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Research Article

Role of Inflammatory Markers in Predicting Severity and Outcome in COVID-19 Patients Attending a Tertiary Care Institute of Tamil Nadu

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A B S T R A C T

Background: Severe acute respiratory syndrome Coronavirus 2 (SARS-COV 2) infection elicits an inflammatory response which is responsible for severe clinical manifestations, disease progression and, poor outcomes.

Objectives: This study aims to assess the pattern of elevation of inflammatory markers in COVID-19 and to determine their association with clinical, radiological severity and outcome of COVID 19.

Methodology: This is a retrospective single-center cross-sectional study conducted at Chettinad Hospital and Research Institute, a tertiary care Hospital in Tamil Nadu, India, encompassing a cohort of 1220 patients. The source population was all cases of COVID-19 admitted at the hospital with a confirmed diagnosis of COVID-19 using RT PCR. The data was obtained from the patient's case sheets and laboratory investigations and from the electronic data management system. The patient's clinical severity on admission, baseline characteristics, co-morbid illnesses, presenting complaints, vitals, and inflammatory markers like D-dimer, C-reactive protein IL-6, Serum ferritin, and Lactate dehydrogenase were collected. The data for radiological severity and outcome were coded and analysed.

Results: Diabetes and hypertension were found to be the most common comorbidities in the study population; females more affected than males. Fever and cough are the most common presenting symptoms. The clinical severity of patients was found to have a significant association with radiological severity. D-dimer is having a strong correlation with disease severity and outcome at any point in time. IL-6, CRP, Serum ferritin also showed a strong correlation with outcome in COVID-19.

Conclusion: Our study suggests D-dimer at any point of time in a hospitalized COVID-19 patient as a promising marker for the same. IL-6 is the next best inflammatory marker followed by CRP and Serum ferritin. LDH is the least significant one among these.

Keywords: COVID 19, SARS COV2, D-Dimer, C-reactive protein, IL-6, serum ferritin, Lactate dehydrogenase

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS CoV2) pandemic reached India on 30 January 2020. As of October 2021, India reported more than three crore cases with more than four lakh fatalities.[1] The clinical presentation of SARS CoV2 varies from asymptomatic carriers to severe viral pneumonia-causing respiratory failure, acute respiratory distress syndrome, sepsis, multi-organ dysfunction syndrome and, death.[2] Though we are at the rear end of the pandemic, we know that we are not going to eradicate the disease and this disease is going to stay in the face of the earth in endemic proportions for a few more years.

During the pandemic phase, we witnessed many people were undergoing high-resolution Computed Tomography Chest for assessing the severity of the disease as we were not sure about the predictors of disease progression or severe disease. These practices lead to unnecessary radiation exposure and overzealous and inappropriate treatment for even mild cases of COVID-19. Our attempt with this study is to retrospectively determine inflammatory markers of disease progression and to correlate the same with severity and outcome of the disease. In the future, these readily available serum markers may help us in determining the need for HRCT chest imaging in patients.

Materials and Methods

Study Setting, Design and Population

This is a retrospective single-center cross-sectional study conducted at Chettinad Hospital and Research Institute, a tertiary care Hospital in suburban Tamil Nadu, India encompassing a cohort of 1220 patients. The source population was all cases of COVID-19 admitted at Chettinad Hospital and Research Institute with a confirmed diagnosis of COVID-19 using RT PCR.

Eligibility Criteria

All COVID-19 patients who were COVID RT PCR (reverse transcriptase-polymerase chain reaction) positive and on treatment and follow-up at Chettinad Hospital and Research Institute with complete baseline and laboratory data.

Data Collection Procedures and Quality Assurance

The data was obtained from the patient's case sheets, laboratory investigations were collected from the electronic data management system. Data consistency and completeness was checked before coding and analyzing the data

Statistical Analysis

All the data collected were coded and entered in a Microsoft Excel sheet which was re-checked and analyzed using SPSS statistical software version 25. Quantitative variables were presented as mean and standard deviation (SD) if the data were normally distributed and by using median and interquartile range if data showed skewed distribution. Categorical variables were represented using frequency and percentage. Statistical testing of association of various factors was done using Pearson chi-square test and independent-sample t-test in case of normally distributed data and using Mann-Whitney test in case of the skewed distribution of data. A p-value of < 0.05 was considered statistically significant.

Ethical Consideration

The study was conducted after obtaining ethical committee clearance from Chettinad Hospital and Research Institute, Institutional review board, and Institutional Human Ethics Committee. The patient's identity and personal details were protected and the study had no negative consequence on patients who participated.

Results

1220 patients were enrolled in the study, the majority of the study participants were under 70 years of age (72%) and males (70%) only 28% were more than 70 years. The mean age of the study population was 49.22 ± 0.48 years. In the study group, 34% had diabetes with the mean duration of 32 ± 67.40 months, 28% had hypertension with the mean duration of 24.17 ± 55.84 months, and 30 patients had chronic kidney disease, with a mean duration of 1.98 ± 0.16 months. 43% percentage of chronic kidney disease patients were on hemodialysis with a mean duration of 0.49 ± 6.66 months. 3 patients had chronic liver disease and 11 had a history of stroke. 6% had a history of coronary artery disease with a mean duration of 4.74 ± 24.29 months. 38 patients in the study population had a previous pulmonary parenchymal disease in the form of bronchial asthma or chronic obstructive pulmonary disease; 48 patients had a history of hypothyroidism (Table 1).

Table 1.Characteristics of Study Subjects (N=1220)

Mean	49.22 ± 0.48
Median	50
<20 years	3%
21-30 years	15%
31-40 years	16%
41-50 years	16%
51-60 years	22%
>70 years	28%
Female	367 (30%)
Male	853 (70%)
Diabetes mellitus	417 (34%)
Duration of DM	32 ± 67.40

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Hypertension	344 (28%)
Duration of hypertension	24.17 ± 55.84
Chronic kidney disease	30 (2%)
Duration of chronic kidney disease	1.98 ± 0.16
Duration of HD	0.49 ± 6.66
Cerebrovascular disease	11 (1%)
Duration of cerebrovascular disease	1.99 ± 00
Chronic liver disease	3 (0%)
Duration of chronic liver disease	0.20 ± 4.86
Coronary artery disease	76 (6%)
Duration of CAD	4.74 ± 24.29
Hypothyroidism	48 (4%)
Bronchial asthma/ Chronic obstructive pulmonary disease	38 (3%)

Table 2.Presenting Complaints in COVID-19

Fever	845 (69%)
Duration of fever	2.92 ± 3.20
Cough	664 (54%)
Duration of cough	1.46 ± 0.50
Running nose	429 (35%)
Duration of running nose	0.95 ± 1.67
Myalgia	569 (47%)
Duration of myalgia	1.55 ± 2.43
Anosmia	76 (6%)
Duration of anosmia	0.23 ± 1.08
Breathlessness	363 (30%)
Duration of breathlessness	1.00 ± 2.11
Loose stools	89 (7%)
Duration of loose stools	0.19 ± 0.72
Headache	186 (15%)
Duration of headache	0.50 ± 1.51
Loss of taste	64 (5%)
Duration of loss of taste	0.20 ± 1.08
Duration of hospital stay	8.04 ± 4.59

The common presenting complaints in the study population were fever and cough. 69% presented with fever with a mean duration of 2.92 ± 3.20 days. 54% had a cough with a mean duration of 1.46 ± 0.50 days at the time of presentation. Myalgia (47%), running nose (35%), breathlessness (30%) were the next common symptoms. Anosmia (6%), loose stools (7%), headache (15%), loss of taste (5%) were the least common symptoms (Table 2). The mean pulse rate in the study population was 87.91 ± 10.61 per minute. The mean respiratory rate in the study population was 21.77 ± 4.10 per minute (Table 6). The mean duration of hospital stay was 8.04 ± 4.59 days (Table 2).

Table 3.Clinical severity and HRCT severity

Clinical severity	Number (%)	HRCT severity	Number (%)
Non-severe	794 (65%)	Mild	651 (54%)
Severe	158 (13%)	Moderate	325 (27%)
Critical	268 (22%)	Severe	232 (19%)

Table 4.Outcome in COVID-19

	Outcome	Percentage
Asymptomatic	959	79%
Mild symptoms	16	1%
Moderate symptoms	40	3%
Death	205	17%

65% had a non-severe disease, 13% had severe disease and 22% had critical disease based on clinical severity criteria by WHO (Table 3). It was found that 54% had mild involvement, 27% had moderate involvement and 19% had severe involvement in high resolution computed tomography of the chest (Table 4).

Table 5.Mean of Different Variables Used in Study

Variable	Mean±SD
Pulse Rate	87.91 ± 10.61
Respiratory rate	21.77 ± 4.10
D-Dimer Day 1	466.33 ± 667.33
D-Dimer Day 3	658.62 ± 995.63
D-Dimer Day 5	594.64 ± 878.53
D-DIMER Day7	989.47 ± 1214.49
D-DIMER Day 9	824.58 ± 1051.01
IL-6 Day 1	69.98 ± 216.23
IL-6 Day 3	35.33 ± 59.62
IL-6 Day 5	32.90 ± 142.13
IL-6 Day 7	67.65 ± 198.66
IL-6 Day 9	91.95 ± 194.75
CRP Day 1	119.40 ± 664.75
CRP Day 3	63.73 ± 49.94
CRP Day 5	58.99 ± 50.47
CRP Day 7	52.64 ± 52.42
CRP Day 9	63.92 ± 56.68
Serum Ferritin Day 1	260.43 ± 278.67
Serum Ferritin Day 3	262.75 ± 213.19

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Serum Ferritin Day 5	338.03 ± 263.80
Serum Ferritin Day 7	410.17 ± 344.50
Serum Ferritin Day 9	440.94 ± 323.23
LDH Day 1	336.03 ± 327.55
LDH Day 3	319.33 ± 203.09
LDH Day 5	315.85 ± 135.93
LDH Day 7	440.27 ± 320.43
LDH Day 9	301.00 ± 105.61

The outcomes of the patient studied showed that 79% percentage recovered completely before discharge or at the time of discharge whereas 1% percentage had mild symptoms on discharge and 3% had moderate symptoms like breathlessness requiring home oxygen therapy. The mortality rate in our study population was 17% (Table 4).

The inflammatory markers which were studied were D-dimer, IL-6 (Interleukin 6), CRP (C - reactive protein), serum ferritin, and LDH (Lactate dehydrogenase). All these inflammatory markers were measured on day one, day three, day five, day seven, and day nine as required. On admission the mean D-dimer was 466.33 ± 667.33 ng/mL; the mean IL-6 was 69.98 ± 216.23 pg/mL, the mean CRP was 119.40 ± 664.75 mg/L, mean LDH was 336.03 ± 327.55 U/L, and mean serum ferritin was 260.43 ± 278.67 ng/mL (Table 5).

Association between Various Inflammatory Markers and Clinical Severity

It was found in our study that D-dimer on day one, day three, day five, day seven, and day nine showed significant association with clinical severity. IL-6 done on day one, day three and day seven showed significant association with

Table 6.Association between Different Inflammatory Markers and Severity and Outcome

Variable	Clinical severity	P value	HRCT chest severity	P value	Outcome	P value
D dimer Day 1	0.320	< 0.01*	0.237	< 0.01*	0.351	< 0.01*
D dimer Day 3	0.435	< 0.01*	0.209	< 0.05*	0.459	< 0.01*
D dimer Day 5	0.464	< 0.01*	0.356	< 0.01*	0.580	< 0.01*
D dimer Day 7	0.417	< 0.01*	0.364	< 0.01*	0.451	< 0.01*
D dimer Day 9	0.334	< 0.01*	0.387	< 0.01*	0.478	< 0.01*
IL6 Day 1	0.252	< 0.01*	0.183	< 0.01*	0.213	< 0.01*
IL6 Day 3	0.500	< 0.01*	0.398	< 0.01*	0.400	< 0.01*
IL6 Day 5	0.156	> 0.05	0.180	< 0.05*	0.406	< 0.01*
IL6 Day 7	0.299	< 0.05*	0.252	> 0.05	0.353	< 0.01*
IL6 Day 9	0.302	> 0.05	0.348	< 0.05*	0.489	< 0.01*
CRP Day 1	0.075	> 0.05	0.086	> 0.05	-0.016	>0.05
CRP Day 3	0.330	< 0.01*	0.344	< 0.01*	0.390	< 0.01*
CRP Day 5	0.301	< 0.01*	0.202	< 0.05*	0.312	< 0.01*
CRP Day 7	0.338	< 0.01*	0.291	< 0.05*	0.470	< 0.01*
CRP Day 9	0.206	> 0.05	0.020	> 0.05	0.410	< 0.01*
Serum ferritin Day 1	0.487	< 0.01*	0.465	< 0.01*	0.341	< 0.01*
Serum ferritin Day 3	0.409	< 0.05*	0.257	> 0.05	0.225	> 0.05
Serum ferritin Day 5	0.392	< 0.01*	0.375	< 0.01*	0.322	< 0.01*
Serum ferritin Day 7	0.209	> 0.05	0.186	> 0.05	0.143	> 0.05
Serum ferritin Day 9	0.299	> 0.05	0.434	< 0.05*	0.086	> 0.05
LDH Day 1	0.380	< 0.01*	0.375	< 0.01*	0.388	< 0.01*
LDH Day 3	0.238	> 0.05	0.456	> 0.05	-0.064	> 0.05
LDH Day 5	0.267	> 0.05	0.186	> 0.05	0.704	< 0.01*
LDH Day 7	0.725	> 0.05	0.622	< 0.05*	0.813	< 0.01*
LDH Day 9	0.295	> 0.05	0.279	> 0.05	0.489	> 0.05
HRCT severity	0.650	< 0.01*				

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clinical severity; whereas IL-6 done on the fifth and ninth day showed no significant association. CRP on day three, day five, day seven showed significant association with clinical severity whereas CRP on day one and day nine had no significant association. Serum ferritin done on day one and day five showed significant association with clinical severity and LDH on day one showed significant association with clinical severity (Table 6).

Association between Various Inflammatory Markers and HRCT Chest Severity

In our study D-dimer done on day one, day three, day five, day seven, and day nine showed significant association with HRCT chest severity. IL-6 done on day one, day three, day five, and day nine showed significant association with HRCT chest severity whereas CRP done on day three, day five, and day seven showed significant association. Serum ferritin done on day one, day five, and day nine showed significant association with HRCT chest severity whereas LDH done on day one and day seven showed significant association (Table 6).

Association between Various Inflammatory Markers and Outcome

In our study, it was found D-dimer done on day one, day three, day five, day seven, and day nine showed significant association with outcome in COVID 19. IL-6 done on day one, day three, day five, day seven, and day nine showed significant association with outcome, whereas CRP done on day three, day five, day seven, and day nine showed significant association. Serum ferritin done on day one, day five showed significant association with outcome whereas LDH done on day one, day five, and day seven only showed significant association (Table 6).

Association between Clinical Severity and HRCT Chest Severity

It was found in our study that clinical severity of the disease assessed using WHO (World Health Organization) criteria had a significant association with the HRCT chest severity (Table 6).

DIMSO Discussion

The overall inflammatory profile in COVID-19 patients in the Indian scenario is not reported so far due to insufficient sample size. Understanding the disease and the markers for predicting severity and poor outcome is vital in implementing prevention and early aggressive treatment.

In our study we included 1220 patients with a mean age of 49.22 ± 0.48 years, it was observed that there is a significant association between inflammatory markers such as D dimer, IL-6, CRP, serum ferritin, and LDH with clinical and radiological severity and outcome in COVID-19. To our knowledge, ours is the largest study from India to date examining inflammatory markers and their correlation with severity and outcome in COVID-19.

In our study 70% of the patient were females, this is in contrast to the study reported by Jin et al. which found that male and female patients had the same prevalence though men were at risk for developing worse outcomes and death.[3] Izcovich et al. also reported male sex being a poor prognostic factor in COVID-19.[4]

The commonest symptoms were fever and cough, which is in alignment with the study done by Leulseged et al.[5] 34% and 28% of the study population had diabetes or hypertension respectively, indicating an increased predisposition of these groups to the disease. Nath et al. also reported diabetes and hypertension as two major comorbidities in COVID-19 patients admitted in both wave in India.[6] Lim et al. reported the possible pathogenic mechanism as hyperglycemia facilitating the replication of SARS COV 2 via the production of mitochondrial reactive oxygen species and activation of hypoxia-inducible factor one alpha.[7] Clark et al. reported that the prognosis for patients with hypertension is worse when the COVID-19 infection is complicated by myocardial disease or myocardial injury.[8]

The mean pulse rate observed in a study was 87.91 ± 10.61 per minute which is contradictory to the study by Capoferri et al. who reported that there is relative bradycardia observed in COVID-19 patients; about 36% of the COVID-19 patients and even 56% of hospitalized COVID-19 patients with fever had relative bradycardia.[9] They reported that the pathogenesis of this phenomenon is unknown, the direct effect of the pathogen on the sinoatrial node, or the effects of inflammatory cytokines like IL-6 are among the few proposed mechanisms for this.

The mean respiratory rate in our study population was 21.77 ± 4.10 per minute. Chatterjee et al. reported that a respiratory rate of more than 22 per minute or hypoxemia with a saturation of less than 92% room air was associated with elevated mortality in COVID-19.[10] The mean duration of hospital stay in patients with COVID-19 in our study was 8.04 ± 4.59 days. Rees et al. reported in September 2020 meta-analysis that mean hospital stay duration in China ranged from 4 to 53 days whereas it ranged from 4 to 21 days outside China.[11] The difference in the criteria for admission and discharge will contribute to the duration of hospital stay in addition to the severity of the disease.

In our study, 65% had the non-severe disease and only 22% had the critical disease as per clinical severity criteria by WHO. Ariel Izcovich et al reported that patients who presented with clinical signs and symptoms suggestive of respiratory failure were at high risk for developing severe COVID-19 or death.[4] In our study, 19% had severe involvement in radiological imaging. Saeed et al. reported

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that HRCT Chest severity score is positively correlated with length of hospital stay, inflammatory laboratory markers, and oxygen requirement in patients with COVID-19 infection.[12]

In our study, 79% of patients recovered completely at the time of discharge whereas the mortality rate was 17%. In the study, we did not focus on clinical outcomes with respect to clinical severity, or radiological severity, or inflammatory markers. The mortality rate in our study population is higher compared to the National standards as this study is conducted in a tertiary care center that was a referral center in the pandemic.

D-dimer is a fibrin degradation product that is widely used as a marker for thrombotic disorders. In the emergency room, the most common cause of D-dimer elevation is still infection and during COVID-19 pandemic this was identified as a potential indicator of prognosis. The mean D-dimer on admission in our study population was 466.33 ± 667.33 ng/mL, Yu et al. reported the mean D-dimer in patients with COVID-19 as 0.9 to 4.6 µg/mL and he concluded after analysis that elevated D-dimer is associated with severe disease on COVID-19.[13] Poudel et al. reported admission day D-dimer of more than 1.5 µg/ml as an important predictor of mortality in COVID-19 patients.[14] In our study, we have serially done D-dimer on day three, day five, day seven, and day nine and found that all these showed significant association with clinical severity, radiological severity, and outcome in COVID 19. Our study suggests that among all the inflammatory markers D-Dimer done at any point of time in a COVID-19 patients is significant and hence it's best among the inflammatory markers to predict severity and outcome of the disease. Conte et al.[15] reported an increase in the value of the D-dimer as the most sensitive change in coagulation parameters in COVID-19 and postulated that this may indicate a greater risk for thrombosis. Thachil et al.[16] emphasized the importance of accurate D-dimer reporting in COVID-19. Ours is a pioneer study that reports persistently elevated D-dimer and not just admission D-dimer as a predictor for progression and severity in COVID-19.

In our study, IL-6 on admission, day three, and day seven showed significant association with clinical severity whereas IL-6 on admission, day three, day five, and day nine showed significant association with radiological severity. IL-6 done on day one, day three, day five, day seven, and day nine showed significant association with outcome in COVID-19. Grifoni et al. supported the pivotal role played by pro-inflammatory cytokines in the pathophysiology of pulmonary damage in COVID-19 patients. They suggested IL-6 levels at hospital admission to be a good prognosticator for outcome in COVID-19.[17] Santa Cruz et al reported that a decreasing IL-6 after admission indicate recovery.[18] From our study, we can say that the persistently elevated IL-6 in hospitalized COVID-19 patient indicates a bad outcome.

The mean IL-6 in our study population on admission was 69.98 ± 216.23 pg/mL. Sabaka et al. studied that the concentration of IL-6 more than 24 pg/mL on admission can be used as a sensitive marker for the development of hypoxia requiring hospitalization.[19] Our study aligned with the study by Bhandari et al. reported that radiological severity of COVID-19 disease correlated directly with IL-6 patients with higher HRCT severity scores had extremely raised IL-6 levels whereas low HRCT severity score had low IL-6.[20]

In our study the mean CRP was 119.40 ± 664.75 mg/L. CRP on day three, day five, and day seven showed significant association with clinical severity whereas CRP on day three and day seven showed significant association with radiological severity. CRP done on day three, day five, day seven, and day nine showed a significant association with outcome in COVID-19. Ali et al. observed a significant increase in CRP 20 to 50 mg/L in patients with COVID-19 and noted that CRP was elevated in up to 86% in severe COVID-19.[21] In our study, we noted that CRP on admission may not be a good predictor of disease progression or mortality. But subsequent CRP's are needed to predict the disease severity. Luan et al. reported that CRP induction is principally regulated by IL-6 at transcription level which may be the reason for this delayed elevation.[22] CRP is normally lacking in viral infection but its role is pivotal in COVID-19 since innate immunity is essential for COVID-19 virus clearance.

Ferritin is an important mediator of immune regulation and hyperferritinemia is known to be a contributing factor for cytokine storm which is reported to have fatal outcomes in COVID-19. In our study, the mean ferritin on admission was 260.43 ± 278.67 ng/mL. Manuel Vargas-Vargas et al reported that the very severe COVID-19 group had significantly high serum ferritin (1006.16 ng/ml) than the severe COVID-19 group (291.13 ng/ml).[23] We found that serum ferritin done on day one, day three, and day five showed significant association with clinical severity, whereas day one, day five, and day nine showed significant association with radiological severity: day one and day five showed significant association with outcome in COVID-19. This is in contrast to the study by Carubbi F et al. who reported for the first time that ferritin levels over the 25th percentile were associated with severe radiological involvement but not with disease outcome.[24]

Lactate dehydrogenase is a less commonly used inflammatory marker in COVID-19 and, in our study, admission LDH showed significant association with clinical severity whereas admission as well as day seven LDH showed significant association with radiological severity

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in COVID-19. LDH done on day one, day five, and day seven showed significant association with outcome in COVID-19 in our study population. Szarpak L et al. reported a mean LDH of 154.49 U/L in COVID-19 and observed LDH as a COVID-19 severity marker and predictor for survival whereas in our study mean LDH was noted as 336.03 ± 327.55 U/L.[25]

We also observed a significant association between clinical severity and radiological severity in COVID-19.

Conclusion

Several inflammatory markers are projected as potential biomarkers to assess the disease progression severity and outcome in COVID-19. Our study suggests D-dimer at any point of time in a hospitalized COVID-19 patient as a promising marker for the same. IL-6 is the next best inflammatory marker followed by CRP and Serum ferritin. LDH is the least significant one among these. It is to be noted that our study suggests a too early CRP may not be a good indicator for disease progression and severity. Further prospective studies are needed to confirm this data.

Limitations

In this study we did not categorize the patients based on clinical severity and compared the mean values of inflammatory markers in each group; this may be carried out separately in a sub-study later. We did not follow up the patients from clinical severity to inflammatory markers and outcome. Moreover, we did not follow up on the progression of inflammatory markers.

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References

1. WHO [Internet]. Emergencies/Coronavirus Disease (COVID-19)/India Situation Report; [cited 2022 Jan 2]. Available from: https://www.who.int/india/emergencies/coronavirus-disease-(covid-19)/india-situation-report.
2. Zaim S, Chong JH, Sankaranarayanan V, Harky A. COVID-19 and Multiorgan Response. Curr Probl Cardiol. 2020 Aug;45(8):100618. [PubMed] [Google Scholar]
3. Jin JM, Bai P, He W, Wu F, Liu XF, Han DM, Liu S, Yang JK. Gender differences in patients with COVID-19: focus on severity and mortality. Front Public Health. 2020 Apr;8:152. [PubMed] [Google Scholar]
4. Izcovich A, Ragusa MA, Tortosa F, Lavena Marzio MA, Agnoletti C, Bengolea A, Ceirano A, Espinosa F, Saavedra E, Sanguine V, Tassara A, Cid C, Catalano HN, Agarwal A, Foroutan F, Rada G. Prognostic factors for severity and mortality in patients infected with COVID-19: A systematic review. PLoS One. 2020 Nov;15(11):e0241955. [PubMed] [Google Scholar]
5. Leulseged TW, Hassen IS, Ayele BT, Tsegay YG, Abebe DS, Edo MG, Maru EH, Zewde WC, Naylor LK, Semane DF, Dresse MT, Tezera BB. Laboratory biomarkers of COVID-19 disease severity and outcome: Findings from a developing country. PLoS One. 2021 Mar;16(3):e0246087. [PubMed] [Google Scholar]
6. Nath R, Gupta NK, Jaswal A, Gupta S, Kaur N, Kohli S, Saxena A, Ish P, Kumar R, Tiwari P, Kumar M, Kishore J, Yadav G, Marwein F, Gupta N. Mortality among adult hospitalized patients during the first wave and second wave of COVID-19 pandemic at a tertiary care center in India. Monaldi Arch Chest Dis. 2021 Oct 11. [PubMed] [Google Scholar]
7. Lim S, Bae JH, Kwon HS, Nauck MA. COVID-19 and diabetes mellitus: from pathophysiology to clinical management. Nat Rev Endocrinol. 2021 Jan;17(1):11-30. [PubMed] [Google Scholar]
8. Clark CE, McDonagh STJ, McManus RJ, Martin U. COVID-19 and hypertension: risks and management. A scientific statement on behalf of the British and Irish Hypertension Society. J Hum Hypertens. 2021 Apr;35(4):304-7. [PubMed] [Google Scholar]
9. Capoferri G, Osthoff M, Egli A, Stoeckle M, Bassetti S. Relative bradycardia in patients with COVID-19. Clin Microbiol Infect. 2021 Feb;27(2):295-6.[PubMed] [Google Scholar]
10. Chatterjee NA, Jensen PN, Harris AW, Nguyen DD, Huang HD, Cheng RK, Savla JJ, Larsen TR, Gomez JMD, Du-Fay-de-Lavallaz JM, Lemaitre RN, McKnight B, Gharib SA, Sotoodehnia N. Admission respiratory status predicts mortality in COVID-19. Influenza Other Respir Viruses. 2021 Sep;15(5):569-72.[PubMed] [Google Scholar]
11. Rees EM, Nightingale ES, Jafari Y, Waterlow NR, Clifford S, B Pearson CA, Group CW, Jombart T, Procter SR, Knight GM. COVID-19 length of hospital stay: a systematic review and data synthesis. BMC Med. 2020 Sep;18(1):270. [PubMed] [Google Scholar]
12. Saeed GA, Gaba W, Shah A, Al Helali AA, Raidullah E, Al Ali AB, Elghazali M, Ahmed DY, Al Kaabi SG, Almazrouei S. Correlation between chest CT severity scores and the clinical parameters of adult patients with COVID-19 pneumonia. Radiol Res Pract. 2021 Jan;2021:6697677. [PubMed] [Google Scholar]
13. Yu HH, Qin C, Chen M, Wang W, Tian DS. D-dimer level is associated with the severity of COVID-19. Thromb Res. 2020 Nov;195:219-25. [PubMed] [Google Scholar]
14. Paudel N, Shrestha S, Marasine NR, Khanal P, Aryal S, Erku D, Poudel A. D-dimer as a biomarker for assessment of COVID-19 prognosis: D-dimer levels on admission and its role in predicting disease outcome in

hospitalized patients with COVID-19. PLoS One. 2021 Aug;16(8):e0256744. [PubMed] [Google Scholar]
15. Conte G, Cei M, Evangelista I, Colombo A, Vitale J, Mazzone A, Mumoli N. The Meaning of D-Dimer value in COVID-19. Clin Appl Thromb Hemost. 2021 Jan-Dec;27:10760296211017668. [PubMed] [Google Scholar]
16. Thachil J, Longstaff C, Favaloro EJ, Lippi G, Urano T, Kim PY; SSC Subcommittee on Fibrinolysis of the International Society on Thrombosis and Haemostasis. The need for accurate D-dimer reporting in COVID-19: Communication from the ISTH SSC on fibrinolysis. J Thromb Haemost. 2020 Sep;18(9):2408-11. [PubMed] [Google Scholar]
17. Grifoni E, Valoriani A, Cei F, Lamanna R, Gelli AMG, Ciambotti B, Vannucchi V, Moroni F, Pelagatti L, Tarquini R, Landini G, Vanni S, Masotti L. Interleukin-6 as prognosticator in patients with COVID-19. J Infect. 2020 Sep;81(3):452-82. [PubMed] [Google Scholar]
18. Santa Cruz A, Mendes-Frias A, Oliveira AI, Dias L, Matos AR, Carvalho A, Capela C, Pedrosa J, Gil Castro A, Silvestre R. IL-6 is a biomarker for the development of fatal SARS-CoV-2 pneumonia. Front Immunol. 2021;12:263. [Google Scholar]
19. Sabaka P, Koščálová A, Straka I, Hodosy J, Lipták R, Kmotorková B, Kachlíková M, Kušnírová A. Role of interleukin 6 as a predictive factor for a severe course of Covid-19: retrospective data analysis of patients from a long-term care facility during Covid-19 outbreak. BMC Infect Dis. 2021 Mar;21(1):308.[PubMed] [Google Scholar]
20. Bhandari S, Rankawat G, Singh A, Wadhwani D, Patel B. Evaluation of interleukin-6 and its association with the severity of disease in COVID-19 patients. Indian J Medi Spec. 2020;11(3):132. [Google Scholar]
21. Ali N. Elevated level of C-reactive protein may be an early marker to predict risk for severity of COVID-19. J Med Virol. 2020 Nov;92(11):2409-11. [PubMed] [Google Scholar]
22. Luan Y, Yin C, Yao YM. Update advances on C-reactive protein in COVID-19 and other viral infections. Front Immunol. 2021 Aug;12:720363. [PubMed] [Google Scholar]
23. Vargas-Vargas M, Cortés-Rojo C. Ferritin levels and COVID-19. Rev Panam Salud Publica. 2020 Jun;44:e72. [PubMed] [Google Scholar]
24. Carubbi F, Salvati L, Alunno A, Maggi F, Borghi E, Mariani R, Mai F, Paoloni M, Ferri C, Desideri G, Cicogna S, Grassi D. Ferritin is associated with the severity of lung involvement but not with worse prognosis in patients with COVID-19: data from two Italian COVID-19 units. Sci Rep. 2021 Mar;11(1):4863. [PubMed] [Google Scholar]
25. Szarpak L, Ruetzler K, Safiejko K, Hampel M, Pruc M, Kanczuga-Koda L, Filipiak KJ, Jaguszewski MJ. Lactate dehydrogenase level as a COVID-19 severity marker. Am J Emerg Med. 2021 Jul;45:638-9. [PubMed] [Google Scholar]

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Appendix

WHO Severity Definitions

1. **Critical COVID-19:** Defined by the criteria for acute respiratory distress syndrome (ARDS), sepsis, septic shock, or other conditions that would normally require the provision of life sustaining therapies such as mechanical ventilation (invasive or non-invasive) or vasopressor therapy.
2. **Severe COVID-19:**

- Oxygen saturation < 90% on room air.
- Respiratory rate > 30 breaths/min in adults and children > 5 years old; ≥ 60 breaths/min in children < 2 months old; ≥ 50 in children 2–11 months old; and ≥ 40 in children 1–5 years old.
- Signs of severe respiratory distress (accessory muscle use, inability to complete full sentences, and, in children, very severe chest wall in drawing, grunting, central cyanosis, or presence of any other general danger signs).

3. **Non-severe COVID-19:** Defined as absence of any criteria for severe or critical COVID-19.

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