Available online at www.medicinescience.org

ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2022;11(2):457-61

Prediction of mortality at first admission in COVID-19 pneumonia: A retrospective cohort study

Ibrahim Hakki Koker[1], Ismail Yurtsever[2], Omer Uysal[3], Nurlan Huseynov[4], Hakan Senturk[1]

[1]Bezmialem Vakif University, Faculty of Medicine, Department of Gastroenterology, Istanbul, Turkey
[2]Bezmialem Vakif University, Faculty of Medicine, Department of Radiology, Istanbul, Turkey
[3]Bezmialem Vakif University, Faculty of Medicine, Department of Biostatistics, Istanbul, Turkey
[4]Bezmialem Vakif University, Faculty of Medicine, Department of Internal Medicine, Istanbul, Turkey

Received 30 July 2021; Accepted 02 November 2021
Available online 06.03.2022 with doi: 10.5455/medscience.2021.07.237

Abstract

The Coronovirus-19 (COVID-19) pandemic that started in Wuhan, China, at the end of 2019 may cause severe acute respiratory syndrome in some patients. We aimed to investigate the factors that can provide admission mortality prediction in patients with a definite diagnosis of COVID-19. We included patients with radiologically confirmed COVID-19 pneumonia with any significant comorbidities between February 2020-May 2020. We included 129 patients with a mean age of 58 ±15.3 years (range 16-88), 74 (57.4%) men, and of which 27 (21%) died in hospital. Age, aspartate aminotransferase (AST), gamma-glutamyltranspeptidase (GGT), albumin, international normalization ratio (INR), C-reactive protein (CRP), ferritin, d-dimer, and leukocyte levels differed between those who survived and died in the hospital. Multivariable regression showed increased odds of in-hospital death associated with older age (odds ratio 1.09 95% Confidence Interval [CI] (1.021-1.169; p=0.01), and ferritin 1.003 (1.001-1.004; p<0.001) which could help clinicians to identify patients with poor prognosis at an early stage. The area under the receiver operating characteristic curve was 0.886 (95% CI, 0.811-0.939; p<0.0001) for ferritin and 0.763 (95% CI, 0.673-0.85; p<0.0001) for age in differentiating between survived and died in-hospital patients with cutoffs >289,1 ng/mL and >51 years, respectively. Elevated ferritin and advanced age significantly predicted mortality at the first admission in COVID-19 infection. A ferritin cutoff >289 ng/mL had a 100% negative predictive value to differentiate surviving from in-hospital dead patients.

Keywords: COVID-19, ferritin, age, mortality

Introduction

Coronavirus disease 2019 (COVID-19) can cause fatal acute respiratory syndrome (ARDS) via the SARS-CoV-2 hybrid virus [1]. This virus is the cause of the ongoing pandemic affecting millions of people around the world. While most patients survive the disease mildly or asymptomatically, it causes life-threatening and fatal respiratory failure in some. Many studies have shown that COVID-19 affects the respiratory system and other systems and organs such as the heart, liver, and gastrointestinal tract. While the disease may be asymptomatic, an inflammatory cytokine storm begins with macrophage activation and may progress to severe ARDS in some individuals. It has been found that some laboratory parameters vary in studies conducted in patients with a diagnosis of COVID-19. Meanwhile, serum ferritin levels, d-dimer, and some other markers also increase [2,3].

Investigation of hematological and biochemical markers that will predict the severity of the disease in the ongoing pandemic continues. Information on laboratory findings of the disease is still limited. We aimed to determine the factors that can predict mortality of COVID-19 pneumonia at the first admission to the hospital in patients diagnosed with the typical appearance on thorax computed tomography (CT).

Materials and Methods

Patients

Our retrospective observational design study recruited 129 consecutive real-time reverse transcriptase polymerase chain reaction (RT-PCR) confirmed COVID-19 infected patients with no significant comorbidity, admitted in the first wave of COVID-19 pandemic between February 2020 and June 2020, with CO-RADS

***Corresponding Author:** Ibrahim Hakki Koker, Bezmialem Vakif University, Faculty of Medicine, Department of Gastroenterology, Istanbul, Turkey
E-mail: koker34@yahoo.com

[4] 4 or 5 viral pneumonic infiltration of the lungs by thorax CT. We excluded patients with additional causes of mortality such as pulmonary edema, severe congestive heart failure, or terminal-stage malignancies among the exclusion criteria. We obtained the laboratory results from the electronic database. We determined that 27 (20.9%) of the patients had died in the hospital after admission. We investigated the parameters that can predict mortality among the survivors and those who died. Our study was approved by the local ethics committee (06/110.05.05.2020) and the Turkish Republic, the Ministry of Health General Directorate of Health Services (2020-05-21T08-_23_03).

Radiological evaluation

Thoracic CT scans of the patients were taken with the Toshiba Aquilion Cx 128 computed tomography device.

Laboratory tests and data collection

Demographic data and laboratory results of patients who were found to have COVID-19 pneumonia findings on thorax CT during the first admission were obtained from the electronic database. The biochemistry tests of the patients were evaluated with the Abbott Architect c16000-Photometric method, the Ferritin Abbott Architect i2000-chemiluminescence method; the hemograms were evaluated with the Cell Dyn Ruby-laser impedance method, and the international normalization ratio (INR) were evaluated with Trinity Biotech Amax 200-Magnetic method.

Statistical analysis

All statistical analyses were done with SPSS Statistics software version 25 (IBM Corp., Armonk, NY, USA) and MedCalc® Statistical Software version 20 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2021). The Kolmogorov–Smirnov and Shapiro–Wilk tests indicated a nonparametric data distribution. Descriptive analyses are presented using median (min-max) for nonparametric and ordinal variables. The univariate analyses to identify variables associated with patient outcome (survived / in-hospital death) during the COVID-19 infection were investigated using the Mann-Whitney U test due to nonparametric data distribution.

For the multivariate analysis, the possible factors identified with univariate analyses as age, Aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT), serum albumin level, International normalization ratio (INR), C-reactive protein (CRP), Ferritin, d-dimer, and White blood cells (WBC) were further entered the logistic regression analysis to determine independent predictors of patient outcome. Serum ferritin level and age data were used to plot a ROC curve to differentiate survived and in-hospital dead patients. The area under the receiver operating curve (AUROC) was calculated. MedCalc Statistical Software version 19.2.5 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2021) was used to accurately determine the serum ferritin level and age cutoff level to differentiate between survived and in hospital dead patients. A p-value of < 0.05 was considered significant.

Results

We recruited 129 consecutive RT-PCR confirmed COVID-19 patients who presented to the COVID-19 outpatient clinic with CT confirmed pulmonary involvement and no significant comorbidity or known disease to identify relationships between the clinical, laboratory, and disease outcomes in patients with COVID-19.

Demographic findings of the patients are given in Table 1.

Table 1. Demographic findings of the patients

Patients n	**129**
Age, y, mean ±SD, min-max	58.0 ±15.3, 16-88
Gender M (%)	74 (57.4)
Survived / In-hospital death, n (%)	102 (79) / 27 (21)
Additional morbidities	Survived / In-hospital death, n (%)
1. None	38 (37.3) / 8 (29.6)
2. Diabetes mellitus	24 (23.5) / 6 (22.2)
3. Hypertension	12 (11.8) / 3 (11.1)
4. CABG history	4 (3.9) / 3 (11.1)
5. COPD	5 (4.9) / 2 (7.4)
6. CHF	2 (2) / 2 (7.4)
7. CRF	1 (1) / 1 (3.7)
8. Ulcerative colitis	0 / 1 (3.7)
9. Cardiac valve pathology	1 (1) / 0
10. Arrhythmia	1 (1) / 0
11. Epilepsy	1 (1) / 0
12. Alzheimer's disease	1 (1) / 0
13. Cervix Carcinoma	1 (1) / 0
14. Psoriasis	1 (1) / 0
15. ITP	1 (1) / 0
16. Unknown	9 (8.8) / 1 (3.7)

CABG; coronary artery bypass grafting, COPD; chronic obstructive pulmonary disease, CHF; congestive heart failure, CRF; chronic renal failure M; male, min-max: minimum-maximum, ITP; idiopathic thrombocytopenic purpura.

In Table 2, when all the patients were evaluated together, we found the biochemical parameters within the reference values at the first application.

Comparison of laboratory findings

Then, we divided the patients into two groups: those who survived and those who died in-hospital after admission. Table 3 compares those who survived and those who died in the hospital after the first admission.

Age, AST, alanine transaminase (ALT), GGT, albumin, INR, CRP, Ferritin, d-dimer, and WBC significantly differed in univariate analysis between survivors and in-hospital deaths. Although ALT levels differed significantly between the groups, they were within normal limits.

Table 2. Laboratory results in all patients

Parameter	Patient Results	Reference Values
Glucose mg/dL, median (range)	115 (75-700)	70-105
ACE, IU/mL, median (range)	17 (2-64)	8-52
Creatine kinase, U/L, median (range)	89 (11-3092)	30-200
AST, U/L, median (range)	27.5 (11-129)	5-34
ALT, U/L, median (range)	23 (7-92)	0-55
ALP, U/L, median (range)	60 (19-395)	40-150
GGT, U/L, median (range)	35.5 (10-428)	12-64
T.Bil, mg/dL, median (range)	0.5 (0.1-1.1)	0.3-1.2
D.Bil, mg/dL, median (range)	0.2 (0.1-0.5)	0-0.5
Albumin, g/dL, median (range)	3.6 (1.0-5)	3.4-4.8
INR, median (range)	1.1 (0.9-3.9)	0.8-1.2
CRP, mg/dL, median (range)	53.6 (0.2-304)	0-5
Ferritin, ng/mL, median (range)	333.6 (11.2-21130)	21.8-274.6
D-dimer, ng/mL, median (range)	291.5 (72-3940)	0-300
Wbc, (x10^3/mm^3), median (range)	6785 (1000-24850)	4.500-11.000
Hg, g/dL, median (range)	13.4 (7.7-17.2)	14.1-17.5
Platelet, (x10^3/mm^3), median (range)	200 (80-547)	142-424

ACE; angiotensin-converting enzyme, ALT; alanine aminotransferase, AST; aspartate aminotransferase, ALP; alkaline phosphatase, CRP; C-reactive protein, GGT; gamma-glutamyltransferase, Hg; hemoglobin, T.Bil; total bilirubin, D.Bil; direct bilirubin, INR; international normalization ratio, Wbc; white blood cell.

Table 3. Comparison of laboratory parameters at first admission among the surviving and in-hospital death patients

Parameter	Survived (n=102)	In-hospital death (n=27)	P
Gender, F/M (%)	45 (44.1) /57 (55.9)	10 (37) / 17 (63)	0.662
Age, y, mean±SD	53.5±15.8	67.4±12	<0.001
Glucose, mg/dL	113 (75-700)	124 (91-649)	0.252
ACE, IU/mL	17 (2-64)	18.5 (8-41)	0.234
CK, U/L	81 (11-1823)	113 (17-3092)	0.236
AST, U/L	25.0 (11-85)	43 (20-129)	<0.001
***ALT, U/L**	22 (7-89)	30 (11-92)	0.005
ALP, U/L	58.5 (19-225)	73.5 (33-395)	0.092
GGT, U/L	28 (10-241)	59 (20-428)	<0.001
T.Bil. mg/dL	0.5 (0.1-1.1)	0.6 (0.3-1)	0.405
Albumin, g/dL	3.8 (2.7-5)	3.2 (1-4.2)	<0.001
INR	1.1 (0.9-1.4)	1.1 (1.1-3.9)	0.001
CRP, mg/dL	39,7 (0.2-255)	117,4 (7.9-304)	<0.001
Ferritin, ng/mL	221,4 (11.2-1532.7)	1116 (290-21130)	<0.001
d-dimer, ng/mL	279 (72-2616)	319 (217-3940)	0.007
WBC (/mm^3)	6625 (2280-24850)	7865 (1000-17420)	0.039
Hg, g/dL	13.4 (9.2-17.2)	13.5 (7.716.1)	0.448
Platelets, (x10^3/mm^3)	200 (80-480)	209 (135-547)	0.683

* Although ALT differs significantly between the two groups, the median values in both groups are between the reference values. ACE; angiotensin-converting enzyme, ALP; alkaline phosphatase, ALT; alanine aminotransferase, AST; aspartate aminotransferase, CK; creatinine kinase, CRP; C-reactive protein, GGT; gamma-glutamyl transferase, Hg; hemoglobin, INR; international normalization ratio, T.bil; Total bilirubin, WBC; White blood cell, Mann-Whitney test, independent samples' T-test as appropriate

Prediction of mortality in patients presenting with Covid-19 pneumonia

We evaluated age, AST, GGT, serum albumin, INR, CRP, Ferritin, d-dimer, and WBC, which were significant in comparing surviving and in-hospital death patients, using the logistic regression test (Table 4). Then, we reduced these 9 parameters, which we determined as significant in the univariate analysis, to 5 parameters like age, INR, CRP, Ferritin, and WBC by using the binary logistic regression model backward LR elimination method. Among them, we found age and Ferritin to be significant (Table 4).

Table 4. Binary logistic regression analyses of predictors for mortality

Independent Variables	Reduced (enter) method	
	Odds Ratio (95% CI)	P-Value
Age	1.12 (1.007-1.245)	0.010
INR	10.5 (0.114- 967)	0.308
CRP	0.096 (0.998-1.021)	0.096
Ferritin	1.003 (1.001-1.004)	0.001
WBC	1.000 (1.000-1.001)	0.056

CI; confidence interval, CRP; C-reactive protein, INR; international normalization ratio, OR; odds ratio, WBC; white blood cell

We found that the patient's advanced age and increased serum ferritin were significant in predicting mortality at the first admission to the hospital. Therefore, we calculated the cutoff levels, which can be used practically at the first admission to the hospital, as a univariate variable for age and Ferritin using AUROC.

Calculation of ferritin cutoff value in mortality prediction

Accordingly, we calculated the optimal cutoff value for ferritin as >289.1 ng/mL with an AUROC 0.886 (95% CI, 0.811-0.939; p<0.0001) with Sensitivity: 100%, Specificity: 61.4%, Positive Predictive Value: 44.8%, Negative Predictive Value: 100%. We found the Sensitivity and Negative Predictive Value of this ferritin cutoff value to be 100%. When we take the cutoff value as 989.3 ng/mL, we determined Sensitivity: 53.8%, Specificity: 93.9%, PPV: 73.7%, NPV: 86.7%, with an increased specificity (Figure 1).

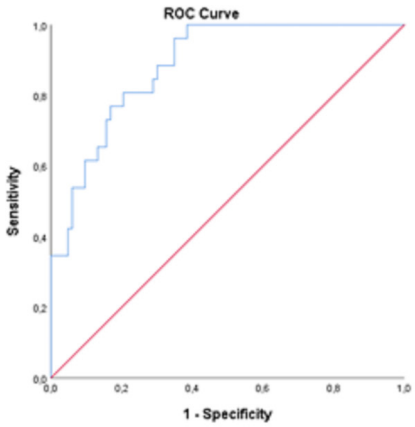

Figure 1. Receiver operating characteristic (ROC) curve analysis to differentiate surviving from in-hospital dead patients. A ferritin cutoff level of >289.1 ng/mL resulted in an area under the ROC of 0.88 (95% confidence interval, 0.81-0.93)

Age cutoff value

Accordingly, we calculated the optimal age limit as >51 years. The AUROC was 0.763 (95% CI, 0.673-0.853; p<0.0001). Accordingly, we calculated the Sensitivity: 96.3%, Specificity: 44.1%, PPV: 31.3%, NPV: 97.8%. At age >80 years, the specificity increases to 96 % for the optimal criterion (Figure 2).

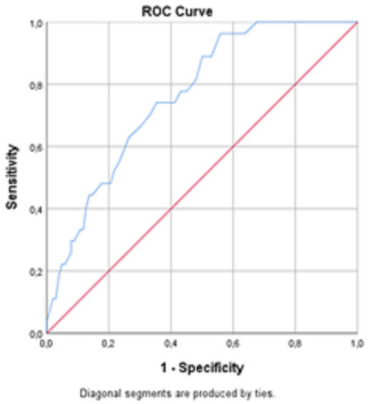

Figure 2. Receiver operating characteristic (ROC) curve analysis to differentiate surviving from in-hospital dead patients. An age cutoff level of >51 years resulted in an area under the ROC of 0.76 (95% confidence interval, 0.67-0.85)

Discussion

The COVID-19 pandemic, created by the Coronavirus SARS-CoV-2, poses a severe threat to the health, freedom of life, and economic freedom of the world's people. The virus, which undergoes intermittent mutations, can cause reinfection and a more severe course in surviving the disease. Therefore, it is essential to identify markers that will predict the course of the disease.

We included 129 patients 74 M (57.4%) with a mean age of 58±15.3 years (range 16-88) in our study. Hundered and two (79%) of the patients survived, and 27 (21%) died in-hospital. When all the patients were taken into account, glucose, angiotensin-converting enzyme levels, creatine kinase, AST, ALT, ALP, GGT, total bilirubin, and albumin median levels evaluated at the first admission were among the reference values. However, CRP and ferritin levels were elevated (Table 2). After dividing the patients as surviving and in-hospital dead, a univariate assessment was performed between the two groups. In the univariate comparison between these two groups, age (p<0.001), AST (p<0.001), GGT (p<0.001), albumin (p<0.001), INR (p=0.001), CRP (p<0.001), ferritin (p<0.001), d-dimer (p=0.007) and WBC (p=0.039) were significant. Then, we reduced these 9 parameters, which we determined as significant in the univariate analysis, to 5 parameters with the binary logistic regression model backward elimination method. Therefore, we found that only age and ferritin levels at presentation were predictive of disease mortality (Table 4). Accordingly, we have shown that the increase in Ferritin measured at the first time of hospital admission and older age are associated with in-hospital death. Then, as a univariate variable, the serum ferritin cutoff value was >289.1 ng/mL to be used in practice at the first admission of the patients to the hospital with a sensitivity: 100%, and NPV: 100%, while age cutoff was >51 years with a sensitivity: 96.3%, and NPV: 97.8%.

Serum ferritin is an acute-phase protein that can be elevated due to many infectious or non-infectious causes. It can increase to very extreme levels, especially in macrophage activation syndrome (MAS) [5,6]. Serum ferritin level is also closely related to disease

activity and is a valuable biomarker in macrophage activation [7]. Ferritin increases in infectious diseases as Influenza A, Influenza B, Ebola hemorrhagic fever [8]. In a febrile patient, MAS diagnosis made with a serum ferritin level >684 ng/mL plus any 2 of the following: thrombocyte count ≤181x109/L, aspartate aminotransferase >48 U/L, triglyceride concentration >156 mg/dL, or fibrinogen ≤360 mg/dL [9]. MAS is a fatal inflammatory condition if not adequately treated. In this study, that the high ferritin level at the patient's first presentation indicates MAS. However, AST elevation and low platelet count, which are other MAS criteria, did not show any significance between the surviving and in-hospital death groups. In addition, the cutoff value of Ferritin we calculated is lower than that specified in the MAS criterion. However, a high ferritin level at the first admission is the only laboratory finding in our study that predicted mortality.

In line with our findings, Zhou et al. reported that elevated Ferritin was related to in-hospital death [10]. They also determined the cutoff value of Ferritin as 300 ng/mL. However, Zhou et al. did not perform a multivariable analysis on the significance of serum ferritin level in mortality. In this study, we determined the ferritin cutoff value similar to Zhou et al. and found serum ferritin levels to be significant on mortality. In a recent study, ferritin levels were associated with severe pulmonary involvement but not with the disease outcomes [11]. Also, in another recent study, it was concluded that Ferritin could be used to predict mortality [12].

In another retrospective study of 201 patients, Wu et al. reported that while Ferritin was associated with ARDS development, serum ferritin did not significantly correlate with death in the bivariate cox model (HR=5.28; 95%CI: 0.72-38.48; p=0.10) [13]. In a meta-analysis by Taneri et al., [14] hemoglobin and Ferritin levels varied according to the severity of COVID-19. Besides, some studies are indicating that there is no significant difference in ferritin levels in COVID-19 infection [15,16]. In this study, we found a significant difference in ferritin levels between those who died due to COVID-19 pneumonia and those who survived, but we did not detect a significant difference between Hg levels.

Older age, leucocytosis, high lactate dehydrogenase (LDH), and hyperglycemia were associated with in-hospital death in previous studies [17]. However, we did not detect any significance in leukocytosis and hyperglycemia in univariate/multivariate calculations regarding mortality prediction among the groups. Although d-dimer was significant in our study at the first stage, it was eliminated with the binary logistics analysis backward LR elimination method. Therefore, we did not find the d-dimer difference significant among the groups. Nevertheless, some studies indicate that it is significant [10].

The limitation of our study is that it is a retrospective single-center study. However, we did not include patients with additional factors that increase mortality risk, such as terminal malignancy. Since COVID-19 infection was the only significant risk factor for in-hospital mortality in our cohort, we think that the group is more homogeneous, and the results are more valid.

Conclusions

Serum ferritin level and age may help identify patients with high mortality risk at first admission in patients with COVID-19. A serum ferritin cutoff of >289.1 ng/mL had a 100% NPV to differentiate surviving from in-hospital death patients at the first admission.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
All authors declare no financial support.

Ethical approval
Our study was approved by the local ethics committee (06/110.05.05.2020) and the Turkish Republic, the Ministry of Health General Directorate of Health Services (2020-05-21T08-_23_03).

References

1. 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;395,507-13.
2. Lippi G, Plebani M. Laboratory abnormalities in patients with COVID-2019 infection. Clin Chem Lab Med. 2020;58:1131-4.
3. Bohn MK, Lippi G, Horvath A, et al. Molecular, serological, and biochemical diagnosis and monitoring of COVID-19: IFCC task force evaluation of the latest evidence. Clin Chem Lab Med. 2020 25;58:1037-52.
4. Prokop M, van Everdigen W, van Rees Vellinga T, et al. CO-RADS: A Categorical CT Assesment Scheme for Patients Suspected of Having COVID-19- Definition and Evaluation. Radiology. 2020;296:E97-E104.
5. Rosario C, Zandman-Goddard G, Meyron-Holtz E, et al. The hyperferritinemic Syndrome: macrophage activation syndrome, Still's disease, septic shock, and catastrophic antiphospholipid syndrome. BMC Medicine. 2013;11:185.
6. Crayne CB, Albeituni S, Nichols KE, et al. The immunology of macrophage activation syndrome. Front Immunol. 2019;10:119.
7. Sandler RD, Tattersall RS, Schoemans H, et al. Diagnosis and Management of Secondary HLH/MAS Following HSCT and CAR-T Cell Therapy in Adults; A Review of the Literature and a Survey of Practice Within EBMT Centres on Behalf of the Autoimmune Diseases Working Party (ADWP) and Transplant Complications Working Party (TCWP). Front. Immunol. 2020;11;524.
8. Kappert K, Jahic A, Tauber R. Assessment of serum ferritin as a biomarker in COVID-19: bystander or participant? Insights by comparison with other infectious and non-infectious diseases. Biomarkers. 2020;25:616-25.
9. Ravvelli A, Minoia E, Davi S, et al. Classification criteria for macrophage activation. Annals of the Rheumatic Diseases. 2016;75:481-9.
10. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395:1054-62.
11. Carubbi F, Salvati L, Alunno A, et al. 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. Scien Rep. 2021;11:4863.
12. Tural Onur S, Altın S, Sokucu SN, et al. Could ferritin level be an indicator of COVID-19 disease mortality? J Med Virol. 2021; 93:1672-7.
13. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Int Med. 2020:180:934.
14. Taneri PE, Gomez-Ochoa SA, Llanaj E, et al. Anemia and iron metabolism in COVID-19: a systematic review and meta-analysis. Europ J of Epidem. 2020:35;763-73.
15. Rutledge AC, Choi YH, Karp I, et al. Biochemistry tests in hospitalized COVID-19 patients: Experience from a Canadian tertiary care centre. Clin Biochem. 2021;19:S0009-9120:00149-1. Online ahead of print.
16. Shah A, Frost JN, Aaron L, et al. Systemic hypoferremia and severity of hypoxemic respiratory failure in COVID-19. Crit Care. 2020;24:320.
17. Li X, Xu S, Yu M, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. J Allergy Clin Immunol. 2020;146:110-8.