

Article

Serum Ferritin as a Predictor of Hospital Mortality in Critically Ill COVID-19 Patients

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Abstract: Serum ferritin levels increase in severe COVID-19 patients. However, few data correlating the sensitivity and specificity of ferritin levels and mortality prediction in COVID-19 exist. The current study aims to investigate the sensitivity and specificity of ferritin for the prediction of mortality risks relative to COVID-19. Retrospectively, critically ill COVID-19 patients admitted to the general intensive care unit (ICU) of Ankara Bilkent City Hospital, Türkiye, were examined. The median baseline ferritin level in the survivor group was 184.7 µg/L (90.1–430.7), while it was 297.0 µg/L (150.3–851.3) in the deceased group ($p = 0.001$). The median maximum ferritin in the survivor group was 486.6 µg/L (187.9–1020.0), while it was 1456.7 µg/L (578.5–4388.1) in the deceased group ($p < 0.001$). In the receiver operating characteristic (ROC) curve analysis, the cut-off baseline ferritin value was 201.5 µg/L for the prediction of mortality (area under the curve [AUC] = 0.615, $p < 0.001$, 95% Confidence interval [CI]: 0.557–0.671). Baseline ferritin levels were associated with increased in-hospital mortality ($p < 0.001$, odds ratio: 2.347, 95% CI: 1.5–3.7). Baseline ferritin exhibited 66% sensitivity and 54.2% specificity in predicting mortality. The maximum ferritin cut-off value was 878.6 µg/L (AUC = 0.754, $p < 0.001$, 95% CI: 0.701–0.802), exhibiting 68% sensitivity and 73.2% specificity for mortality prediction. Ferritin has a moderately effective prediction potential for mortality in COVID-19 patients admitted to the ICU.



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1. Introduction

Serum ferritin is an acute phase reactant, and its levels may increase in bacterial, viral, and fungal infections. Ferritin levels may increase in the following scenarios: sepsis, septic shock, macrophage activation syndrome, catastrophic antiphospholipid syndrome, adult-onset Still's disease, porphyria cutanea tarda, chronic liver disease, malignancy, some autoimmune diseases, metabolic syndrome, hemophagocytic lymphohistiocytosis, iron overload, and in critically ill patients. Moreover, it can be used for predicting the disease prognosis [1–3].

In COVID-19 patients, ferritin elevation can be a predictor pointing to the need for intensive care [4]. Highly increased ferritin levels could be associated with cardiac arrest and immunosuppression. Cytokine storm, chronic hypoxia, high levels of iron, oxidative stress, and acidosis in COVID-19 patients may play a role in the damage of cardiac cells and cause sudden cardiac arrest. High H-ferritin levels may suppress lymphoid cell proliferation and cause sepsis [5–7].

Ferritin may be a possible immunological biomarker for severe and fatal COVID-19. It is a major mediator of immune dysregulation, particularly in extreme hyperferritinemia, through direct immunosuppressive and proinflammatory effects that contributes to cytokine storm syndrome. The fatal consequences of COVID-19 are accompanied by cytokine storm syndrome; hence, the severity of the disease depends on the syndrome. Patients with very severe COVID-19 have increased serum ferritin levels. Moreover, ferritin levels are high in deceased patients upon admission to the hospital and during their hospital stay [8,9].

Serum ferritin levels are closely related to the severity of COVID-19. However, ferritin levels are insufficient for predicting mortality, and the levels measured at the time of hospital admission cannot adequately predict mortality in COVID-19 patients [1,10]. Recent studies indicate mixed results regarding the prognostic significance of elevated ferritin levels in COVID-19 patients, with some suggesting a link to poor outcomes [11–14]. This study aims to determine the sensitivity and specificity of ferritin in predicting mortality among COVID-19 patients admitted to ICU in order to reveal their relationship.

2. Materials and Methods

2.1. Patients

A retrospective observational analytical study was designed, involving both male and female patients aged more than 18 who were admitted to ICU at the Ankara Bilkent City Hospital, Türkiye, between 1 July 2022, and 31 December 2022. All included patients tested positive via the reverse-transcriptase polymerase chain reaction test for SARS-CoV-2. Patients with comorbid diseases having a risk of hyperferritinemia, patients admitted to the ICU upon cardiac arrest, and patients with missing data were excluded from the study. Study data were obtained retrospectively from the hospital's electronic records.

2.2. Clinical Assessment and Data Collection Instruments

Age, gender, respiratory support methods (invasive mechanical ventilation, nasal cannula, face mask, non-invasive ventilation, or high-flow nasal cannula), newly started renal replacement therapy, previously initiated scheduled renal replacement therapy, acute physiology and chronic health evaluation II (APACHE II), ratio of partial pressure arterial oxygen and fraction of inspired oxygen ($\text{PaO}_2/\text{FiO}_2$ ratios), and comorbidities were noted. Upon admission to the ICU, the following were recorded: baseline ferritin, lactate dehydrogenase, troponin I, creatinine, neutrophil, lymphocyte, eosinophil, hemoglobin, platelet, bilirubin, C-reactive protein, procalcitonin, international normalized ratio (INR), D-dimer, lactate, and Interleukin 6 (IL-6). The maximum ferritin level was evaluated as the highest ferritin value at any time during a patient's stay in the ICU. During COVID-19, ferritin levels were routinely monitored in all patients with suspected COVID-19 in our hospital, and no specific ferritin analysis was performed for this study. Ferritin levels were measured by analyzing serum samples via the chemiluminescent method on the Siemens Healthineers Atellica platform (Siemens Healthineers AG, Forchheim, Germany) at Ankara Bilkent City Hospital, Türkiye. The length of hospital stay and in-hospital mortality were recorded.

The patients were categorized clinically according to the method reported by Chen et al. [8].

Severe cases had at least one of the following:

- (1) Respiratory distress over 30/min;
- (2) Oxygen saturation $\leq 93\%$;
- (3) $\text{PaO}_2/\text{FiO}_2 \leq 300$ mmHg;

Critically ill cases had at least one of the following:

- (1) Invasive mechanical ventilation;

- (2) Shock;
- (3) Other organ dysfunction.

The study was a retrospective study. All patients who met the criteria between a certain time period were included in the study. Therefore, the sample size was not calculated. After the completion of the study, post hoc power analysis was performed according to the results of comparing the baseline ferritin values between mortality conditions. Power analysis was performed using the statistical package program G*Power 3.1.9.7 (Franz Foul, Universitat Kiel, Kiel, Germany): $n_1 = 142$ (436.3 ± 907.4), $n_2 = 158$ (870.3 ± 1336.6), $\alpha = 0.05$; effect size (d) = 0.38; power = 89%.

2.3. Statistical Analyses

Data were analyzed via IBM SPSS 25.0 (Armonk, NY, USA: IBM Corp.). The patients were divided into two groups, survivors and deceased, in the hospital. The chi-square test was used to compare qualitative data and descriptive statistical methods (frequency, percentage, mean, standard deviation, median, min–max, and interquartile range). The data for the normal distribution were evaluated using the Kolmogorov–Smirnov test, skewness–kurtosis, and graphical methods (histogram, Q–Q plot, stem and leaf, and box-plot). An independent-sample *t*-test (*t*-test in independent groups) and Mann–Whitney U test were employed to evaluate any data that did not show normal distributions. For statistical analyses, an ROC curve was utilized to evaluate the discriminative ability of ferritin levels for mortality. Binary logistic regression was used to identify risk ratios. Kaplan–Meier, log-rank, Breslow, and Tarone–Ware tests were used for survival analysis. The data, exhibiting a non-normal distribution, were presented as medians with interquartile ranges. Spearman’s rho correlation test was used to evaluate the relationships between variables. The significance level was set at $p \leq 0.05$.

3. Results

A total of 398 COVID-19 patients were admitted to the ICU between July 2022 and December 2022. Patients diagnosed with cardiac arrest ($n = 14$) and patients with missing data ($n = 84$) were excluded from the study. Data from 300 patients who met the inclusion criteria were analyzed. The mean age of patients was 74.4 ± 14.7 , with 55% being male. APACHE II was 32.4 ± 12.5 , the $\text{PaO}_2/\text{FiO}_2$ ratio was 200.5 ± 139.5 , and the most common comorbidity was cardiac disease (49%). The patients were divided into two groups: living (survivor patient group) and deceased (non-survivor patient group). The characteristics of living ($n = 142$) and deceased ($n = 158$) patients are shown in Table 1. The age of deceased patients (77.0 ± 12.7) was higher than the surviving ones (71.5 ± 16.2) ($p = 0.001$). APACHE II was higher in the deceased patient group than in the living group ($p < 0.001$). The $\text{PaO}_2/\text{FiO}_2$ ratio was lower in the deceased group ($p < 0.001$). Similarly, the median baseline ferritin level of the survivor group— $184.7 \mu\text{g/L}$ (90.1 – 430.7)—was significantly different ($p = 0.001$) from the non-survivor group, which was $297.0 \mu\text{g/L}$ (150.3 – 851.3). The median maximum ferritin level was $486.6 \mu\text{g/L}$ (187.9 – 1020.0) in the survivor group, while it was $1456.7 \mu\text{g/L}$ (578.5 – 4388.1) in the deceased group, and the difference between the two groups was significant ($p < 0.001$). The lactate dehydrogenase, troponin I, creatinine, neutrophils, C-reactive protein, procalcitonin, international normalized ratio (INR), D-dimer, lactate, and IL-6 values were higher in the non-survivor patient group than in the survivor group. Lymphocytes, hemoglobin, and platelet levels were lower in the non-survivor group. Compared to the survivor group, the rates of invasive mechanical ventilation as a respiratory support method, newly started renal replacement therapy, and disease severity were higher in the deceased group (Table 1).

Table 2 shows the univariate and multivariate logistic regression analysis for mortality. p values were calculated using the binary logistic regression test. Variables found to be different in pairwise comparisons between survival–mortality conditions were first evaluated with univariate logistic regression, where variables found to be risk factors and thought to be clinically more significant and not highly correlated with each other; age, maximum ferritin, international normalized ratio, d-dimer, $\text{PaO}_2/\text{FiO}_2$, cardiac disease, baseline ferritin, lactate dehydrogenase, hemoglobin, gender, troponin-I, creatinine, lymphocytes, platelet, C-reactive protein, and chronic renal failure were included in the model, and the backward stepwise method was used in the analysis. The model was terminated in the eleventh step. In this model, approximately 78% of the dependent variable (survival–mortality) could be explained (Nagelkerke $R^2 = 0.781$). According to this model, there is a statistically significant relationship between survival–mortality status and age, maximum ferritin, international normalized ratio, d-dimer, $\text{PaO}_2/\text{FiO}_2$, and cardiac disease ($p < 0.05$).

Table 3 shows the ROC analysis of the data of the survivor and deceased patient groups. The baseline ferritin cut-off value was 201.5 (AUC = 0.615, $p < 0.001$, 95% CI: 0.557–0.671), exhibiting 66% sensitivity and 54.2% specificity in predicting survived and deceased patients. The maximum ferritin cut-off value was 878.6 (AUC = 0.754, $p < 0.001$, 95% CI: 0.701–0.802), with a sensitivity of 68% and a specificity of 73.2% for predicting mortality. Figure 1 shows the receiver operating characteristic analysis of the predictive power of baseline ferritin and maximum ferritin levels for in-hospital mortality.

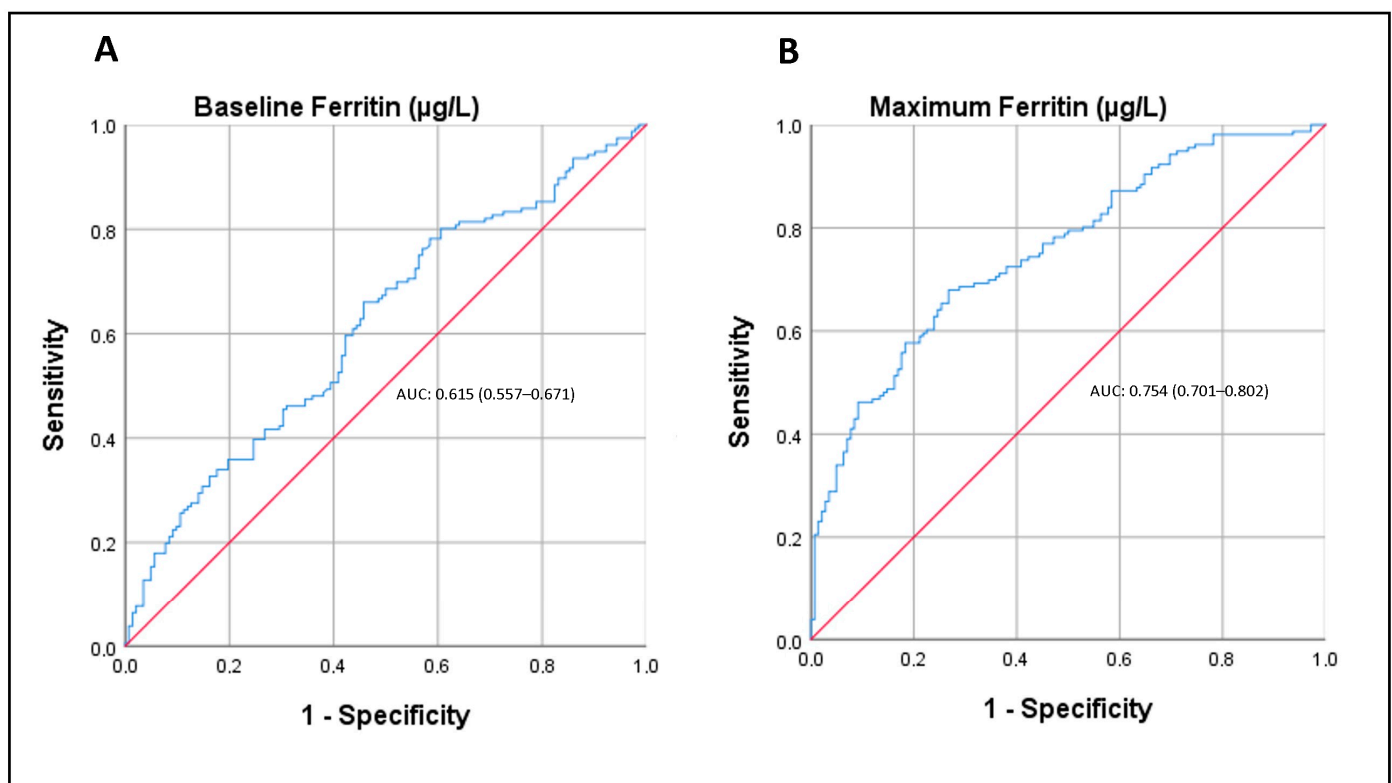


Figure 1. Receiver operating characteristic analysis of predictive power of baseline ferritin (A) and maximum ferritin (B) levels for in-hospital mortality.

Followed by classification in two categories according to the cut-off value, patients with high baseline ferritin values exhibited approximately two times more probability of death than those with low baseline ferritin values (odds ratio: 2.347, 95% CI: 1.5–3.7, $p < 0.001$) (Table 4). Figure 2 shows the Kaplan–Meier estimates of the probability of survival.

Table 1. Characteristics of survivor and deceased groups.

Parameter		Survivor	Non-Survivor	<i>p</i> Value
		N = 142	N = 158	
Age (yr)		71.5 ± 16.2	77.0 ± 12.7	0.001 ^b
Gender	Female	73 (51.4%)	61 (38.6%)	0.026 ^a
	Male	69 (48.6%)	97 (61.4%)	
APACHE II		21.3 ± 5.4	42.3 ± 7.9	<0.001 ^b
PaO ₂ /FiO ₂ ratio		311.8 ± 121.5	100.4 ± 50.4	<0.001 ^b
Baseline ferritin (µg/L)		184.7 (90.1–430.7)	297.0 (150.3–851.3)	0.001 ^c
Maximum ferritin (µg/L)		486.6 (187.9–1020.0)	1456.7 (578.5–4388.1)	<0.001 ^c
Lactate dehydrogenase (U/L)		304.5 (251.5–425.5)	393.0 (309.8–537.5)	<0.001 ^c
Troponin-I (ng/L)		23.0 (10.0–80.7)	75.0 (26.5–256.5)	<0.001 ^c
Creatinine (mg/dL)		0.9 (0.7–1.5)	1.3 (0.8–1.9)	<0.001 ^c
Neutrophils (%)		86.1 (77.7–90.0)	88.9 (82.8–92.5)	0.001 ^c
Lymphocytes (%)		8.5 (5.6–13.6)	5.9 (3.2–10.3)	<0.001 ^c
Eosinophils (%)		0.20 (0.10–0.40)	0.10 (0.10–0.40)	0.095 ^c
Hemoglobin (g/dL)		11.7 ± 2.6	11.0 ± 2.1	0.008 ^b
Platelet (×10 ⁹ /L)		252.0 ± 108.9	224.1 ± 120.0	0.036 ^b
Bilirubin (mg/dL)		0.6 (0.3–1.0)	0.7 (0.4–1.0)	0.066 ^c
C-reactive protein (g/L)		119.4 ± 109.5	152.9 ± 114.7	0.010 ^b
Procalcitonin (µg/L)		0.24 (0.09–1.15)	0.87 (0.23–5.79)	<0.001 ^c
International normalized ratio		1.2 (1.1–1.3)	1.3 (1.1–1.4)	<0.001 ^c
D-dimer (mg/L)		2.0 (1.1–3.9)	3.2 (1.4–6.7)	0.001 ^c
Lactate (mmol/L)		2.1 (1.5–2.6)	2.4 (1.7–3.4)	0.004 ^c
IL-6 (pg/mL)		28.0 (10.9–86.4)	46.8 (16.0–193.7)	0.044 ^c
Comorbidities	Cardiac disease	57 (40.1%)	90 (57.0%)	0.004 ^a
	Chronic lung disease	48 (33.8%)	70 (43.3%)	0.063 ^a
	Neurological disease	62 (43.7%)	55 (34.8%)	0.117 ^a
	Chronic renal failure	19 (13.4%)	38 (24.1%)	0.019 ^a
	Liver cirrhosis	2 (1.4%)	8 (5.1%)	0.109 ^a
	Cancer or hematological malignancy	20 (14.1%)	36 (22.8%)	0.053 ^a
Respiratory support methods	Invasive mechanical ventilation	18 (12.7%)	152 (96.2%)	<0.001 ^c
	Nasal cannula or face mask	74 (52.1%)	5 (3.2%)	
	Non-invasive ventilation	24 (16.9%)	1 (0.6%)	
	High-flow nasal cannula	14 (9.9%)	0 (0.0%)	
	No support	12 (8.5%)	0 (0.0%)	
Renal replacement therapy	No	126 (88.7%)	98 (62.0%)	<0.001 ^c
	Newly started	14 (9.9%)	56 (35.4%)	
	Previously scheduled dialysis	2 (1.4%)	4 (2.5%)	
Clinical classification	Severe cases	123 (86.6%)	4 (2.5%)	<0.001 ^c
	Critically ill cases	19 (13.4%)	154 (97.5%)	
Hospital stay (days)		13.0 (7.0–23.3)	12.5 (5.0–24.0)	0.509 ^c

^a: *p* values were calculated using chi-square test as appropriate (n(%)); ^b: *p* values were calculated using independent-sample *t*-test as appropriate (mean ± SD); ^c: *p* values were calculated using Mann–Whitney U test as appropriate (median (Q1–Q3)).

Table 2. Univariate and multivariate logistic regression analysis for mortality.

Variables	Univariate Logistic Regression Analysis						Multivariate Logistic Regression Analysis					
	B	SE	Wald	Odds	95% CI	<i>p</i> Value *	B	SE	Wald	Odds	95% CI	<i>p</i> Value *
Age (years)	0.027	0.009	10.115	1.03	1.01–1.05	0.001	0.028	0.014	3.928	1.03	1.00–1.06	0.047
Maximum ferritin (µg/L)	<0.001	<0.001	24.656	1.00	1.00–1.00	<0.001	<0.001	<0.001	7.146	1.00	1.00–1.00	0.008
International normalized ratio	0.438	0.223	3.877	1.55	1.00–2.40	0.049	1.082	0.451	5.753	2.95	1.22–7.15	0.016
D-dimer (mg/L)	0.045	0.020	5.178	1.05	1.01–1.09	0.023	0.114	0.048	5.581	1.12	1.02–1.23	0.018
PaO ₂ /FiO ₂	−0.022	0.003	69.589	0.98	0.97–0.98	<0.001	−0.024	0.003	54.720	0.98	0.97–0.98	<0.001
Cardiac disease	0.680	0.235	8.386	1.97	1.25–3.13	0.004	0.984	0.444	4.915	2.67	1.12–6.38	0.027
Baseline ferritin (µg/L)	0.001	<0.001	7.871	1.00	1.00–1.00	0.005	--	--	--	--	--	--
Lactate dehydrogenase (U/L)	0.002	0.001	11.307	1.00	1.00–1.00	0.001	--	--	--	--	--	--
Hemoglobin (g/dL)	−0.133	0.050	7.099	0.88	0.79–0.97	0.008	--	--	--	--	--	--
Gender	0.520	0.234	4.929	1.68	1.06–2.66	0.026	--	--	--	--	--	--
Troponin-I (ng/L)	<0.001	<0.001	4.720	1.00	1.00–1.00	0.030	--	--	--	--	--	--
Creatinine (mg/dL)	0.233	0.113	4.225	1.26	1.01–1.57	0.040	--	--	--	--	--	--
Lymphocytes (%)	−0.035	0.016	4.755	0.97	0.94–1.00	0.029	--	--	--	--	--	--
Platelet (×10 ⁹ /L)	−0.002	0.001	4.308	1.00	1.00–1.00	0.038	--	--	--	--	--	--
C-reactive protein (g/L)	0.003	0.001	6.473	1.00	1.00–1.00	0.011	--	--	--	--	--	--
Chronic renal failure	0.718	0.309	5.401	2.05	1.12–3.76	0.020	--	--	--	--	--	--
APACHE II	0.580	0.083	48.673	1.79	1.52–2.10	<0.001	--	--	--	--	--	--
Neutrophils (%)	0.019	0.011	2.991	1.02	1.00–1.04	0.084	--	--	--	--	--	--
Procalcitonin (µg/L)	0.002	0.003	0.875	1.00	1.00–1.01	0.350	--	--	--	--	--	--
Lactate (mmol/L)	−0.007	0.013	0.289	0.99	0.97–1.02	0.591	--	--	--	--	--	--
IL-6 (pg/mL)	<0.001	<0.001	1.918	1.00	1.00–1.00	0.166	--	--	--	--	--	--

*: Binary Logistic Regression Test (Results are given only for variables remaining in the model), Nagelkerke $R^2 = 0.781$, Hosmer and Lemeshow Test = 0.441, Variable(s) removed on step 2: Baseline ferritin (µg/L), step 3: Creatinine (mg/dL), step 4: Troponin-I, step 5: Platelet (×10⁹/L), step 6: C-Reaktiv Protein (g/L), step 7: Chronic renal failure, step 8: Lymphocytes (%), step 9: Gender, step 10: Lactate dehydrogenase (U/L), step 11: Hemoglobin (g/dL).

Table 3. Receiver operating characteristic analysis of the predictive performance of survivor and deceased patient groups.

	AUC	95% CI	Cut-Off	Sensitivity (%)	Specificity (%)	Youden Index	+PV	−PV	<i>p</i> Value
Age (years)	0.598	0.540–0.654	>67	82.9	35.2	0.181	58.7	64.9	0.003
Baseline ferritin (µg/L)	0.615	0.557–0.671	>201.5	66.0	54.2	0.203	61.3	59.2	<0.001
Maximum ferritin (µg/L)	0.754	0.701–0.802	>878.6	68.0	73.2	0.412	73.6	67.5	<0.001
Lactate dehydrogenase (U/L)	0.647	0.590–0.701	>301	76.6	50.0	0.266	63.0	65.7	<0.001
Troponin-I (ng/L)	0.681	0.624–0.733	>33	73.9	59.6	0.335	67.1	67.2	<0.001
Creatinine (mg/dL)	0.626	0.568–0.681	>0.99	68.4	55.6	0.240	63.2	61.2	<0.001
Neutrophils (%)	0.611	0.553–0.667	>89.8	46.8	73.9	0.208	66.7	55.6	0.001
Lymphocytes (%)	0.632	0.575–0.687	≤5.4	47.5	76.8	0.242	69.4	56.8	<0.001
Hemoglobin (g/dL)	0.585	0.527–0.642	≤11.5	63.9	50.7	0.146	59.1	55.8	0.010
Platelet (×10 ⁹ /L)	0.576	0.518–0.632	≤111	20.3	95.1	0.153	82.1	51.7	0.021
C-reactive protein (g/L)	0.592	0.534–0.648	>93	60.8	55.6	0.164	60.4	56.0	0.005
Procalcitonin (µg/L)	0.666	0.609–0.719	>0.39	67.1	62.0	0.291	66.2	62.9	<0.001
International normalized ratio	0.620	0.562–0.675	>1.13	72.2	49.3	0.215	61.3	61.4	<0.001
D-dimer (mg/L)	0.613	0.555–0.668	>2.06	66.9	53.5	0.204	61.4	59.4	0.001
Lactate (mmol/L)	0.598	0.539–0.654	>2.22	56.8	65.0	0.217	64.7	57.1	0.003
IL-6 (pg/mL)	0.594	0.515–0.669	>38.8	57.6	61.7	0.192	72.6	45.1	0.036

Table 4. Comparison of patients according to cut-off value of baseline ferritin level.

Baseline Ferritin	Survivor	Non-Survivor	<i>p</i> Value	Odds Ratio
Low	77 (54.2%)	53 (33.5%)	<0.001	2.347 (95% CI: 1.5–3.7)
High	65 (45.8%)	105 (66.5%)		

p value was calculated using chi-square test (n (%)).

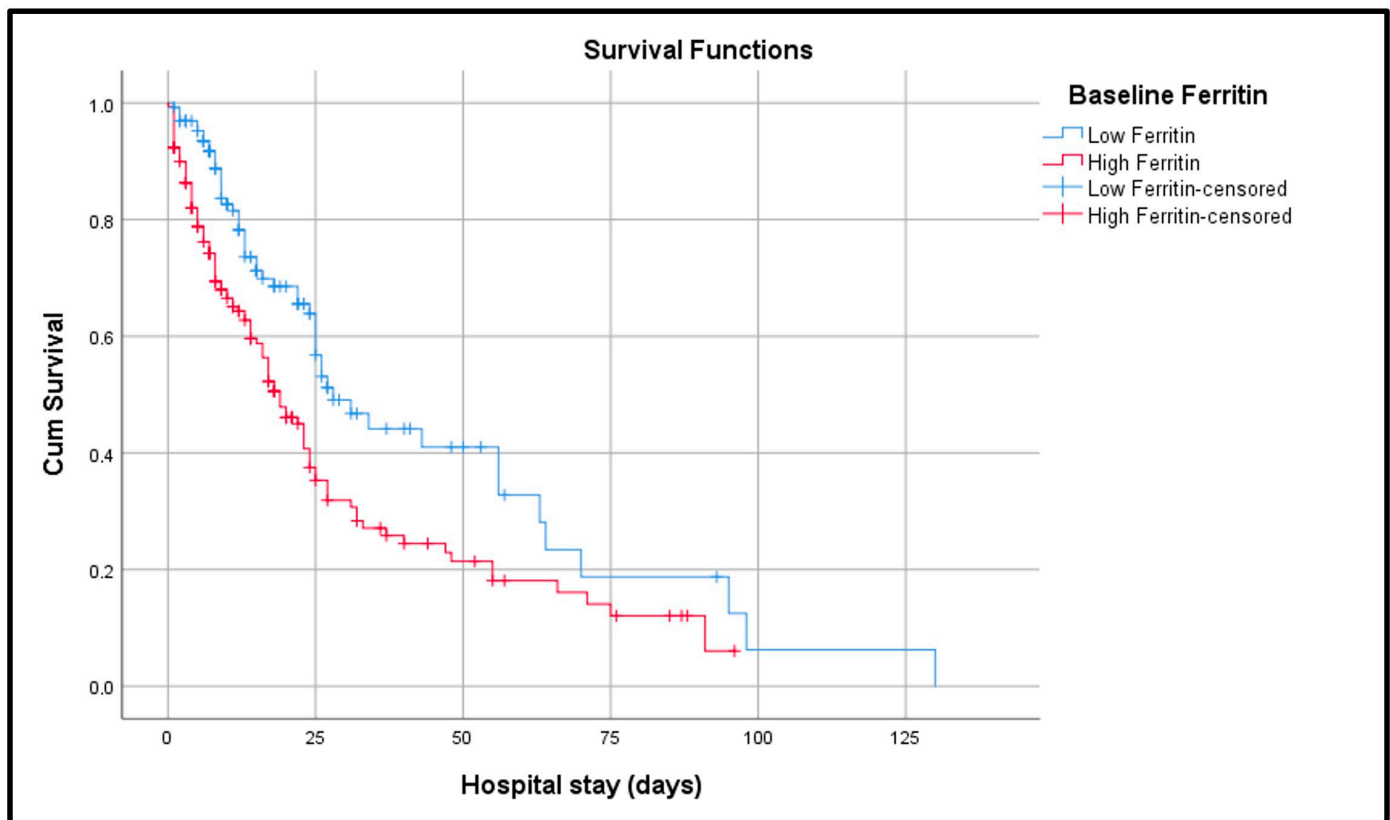


Figure 2. Kaplan–Meier estimates of survival function of low and high ferritin levels.

4. Discussion

We found that high ferritin levels were associated with poor prognoses in COVID-19 patients. Both baseline and maximum ferritin values were higher in the non-survivor group. The cut-off baseline value for ferritin was 201.5 $\mu\text{g/L}$ (AUC: 0.615, $p < 0.001$, 95% CI: 0.557–0.671). Baseline ferritin levels exhibited 66% sensitivity and 54.2% specificity in predicting living and dead patients. The maximum ferritin cut-off value was 878.6 $\mu\text{g/L}$ (AUC: 0.754, $p < 0.001$, 95% CI: 0.701–0.802). The maximum ferritin value exhibited 68% sensitivity and 73.2% specificity as a mortality indicator. Both baseline ferritin and maximum ferritin levels are not strong predictors in differentiating surviving and deceased patients with respect to moderate sensitivity and specificity.

Feld et al. analyzed the serum ferritin levels of 942 patients with COVID-19 who were admitted to multiple hospitals in New York from March 2020 to April 2020 [10]. They reported 799 $\mu\text{g/L}$ as the cut-off value and 0.638 AUC for admission ferritin levels in predicting mortality (sensitivity of 0.557, specificity of 0.603; positive predictive value of 0.356 and negative predictive value of 0.776). The cut-off value was 862 $\mu\text{g/L}$, and AUC was 0.677 for the maximum ferritin value in predicting mortality (sensitivity of 74% and specificity of 49.3%; positive predictive value of 0.364 and negative predictive value of 0.829). They postulated that ferritin has poor discrimination ability for the prediction of mortality [10]. Lanchmann et al. analyzed the maximum ferritin levels of 2623 critically ill patients admitted to the adult ICU between January 2006 and August 2018, before the COVID-19 pandemic. Ferritin was not strongly associated with hospital mortality, and the cut-off value determined in the ROC analysis was insufficient for discriminating mortality estimations (AUC: 0.655, 95% CI: 0.631–0.679) [1].

Hammad et al. divided a total of 160 COVID-19 patients into two groups: 80 mild to moderate and 80 severe. This division was carried out based on fever, respiratory symptoms, oxygen saturation, and CT images. While ferritin was $411 \pm 76.1 \mu\text{g/L}$ in severe cases, it

was 85.6 ± 31.4 $\mu\text{g/L}$ in mild to moderate cases, and the difference between the groups was statistically significant ($p < 0.001$). Receiver operating characteristic curves for ferritin predicted COVID-19 severity as follows: a cut-off of 57.15 $\mu\text{g/L}$, AUC of 0.816, sensitivity of 80%, specificity of 70%, and 95% CI ($p < 0.0011$) [11]. Abdelhakam et al. investigated ferritin in 66 severe and 58 mild COVID-19 patients to predict COVID-19 severity. The median ferritin level in mild cases was 227 $\mu\text{g/L}$ (minimum of 127 and maximum of 290), while in severe cases, the median was 778 $\mu\text{g/L}$ (minimum of 455 and maximum of 1225) ($p < 0.001$). The cut-off value for ferritin in predicting COVID-19 severity was 397 $\mu\text{g/L}$ (AUC of 0.86, sensitivity of 83.3%, and specificity of 93.1%) [12]. Zhou et al. analyzed iron homeostasis as a predictor of COVID-19 severity. The serum ferritin levels of 12 COVID-19 severe patients and 38 mild COVID-19 patients were compared with 50 healthy participants. Serum ferritin was 207.8 ± 45.2 $\mu\text{g/L}$ in the severe group, 135.6 ± 20.7 $\mu\text{g/L}$ in the mild group, and 85.2 ± 18.6 $\mu\text{g/L}$ in the healthy group ($p < 0.001$). Serum ferritin levels (OR = 10.01 [95% CI = 2.306, 43.362], $p = 0.002$) independently influenced the prediction of COVID-19 severity. The ferritin cut-off value for COVID-19 severity was 162 $\mu\text{g/L}$ (86.9% sensitivity and 70.3% specificity) [13]. Lino et al. suggested that the serum ferritin levels of COVID-19 patients admitted to the hospital were associated with mortality. The laboratory characteristics of 44 deceased and 53 surviving patients discharged from the hospital were compared. The mean serum ferritin levels were 1717.7 ± 2789.8 $\mu\text{g/L}$ in the group discharged from the hospital and 4207.7 ± 3530.3 $\mu\text{g/L}$ in the deceased group ($p < 0.05$). The cut-off value of ferritin for mortality prediction was 1873 $\mu\text{g/L}$ (AUC of 0.79, sensitivity of 68.4%, and specificity of 79.3%, $p < 0.001$) [14].

Colafrancesco et al. studied the common features of septic shock, adult-onset Still's disease, macrophage activation syndrome, and catastrophic anti-phospholipid syndrome with respect to the severe clinical picture of COVID-19. The common features of all these pathological characteristics are cytokine storm, multiorgan failure, and high ferritin levels [15]. Ferritin levels were higher in deceased COVID-19 patients. Ahmet et al. studied COVID-19 patients between 1 March 2020, and 10 August 2020, at the Aga Khan University Hospital in Karachi, Pakistan. They divided them into two groups: living ($n = 129$) and deceased ($n = 28$). The median ferritin level was high (1096.4 ng/mL) in the deceased group, while it was lower (548.9 ng/mL) in the surviving group. This difference was statistically significant according to the Mann–Whitney U test ($p < 0.05$) and binary logistic regression analysis ($p < 0.05$) [16].

Deng et al. divided 100 COVID-19 patients—admitted to the Sino-French New City Branch of Tongji Hospital (Wuhan, China) from 30 January 2020, to 30 March 2020—into two groups: living ($n = 50$) and deceased ($n = 50$). The median ferritin level was 1722.25 $\mu\text{g/L}$ in the deceased group and 501.90 $\mu\text{g/L}$ in the survivor group ($p < 0.01$) [17], indicating higher values in deceased COVID-19 patients than in the surviving COVID-19 patients. Mehta et al. postulated that severe COVID-19 is associated with secondary hemophagocytic lymphohistiocytosis, which is mostly triggered by viral infections. Sepsis may result in hemophagocytic lymphohistiocytosis. Increased cytokine levels result in inflammation and ultimately multiorgan failure. One of the common features of secondary hemophagocytic lymphohistiocytosis cases with severe COVID-19 is high ferritin levels [18]. Hyperferritinemia in COVID-19 patients causes cardiovascular damage, resulting in cardiac arrest [6].

Various pathophysiological mechanisms have been proposed for severe COVID-19. Virus replication, the invasion of tissues by viruses, cell damage, inflammation, and hypercoagulation are potential reasons for clinically severe disease. Furthermore, this virus triggers iron release from porphyrins by destroying hemoglobin. Ferritin levels increase to compensate for the high iron levels, which may lead to the death of hepatic cells. The death of hepatic cells also elevates ferritin levels. Extremely high free iron increases the oxidative

damage induced by reactive oxygen species. This results in ferroptosis, causing increased inflammation and multiple organ failures [19]. The current study showed that there were increased C-reactive protein, procalcitonin, and IL-6 profiles in deceased patients compared to surviving patients. A comparison of severe and mild COVID-19 for IL-2R/lymphocytes and ferritin revealed a lower AUC ferritin value (0.812) compared to IL-2R/lymphocytes (0.948). The IL-2R/lymphocytes predicted the clinical progression of COVID-19 more accurately than ferritin [9].

Our findings indicate a correlation between elevated ferritin levels and mortality in COVID-19 patients. While ferritin's sensitivity and specificity in mortality prediction are moderate, it can serve as a supplementary tool in patient risk assessment. Earlier studies also suggested ferritin as an independent mortality risk factor for COVID-19. The cut-off values of 201.5 µg/L for baseline ferritin and 878.6 µg/L for the maximum ferritin level in the current study align with earlier studies.

The limitations of the current study are as follows: low number of cases, lack of analysis of various situations, retrospective observational design, different variants of the virus, previous infections by the virus, affectedness of lungs, and single-center design. Unfortunately, there are many factors that may yield biased results. Future research should be focused on ferritin levels in different clinical situations relative to intensive care patients.

5. Conclusions

The current study indicates that, while serum ferritin can be a valuable indicator for predicting hospital mortality in critically ill COVID-19 patients, its predictive capacity is moderate. These findings are particularly relevant for patients admitted to the ICU. However, further studies should be performed to comprehend the relationship between COVID-19 and ferritin.

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