q, Liu K, Luo Z, Chen X, Chen S, Yu K, Huang Z, HuB. D-dimer as a biomarker for disease severity and mortality in COVID-19 patients: a case control study. J Intensive Care. 2020; 8:49.
25. Querol-Ribelles JM, Tenias JM, Grau E, Querol-Borras JM, Climent JL, Gomez E, Martinez I. Plasma d-dimer levels correlate with outcomes in patients with community-acquired pneumonia Chest. 2004; 126:1087–92.
26. Snijders D, Schoorl M, Schoorl M, Bartels PC, Vander Werf TS, Boersma WG. D-dimer levels in assessing severity and clinical outcome in patients with community-acquired pneumonia. A secondary analysis of a randomised clinical trial Eur J Intern Med. 2012; 23:436–41.
27. Gralinski LE, Bankhead A 3rd, Jeng S, Menachery VD, Proll S, Belisle SE, et al. Mechanisms of severe acute respiratory syndrome coronavirus-induced acute lung injury mBio. 2013;4: e00271–13.
28. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy J Thromb Haemost. 2020; 18:1094–9.
29. Li XY, Du B, Wang YS et al. The key points in treatment of the critical coronavirus disease 2019 patient (1). Chinese journal of tuberculosis and respiratory disease 2020;43: E026.