Original Article

Inflammatory Biomarkers in COVID-19: Associations with Clinical Characteristics and Outcomes among COVID 19 Patients Hospitalized in Sukraraj Tropical and Infectious Disease Hospital

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Abstract

Background: Coronavirus disease (COVID-19) is an infectious disease caused by a newly discovered coronavirus referred to as SARS-CoV-2. Biomarkers has been linked with severity and appears to influence clinical outcomes among COVID-19 patients.

Aims: This study aimed to describe the association of inflammatory biomarkers with clinical characteristics, severity and outcomes among COVID 19 patients in a tertiary tropical and infectious disease hospital in Nepal.

Methods: This was a retrospective observational study where medical and lab records of COVID-19 inpatients (patients tested positive for SARS-CoV-2 via reverse transcriptase-polymerase chain reaction (RT-PCR)) admitted between April 2021 and September 2021 at Sukraraj Tropical and Infectious Disease Hospital, representing the second wave of COVID-19 were reviewed. Medical records of the patients were collected till discharge and inflammatory biomarkers were evaluated in relation to clinical presentations, severity and outcome among patients. Statistical analysis was done using SPSS 23.

Results: A total of 628 COVID-19 confirmed patients admitted in the study period were included in the study, 487 patients (77.5%) improved, 118 (18.8%) expired, and 23 (3.7%) were referred. Severity at presentation was significantly associated with Ferritin (p 0.013), CRP (<0.001), D-dimer levels (0.003) and Neutrophil-to-Lymphocyte ratio (NLR) (<0.001). Fever was found to have significant association with CRP (p<0.001) and ferritin (p 0.004), but not with D-dimer (p 0.587). Non-survivors were found to have significant association with higher ferritin (p <0.001), CRP (p<0.001), D-dimer (p <0.001) and NLR (<0.001). The duration of hospital stay was significantly affected by D-dimer (p 0.001) and CRP levels (p<0.001). Similarly need for mechanical ventilation had significant association with higher levels of Ferritin (p 0.002), CRP (p<0.001), D-dimer (p<0.001) and NLR (<0.001). Serial recordings of D-dimer showed increasing values had significant association with poor outcome (p<0.001).

Conclusion: Higher values of D-dimer, ferritin, CRP and NLR were associated with higher severity of the COVID-19 disease and poor clinical outcomes including higher duration of hospital stay, higher need for mechanical ventilation and morbidity. Early stratification of disease based on biomarkers can guide early intervention to prevent bad outcomes.

Introduction

Corona Virus Disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), since its first detection in Wuhan, China in December 2019 h, spread rapidly worldwide causing pandemic and has imposed severe challenges on healthcare facilities and medical infrastructure.1, 2 Globally as of 1st July 2022, there have been 545,226,550 confirmed cases of COVID-19 including 6,334,728 deaths reported worldwide.3 In Nepal, 979,801 cases and 11952 deaths have been reported to Ministry of Health and Population (MOHP), Nepal as of 3rd July, 2022.4

The inflammatory response plays a critical role in coronavirus disease 2019 (COVID-19) and dysregulated immune response

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and hyperinflammation seem to contribute to cytokine storm and detrimental effects on multiple organs. 5, 6 COVID-19 disease has unpredictable clinical course and can progress rapidly causing fatal complications, and hence possess significant challenges. 7, 8 There has been significant progress in the understanding of the molecular biology of SARS-CoV-2 and a variety of laboratory biomarkers has been identified for early recognition and stratification of patient based on risk. 7, 9 Several studies have documented the association between COVID-19 and circulating levels of C-reactive protein (CRP) , ferritin, interleukin 6 and D-dimer, and have been reported as sensitive marker of acute disease and severity and predictor of poor outcome.5, 7, 9-14 Further, critically ill patient groups were found to present progressive decrease of biomarkers on serial laboratory measurements during hospitalization and associated with a high incidence of clinical complications. 15

Sukraraj Tropical and Infectious Disease Hospital (STIDH) has been playing a pivotal role in treating a major proportion of COVID-19 patients in Nepal. This retrospective observational study aimed to determine the level of inflammatory biomarkers – CRP, Ferritin and D dimer, and Neutrophil to Lymphocyte Ratio (NLR) among patients admitted with COVID-19 disease and evaluate their association with clinical features, severity, and outcome.16Similarly , changes in CRP and NLR results from inflammatory processes occurring due to overreacting immune system and surge of cytokines. 17 Blood hypercoagulability is common among hospitalized COVID-19 patients.18 D-dimer represents the activation of coagulation and fibrinolysis systems and pathological episodes such as excessive inflammation (cytokine storm, endothelial, and macrophage activation), diffuse intravascular coagulation (DIC), immobilization, hypoxia secondary to excessive lung injury in COVID-19 can result in coagulopathy and increased levels of D-dimer. 14, 19

As a central tropical and infectious disease hospital in Nepal, experiences of risk stratification to predict severe disease associated with COVID 19 based on biomarkers can help describe situational awareness and can help in identification and management of patient at high risk and can help stratifications in other pandemics as well.

Materials and Methods

2.1. Study Design and Participants

This was an investigator-initiated, single centered hospital based, retrospective cohort study. In this study, we recruited a total of 628 patients who were positive for COVID 19 by real-time reverse transcription polymerase chain reaction (RT-PCR) assay and admitted for COVID-19 to Sukraraj Tropical and Infectious Disease hospital in Kathmandu, Nepal, between April 2021 and September 2021.

2.2. Data Collection

Medical and lab records of reverse transcriptase Polymerase chain reaction (RT-PCR) positive COVID-19 inpatients, admitted between April 2021 to July 2021, representing second wave of COVID -19 in Nepal caused by the Delta strain were explored. Data regarding clinical, epidemiological and laboratory parameters including Ferritin, D-dimer CRP and NLR, Length of Hospital stay and Outcome were extracted into Data Collection Sheet.

COVID-19 cases were classified into the following categories based on severity:20

Asymptomatic or pre-symptomatic infection: Individuals who test positive for SARS-CoV-2 using a virologic test (i.e., a nucleic acid amplification test or an antigen test) but who have no symptoms that are consistent with COVID-19.

Mild illness: Individuals who have any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but who do not have shortness of breath, dyspnoea, or abnormal chest imaging.

Moderate illness: Individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have peripheral capillary saturation of oxygen (SpO2) ≥ 94% on room air at sea level.

Severe illness: Individuals who have SpO2 < 94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) < 300, respiratory frequency >30 breaths/min, or lung infiltrates >50%.

Critical illness: Individuals who have respiratory failure, septic shock and/or multiple organ dysfunctions.

All RT-PCR positive COVID-19 patients, meeting inclusion and exclusion criteria were taken into study. So, there were no selection bias. All the medical records were explored to extract all data of patients. However missing data could have caused information bias.

2.3. Ethics

The study was conducted after approval from the Ethical Review Board of Nepal Health Research Council (Reference number 67, date of approval—24 July 2022) and permission was taken from the hospital director to include medical records of the inpatients of Sukraraj Tropical and Infectious Disease Hospital. The requirement for taking consent was waived off by the ethical review board, this study being a retrospective study and data analysis done anonymously. The study was conducted according to the principles expressed in the Declaration of Helsinki, and the results are reported according to the strengthening the reporting of observational studies in epidemiology (STROBE) guideline

2.4. Statistical Analysis

Reporting of baseline characteristics was done as Medians and interquartile ranges (IQRs) for continuous variables and as counts and percentages for Categorical variables. Kruskal-Wallis test was used for continuous variable and Chi squared tests for comparison across groups. p-values were tabulated with a level of significance set at <0.05. All data were analysed using IBM Statistical Packages for Social Sciences (SPSS), version 23.0 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.).

Results

3.1. Clinical characteristics

Over the period of 6 months from April 2021 to September 2021, 628 patients COVID-19 positive by RT-PCR, who fulfilled our inclusion and exclusion criteria were included in the study.

Among 628 patients admitted, D-dimer, ferritin and C Reactive Protein levels at admission were available for 593 (94.4%), 478 (76.11%) and 434(69.11%) patients respectively.

3.1.1 Gender

Out of 628 admissions, 399(63.5%) were male patients and 229(36.5%) were female. Median age of presentation was 50 years (IQR 40-62).

Age wise distribution of biomarkers is presented in Table 1. D-dimer, CRP and NLR showed statistically significant association with the

age, but ferritin didn't show significant association.

Table 1: Age wise distribution of Biomarkers

Values Median (IQR)	Age Group				p - value
	<40 (n=153)	40-59 (n=275)	60-79 (n=168)	≥80 (n=32)	
D-dimer (mcg/ml)_	0.4 (0.2-0.69)	0.45 (0.2-0.98)	0.62 (0.3-1.21)	0.65 (0.26-1.62)	0.001
CRP (mg/L)	34 (12-61.77)	56 (15.96-104.4)	52.54 (23-105.53)	62.8 (34.34-109.79)	0.003
Ferritin (mcg/L)	340 (165-645.5)	340 (178-636)	340 (158-560)	325.09 (148-523.5)	0.929
NLR	3.6 (2.2-6.62)	5.33 (2.61-8.8)	5.33 (2.6-11)	6.30 (2.97-13.14)	0.002

Level of D-dimer, CRP, ferritin and NLR ratio and gender has no statistically significant association. (Table 2)

Table 2. Biomarker Levels and Sex

Values Median (IQR)	Male	Female	p-value
D-dimer (mcg/ml)	0.45(0.21-0.94)	0.46(0.25-1.0)	0.545
CRP (mg/L)	50(22.4-102)	42(13-91)	0.098
Ferritin (mcg/L)	340(168.5-680)	321(165-560)	0.134
NLR	5.06(2.48-8.95)	4.11(2.4-8.6)	0.143

3.1.2 Disease Severity

Of the total patients, majority, 435 (69.3%) patients presented as severe disease, 136(21.7%) presented as moderate disease, 31(4.9%) presented as critical disease while 26(4.1%) presented as mild. Association of levels of biomarkers with severity is presented in Table 3.

Table 3. Biomarker levels and Severity at presentation

	Mild	Moderate	Severe	Critical	p-value
D-dimer (mcg/ml)	0.30 (0.14-0.45)	0.42 (0.23-0.65)	0.47 (0.21-1.09)	0.95 (0.42-2.80)	0.003
CRP (mg/L)	22.42 (4.6-73.3)	32 (9.31-50)	56 (23-105)	75.18 (34-156)	<0.001
Ferritin (mcg/L)	250 (122-407)	310 (207-503)	340 (165-636.5)	450 (120-860)	0.013
NLR	2.41 (2.0-7.67)	3.18 (2.16-5.15)	5.92 (2.96-9.77)	8.8 (3.9-13)	<0.001

3.1.3 Clinical Presentation

Most common presentations among admitted COVID-19 patients was cough (555(88.4%)), fever 515(82%) and Shortness of breath 509(81.1%). Headache was present in 208 (33.1%) patients, fatigue in 102(16.2%) and diarrhoea in 69(11%) patients. Loss of taste and smell was present in 12.7% (80) and 13.5% (85) patients respectively. Clinical presentation in relation to levels of biomarkers in shown in Table 4.

Table 4. Biomarker levels and Clinical Presentation

		Presence of Symptoms					
		Cough(n)	p- value	Fever (n)	p- value	SOB (n)	p-value
D-dimer (mcg/ml)	<1 (n=468)	411	0.116	385	0.863	371	0.112
	>=1(n=125)	116		102		107	
CRP (mg/L)	≤10 (n=68)	65	0.106	64	>0.001	58	0.875
	11-100 (n=261)	227		217		216	
	>100 (n=105)	90		74		88	
Ferritin (mcg/L)	<500 (n=319)	279	0.837	270	0.004	254	0.116
	>=500 (n=159)	138		117		136	

3.1.4 Comorbidities

The most common comorbidity among admitted COVID-19 patient was Hypertension 152(24.2%), followed by Diabetes 97(15.4%), , Chronic Pulmonary Diseases(62(9.9%), Heart Disease 45(7.2%) and cerebrovascular disease 27 (4.3%).

Comorbidity didn't show significant association with the levels of biomarkers. (Table 5)

Table 5. Biomarker levels and Co-morbidity

Co-morbidities		Values [Median (IQR)]		
		CRP	D-dimer	Ferritin
Diabetes mellitus	Yes	45.24 (15-93.43)	0.45 (0.23-0.97)	340 (156-615)
	NO	50.31 (23-106.09)	0.46 (0.21-0.95)	323.5 (212.7-606)
p-value		0.397	0.876	0.823
Hypertension	Yes	56.0 (21.5-106.8)	0.45 (0.23-0.94)	320 (165-533.5)
	NO	45 (16.5-92.15)	0.45 (0.22-0.97)	340 (165-650)
p-value		0.119	0.703	0.181
Chronic Pulmonary Diseases	Yes	45.0 (28.9-96.26)	0.63 (0.31-0.63)	340 (206-556)
	NO	48.0 (16.55-96.28)	0.45 (0.22-0.94)	340 (164-620)
p-value		0.929	0.069	0.959
Heart Disease	Yes	58.25 (24.47-139.75)	0.45 (0.25-0.81)	340 (151.75-672.25)
	No	45.24 (17.75-93.7)	0.45 (0.23-1.00)	340 (165-602)
p-value		0.337	0.875	0.807

Cerebrovascular Disease	Yes	32.5 (11.61-65.37)	0.57 (0.20-1.01)	340 (230-543)
	No	47.38 (19.01-100)	0.45 (0.23-0.97)	340 (165-615)
		0.240	0.538	0.837

3.1.5. Duration of Hospital Stay

The median duration of hospital stay was 6 days (IQR 4-12 days). Duration of stay had significant association with the levels of biomarkers. (Table 5)

Table 6: Biomarker levels and duration of hospital stay

	Duration of Hospital Stay Median (IQR) Days	p-value
D-dimer(mcg/ml)		
<1	6(4-10)	0.001
≥1	8 (5-15)	
CRP (mg/L)		
≤10	5 (3-9)	0.000
11-100	7 (4-12)	
>100	7 (4-14)	
Ferritin(mcg/L)		
<500	6(4-11)	0.130
>=500	7(4-13)	

3.1.6 Need for Mechanical Ventilation

Among 628 patients, 203 patients required mechanical ventilation. Higher the levels of biomarkers, higher the need for mechanical ventilation.

Table 7: Biomarker levels and Need for Mechanical Ventilation

Values Median (IQR)	Need for Mechanical Ventilation		p-value
	Yes	NO	
D-dimer (mcg/ml)	0.72 (0.32-2.26)	0.43 (0.20-0.83)	<0.001
CRP (mg/L)	67 (30-123)	44.77 (13.0-79.76)	<0.001
Ferritin (mcg/L)	431 (209.5-724)	340 (180-615.44)	0.002
NLR	7.63 (3.5-12.85)	4.15 (2.5-8.4)	<0.001

3.1.8 Outcome

Among 628 total admissions, 487 patients (77.5%) improved and were discharged, 118 (18.8%) expired and 23 (3.7%) were referred to super speciality center for further management.

The levels of biomarkers and NLR ratio had statistically significant association with outcome of the patients in terms of mortality. (Table 7)

Table 7: Biomarker Levels and Outcome

Values Median (IQR)	Improved and Discharged	Expired	Total	p-value
D-dimer	0.43 (0.21-0.76)	1.025 (0.39-3.37)	0.45 (0.22-1.00)	<0.001
CRP	39.8 (12.9-73.75)	90.64 (47.5-138.98)	51.32 (19.64-95.43)	<0.001
Ferritin	320 (156-560)	540 (210-800)	340 (165-609.75)	<0.001
NLR	3.75 (2.23-7.7)	8.8 (6.31-13.29)	4.85 (2.48-8.8)	<0.001

Serial D-dimer measurement of 159 patients were available. It showed significant association with the outcome. (Table 8)

Table 8: Serial D-dimer measurement and Outcome

Survivor (n)		Outcome			p-value
		Non-Survivor (n)	Total		
D-dimer	Not increased	93	11	104	<0.001
	Increased	17	38	55	
		110	49	159	

Discussion

COVID-19 disease is characterized by dysregulated immune responses and have an inflammatory pathophysiology involving a cytokine storm, that can lead to organ damage and multi-organ failure (MOF). 5, 13

Clinical Course and progression of Coronavirus Disease 2019 (COVID-19) is found to vary among individuals based on various factors , challenging disease assessment and treatment. 7 Recent progress in the understanding of the molecular biology of SARS-CoV-2 has led to the identification of a variety of laboratory biomarkers that are documented to have association between COVID-19 severity and help in predicting treatment responses. 11, 13, 17

Our study was aimed to identify association of different laboratory biomarkers with severity and outcome among patients, that can help classify patients based on their risk and prognosis and guide prompt treatment. We evaluated the levels of Ferritin, C-Reactive Protein (CRP), D-dimer and Neutrophil to Lymphocyte Ratio (NLR), among others in relation to clinical characteristics, morbidity and mortality among admitted COVID-19 patients in our center.

The level of D-dimer, CRP and NLR in our study showed significant association with age of the patients. This is similar to finding s from other studies which have shown age to be the major determinant of severity and outcome.21-24 There are studies showing association of increasing age with elevated biomarkers. 23, 25. However, our findings didn't suggest ferritin as factor for biomarker variability. Men are found to be more susceptible to COVID-19 than women and are found to be associated with increased severity. 23, 26, 27 Qeadan however reported lower optical cut off values of ferritin and D-dimer in female for invasive ventilator dependence and in hospital mortality.28 Our study didn't find significant association of sex with biomarker levels. There is still insufficient data pertaining effect of sex on biomarkers with some showing increased biomarker in men

and research on gendered impact of biomarkers in COVID-19 may be necessary.

Our study showed that elevated level of ferritin, CRP and D-dimer are associated with increased severity of disease. This is in line with the previous studies, where high level of inflammatory cytokines was associated with severe disease in COVID-19.6, 8-11, 15, 17 We hence believe that early evaluation of biomarkers can facilitate approach to risk stratification, prevention, and treatment. Similarly, NLR was significantly higher in patients with severe disease and could be effective biomarkers in predicting COVID-19.8, 17, 29, 30.Among symptoms, only fever showed significant association with elevated CRP and ferritin. Fever and elevated CRP and ferritin has been described in various entities. 31-33. However, studies regarding association of symptoms with elevated biomarkers in COVID -19 is still lacking.

Elevated Biomarkers and higher NLR at admission were significantly associated with increased duration of hospital stay and increased need for mechanical ventilation in our patients. This has been the scenario in many previous studies. 11, 12, 24, 28. Similarly, elevated levels of biomarkers and high NLR had significantly significant with increased in hospital mortality. Survivors were found to have lower levels of ferritin, CRP and D-dimer. Besides, NLR was significantly higher in non-survivors. (Median (IQR) 8.8(6.31-13.29) vs 3.75(2.23-7.7), p<0.001). Similar findings have been reported in previous studies.11, 12, 16, 17, 21, 27, 28 Figliozzi reported increased risk of in-hospital deterioration and death with increase in D-dimer. 27 A meta-analysis by Huang-et-al also showed that an elevated serum CRP, PCT, D-dimer, and ferritin were associated with a poor outcome in COVID-19.22 Cheng Li also reported higher ferritin level among nonsurvivors. 16 Qeadan et al reported that optimal cut-offs of ferritin (714 ng/mL) and D-dimer (2.1 mg/L) revealed AUCs ≥ 0.99 for in-hospital mortality.28 In line with these studies, Ergenc et al concluded that neutrophil-lymphocyte ratio and C-reactive protein are significantly higher in patients leading to death and could be effective biomarkers in predicting COVID-19 fatality.17

We observed for serial laboratory measurements during hospitalization in our study. Increase in biomarkers were more common in critically ill patient groups and associated with a high incidence of clinical complications. In our study, serial measurement of D-dimer was available for 159 patients. The increase in D-dimer was significantly associated with mortality. This is in line in other previous studies, which showed that gradual increase in D-dimer during the course of disease is associated with disease worsening and mortality. 18, 19, 29. However, since we had measurement for only a fraction of patients available and it might be possibility that D-dimer was measured because of in hospital deterioration, out result is not likely to represent exact scenario. More study on serial monitoring of biomarkers is needed.

This study showed that an elevated serum CRP, D-dimer, ferritin levels and increased NLR are associated with increased severity, in hospital deterioration and death in COVID-19, and may be used in risk stratification for effective control, monitoring and management of COVID-19 in hospitalised patients.

Conclusion

Serum levels of CRP, D-dimers, ferritin and NLR were associated with higher severity of the COVID-19 disease and poor clinical outcomes including higher duration of hospital stay, higher need for mechanical ventilation and mortality. Clinicians should consider level of biomarkers in risk stratification to predict severe and fatal COVID-19 in hospitalised patients.

Limitations of Study

Our study should be interpreted considering following limitations. Since this was a single centered study, the results cannot be generalized. Secondly, there were missing data. Besides, outcome and follow up of referred patients were not analysed in this study. Despite these limitations, to the best of our knowledge, this is the first study from Nepal regarding association of biomarkers with COVID-19 associated presentations and outcomes. Our study represents the second wave of COVID-19 in Nepal, caused by the delta variant of SARS-CoV-2. It might not be applicable to other variants. There still is scarcity of data regarding implication of variants on biomarkers or other organ dysfunctions. Further studies are needed to describe and analyse the clinical course of patients with biomarkers in COVID-19 patients

Conflicts of Interest

The authors declare no conflict of interest.

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References

1. Ochani R, Asad A, Yasmin F, Shaikh S, Khalid H, Batra S, et al. COVID-19 pandemic: from origins to outcomes. A comprehensive review of viral pathogenesis, clinical manifestations, diagnostic evaluation, and management. Infez Med. 2021;29(1):20-36.
2. Majumder J, Minko T. Recent Developments on Therapeutic and Diagnostic Approaches for COVID-19. Aaps j. 2021;23(1):14.
3. WHO. WHO Coronavirus (COVID-19) Dashboard 2022 [Available from: https://covid19.who.int.
4. Ministry of H, Population N. CoVid19-Dashboard 2022 [Available from: https://covid19.mohp.gov.np/.
5. Chen YM, Zheng Y, Yu Y, Wang Y, Huang Q, Qian F, et al. Blood molecular markers associated with COVID-19 immunopathology and multi-organ damage. Embo j. 2020;39(24):e105896.
6. Liu F, Li L, Xu M, Wu J, Luo D, Zhu Y, et al. Prognostic value of interleukin-6, C-reactive protein, and procalcitonin in patients with COVID-19. J Clin Virol. 2020;127:104370.
7. Li BB, Huang SJ, Fu YL, Li ZL, Wang J, Wang JL. Laboratory Biomarkers for the Diagnosis and Management of Patients with COVID-19: an Updated Review. Discov Med. 2021;31(163):61-8.
8. Ponti G, Maccaferri M, Ruini C, Tomasi A, Ozben T. Biomarkers associated with COVID-19 disease progression. Crit Rev Clin Lab Sci. 2020;57(6):389-99.
9. Velavan TP, Meyer CG. Mild versus severe COVID-19: Laboratory markers. Int J Infect Dis. 2020;95:304-7.
10. Zeng F, Huang Y, Guo Y, Yin M, Chen X, Xiao L, et al. Association of inflammatory markers with the severity of COVID-19: A meta-analysis. Int J Infect Dis. 2020;96:467-74.
11. 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;14:1753466620937175.
12. Feld J, Tremblay D, Thibaud S, Kessler A, Naymagon L. Ferritin

levels in patients with COVID-19: A poor predictor of mortality and hemophagocytic lymphohistiocytosis. Int J Lab Hematol. 2020;42(6):773-9.

13. Bivona G, Agnello L, Ciaccio M. Biomarkers for Prognosis and Treatment Response in COVID-19 Patients. Ann Lab Med. 2021;41(6):540-8.
14. Rostami M, Mansouritorghabeh H. D-dimer level in COVID-19 infection: a systematic review. Expert Rev Hematol. 2020;13(11):1265-75.
15. Tjendra Y, Al Mana AF, Espejo AP, Akgun Y, Millan NC, Gomez-Fernandez C, et al. Predicting Disease Severity and Outcome in COVID-19 Patients: A Review of Multiple Biomarkers. Arch Pathol Lab Med. 2020;144(12):1465-74.
16. Cheng L, Li H, Li L, Liu C, Yan S, Chen H, et al. Ferritin in the coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis. J Clin Lab Anal. 2020;34(10):e23618.
17. Ergenç H, Ergenç Z, Dog An M, Usanmaz M, Gozdas HT. C-reactive protein and neutrophil-lymphocyte ratio as predictors of mortality in coronavirus disease 2019. Rev Assoc Med Bras (1992). 2021;67(10):1498-502.
18. Terpos E, Ntanasis-Stathopoulos I, Elalamy I, Kastritis E, Sergentanis TN, Politou M, et al. Hematological findings and complications of COVID-19. Am J Hematol. 2020;95(7):834-47.
19. Düz ME, Balcı A, Menekşe E. D-dimer levels and COVID-19 severity: Systematic Review and Meta-Analysis. Tuberk Toraks. 2020;68(4):353-60.
20. Health NIo. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines [Available from: https://www.covid19treatmentguidelines.nih.gov
21. Du RH, Liang LR, Yang CQ, Wang W, Cao TZ, Li M, et al. Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2: a prospective cohort study. Eur Respir J. 2020;55(5).
22. Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. Bmj. 2020;368:m1091.
23. Brodin P. Immune determinants of COVID-19 disease presentation and severity. Nat Med. 2021;27(1):28-33.
24. Gallo Marin B, Aghagoli G, Lavine K, Yang L, Siff EJ, Chiang SS, et al. Predictors of COVID-19 severity: A literature review. Rev Med Virol. 2021;31(1):1-10.
25. Vakili S, Savardashtaki A, Jamalnia S, Tabrizi R, Nematollahi MH, Jafarinia M, et al. Laboratory Findings of COVID-19 Infection are Conflicting in Different Age Groups and Pregnant Women: A Literature Review. Arch Med Res. 2020;51(7):603-7.
26. Haitao T, Vermunt JV, Abeykoon J, Ghamrawi R, Gunaratne M, Jayachandran M, et al. COVID-19 and Sex Differences: Mechanisms and Biomarkers. Mayo Clin Proc. 2020;95(10):2189-203.
27. Figliozzi S, Masci PG, Ahmadi N, Tondi L, Koutli E, Aimo A, et al. Predictors of adverse prognosis in COVID-19: A systematic review and meta-analysis. Eur J Clin Invest. 2020;50(10):e13362.
28. Qeadan F, Tingey B, Gu LY, Packard AH, Erdei E, Saeed AI. Prognostic Values of Serum Ferritin and D-Dimer Trajectory in Patients with COVID-19. Viruses. 2021;13(3).
29. Bastug A, Bodur H, Erdogan S, Gokcinar D, Kazancioglu S, Kosovali BD, et al. Clinical and laboratory features of COVID-19: Predictors of severe prognosis. Int Immunopharmacol. 2020;88:106950.
30. Yang AP, Liu JP, Tao WQ, Li HM. The diagnostic and predictive role of NLR, d-NLR and PLR in COVID-19 patients. Int Immunopharmacol. 2020;84:106504.
31. Buist NC, Schauer CK. Fever and elevated CRP-related to clozapine dose. Aust N Z J Psychiatry. 2016;50(2):182-3.
32. Nakagama Y, Inuzuka R, Hayashi T, Shindo T, Hirata Y, Shimizu N, et al. Fever pattern and C-reactive protein predict response to rescue therapy in Kawasaki disease. Pediatr Int. 2016;58(3):180-4.
33. Le Turnier P, Bonifay T, Mosnier E, Schaub R, Jolivet A, Demar M, et al. Usefulness of C-Reactive Protein in Differentiating Acute Leptospirosis and Dengue Fever in French Guiana. Open Forum Infect Dis. 2019;6(9):ofz323.