Elevated serum ferritin level effectively discriminates severity illness and predicts prognosis of COVID-19 patients

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Research

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Abstract

During coronavirus disease 2019 (COVID-19) pandemic, medical resources in every country is in shortage. Efficacious indicators of discriminating severe illness and predicting outcome is in urgent need.

We collected data and clinical records from 79 COVID-19 patients admitted between January 12, 2020 and February 21, 2020 at Wuhan Union hospital, China. Spearman's correlation analysis, receiver operating characteristic (ROC) curve, logistic regression model, and Kaplan-Meier survival curves were employed in the analysis.

Of 79 patients enrolled, 2 died in hospital, 8 were transferred to other hospitals, and 69 were discharged. Patients with elevated ferritin levels (> 200 ng/mL) had a higher incidence of severity illness when compared with those with normal ferritin levels (≤ 200 ng/mL) (50.0% vs 2.9%). In addition, severity illness manifested significantly higher level of ferritin as compared with non-severe ones (median 921.3 vs 130.7 ng/mL, $p < 0.001$). Furthermore, ferritin could effectively discriminate severity and non-severity, with an area under the ROC curve (AUC) reaching 0.873 (sensitivity 96%, specificity 70%), larger than that of age (0.697), C-reactive protein (0.730) and lymphocytes% (0.717). Combined model incorporating multivariate revealed a similar manner with ferritin alone ($p = 0.981$). Furthermore, elevated ferritin group showed longer viral clearance time (median 16 vs 6 days, $p < 0.001$) and in-hospital length (median 18 vs 10 days, $p < 0.001$).

Our results suggest that ferritin could act as a simple and efficacious complementary tool to identify severe COVID-19 patients at early stage and predict their outcome. This indicator would provide guidance for subsequent clinical practice, alleviate the medical stress and reduce the mortality.

1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic has spread to 44 countries on all continents except Antarctica and the number of diagnosed cases worldwide is accelerating every day [1]. Medical resources in every country are in shortage or even overdrawn, so there is an urgent need of seeking indicators for disease severity and prognosis at early stage, which is believed to significantly reduce the medical stress and mortality rate. However, such efficient indicators have not been fully investigated. Currently, the definition of severe cases mainly relies on the observation of clinical manifestation [2, 3], and the prognosis of COVID-19 remains inconclusive.

Ferritin is the primary tissue iron-storage protein in the liver, it is also an acute-phase protein that can be induced in the setting of systemic inflammation [4]. Ferritin is able to act as an independent predictor of discriminating the severity of nonalcoholic fatty liver disease [5]. Recent studies related to COVID-19 have consistently discovered the abnormal level of ferritin in severe COVID-19 patients, but further exploration of its value is halted [6, 7]. Herein, we aimed to assess the ability of ferritin in discriminating severe patients from non-severe ones on admission, and the potential of predicting viral clearance rate and hospitalization duration, to provide guidance for subsequent clinical practice.

2. Methods

2.1 Participants

From January 12, 2020 to February 21, 2020, a total of 147 consecutive patients were initially enrolled from the department of infectious diseases of Wuhan Union Hospital, all of which were confirmed cases of COVID-19 after examination of COVID-19 RNA by RT-PCR (upper respiratory throat swab samples) and chest computerized tomography (CT) scanning. One patient who died of traumatic brain injury with viral pneumonia was excluded. Patients without ferritin detection on admission were excluded. Therefore, 79 inpatients were enrolled in this study. By March 14, 2 patients died, 8 patients were transferred to other hospitals, and the remaining patients were discharged.

According to "diagnosis and treatment of novel coronavirus pneumonia", severe illness on admission was defined when any of the following criteria is met [8]: 1. shortness of breath (respire rate ≥ 30 times/min); 2. the oxygen saturation is less than 93% in resting state; 3. arterial partial pressure of oxygen (PaO_2)/oxygen concentration (FiO_2) ≤ 300 mmHg (1mmHg = 0.133 kPa).

2.2 Data collection

The data of demographics, laboratory examinations, CT scan, clinical characteristics, treatments and outcomes were acquired by the hospitalization management system. All the data were collected by well-trained researchers with a double-blind method. Data collection of laboratory results were defined using the first-time examination at admission. The date of symptom onset, admission, negative detection of COVID-19 RNA, discharge and death were recorded accurately. The date of admission was used as the starting point of the virus clearance process, and the date of the negative detection of COVID-19 RNA was calculated as the ending point of viral clearance.

2.3 Statistical Analysis

The data were presented as mean ± standard deviation (SD) or median (Inter Quartile Range, IQR). Intergroup comparisons between groups were made by the Student's *t* test (normally distributed continuous variables), Mann-Whitney *U* test (nonnormally distributed continuous variables). The categorical variables (shown by percentage) were compared by using Chi-square analysis. Spearman's correlation analysis was used to explore the coefficients of ferritin with other covariates. The performance of the discriminant model was characterized by estimating the area under the receiver operating characteristic (ROC) curve (AUC). The cutoff value of ROC was calculated based on the maximum Youden index, which was used to assess the global diagnostic effectiveness. Cumulative survival curves of hospitalization span and viral clearance time were estimated using the Kaplan-Meier estimation method for two groups with normal and elevated ferritin levels (ferritin ≤ 200 ng/mL and ferritin > 200 ng/mL) by log-rank test. All of the analyses were performed with the R software version 3.4.3 (http://www.R-project.org, The R Foundation) and EmpowerStats version 2.20 (http://www.empowerstats.com, X&Y Solutions, Inc., Boston, MA). A two-sided *P* value < 0.05 was determined as with statistically significant differences.

3. Results

3.1 Baseline data

All participants were divided into two groups by normal and elevation ferritin levels (ferritin ≤ 200 ng/mL and ferritin > 200 ng/mL) according to clinical reference range. As shown in Table 1, severe cases were more frequently found in patients with higher ferritin levels, compared to those who with normal ferritin levels (50.0% vs 2.9%, p < 0.001). There were significant differences of sex between the two groups, with male patients accounting for the 68.2% in elevation ferritin group but only 17.1% in normal ferritin group (p < 0.001). The average age of elevation ferritin group was also significantly older than the normal ferritin group (49.9 vs 36.8 years old). The other characteristics including systolic blood pressure (SBP), diastolic blood pressure (DBP), respire, pulse, smoking, comorbidities and symptoms of both groups were recorded but no statistical difference was found.

3.2 Laboratory examination

As displayed in Supplementary Table 1, the levels of triglyceride (TG), serum amyloid A protein (SAA), alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyl transferase (γ-GT), interleukin-6 (IL-6), creatinine (Cre), lactate dehydrogenase (LDH), fibrinogen (FIB), fibrinogen degradation product (FDP), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) in elevation ferritin group were extremely higher than those of normal ferritin group (p < 0.001). The levels of fasting blood glucose (FBG), alkaline phosphatase (ALP), natural kill-cell (NK-cell), creatine kinase (CK), troponin (TNI), thrombin time (TT), D-dimer, haemoglobin, leucocytes, neutrophils and neutrophil-to-lymphocyte ratio (NLR) in elevation ferritin group were also higher than those of normal group (p < 0.05). However, the levels of high-density lipoprotein cholesterol (HDL-c), albumin, CD3 + and estimated glomerular filtration rate (eGFR) in elevation ferritin group were significantly lower than those of normal ferritin group (p < 0.05). The other indicators showed no insignificance between two groups.

Furthermore, a spearman's correlation analysis was employed to demonstrate the relationship between ferritin and other covariates (Fig. 1). Ferritin was highly positively correlated to FIB, LDH, SAA, γ-GT, NK-cell, FDP, ESR, AST, ALT, CRP, CK, IL-6, Cre and TT (r > 0.4 and p < 0.001), and negatively associated with eGFR and CD3 + with a statistical significance (r<-0.45 and p < 0.0005).

3.3 Determination of ferritin and corresponding CT manifestation

As mentioned above, there existed significantly more severe cases in elevation ferritin group than the normal group. In addition, we compared the ferritin levels among severe and non-severe patients, finding that the ferritin level of severe group is significantly higher than that of non-severe group (median 921.3 (IQR 440.0-1609.8) vs median 130.7 (IQR 58.8-320.4), p < 0.001) (Fig. 2A). Furthermore, we recorded the ferritin levels which were calculated from the onset of symptom of each patient. Likewise, at every stage the ferritin level of sever group was markedly higher than their counterparts (Fig. 2B). On the other side, we observed the CT images that were corresponding to the ferritin values in three representative patients (Fig. 2C). The results demonstrated that the severity of pulmonary imaging was consistent with the ferritin level. Taken together, the ferritin level is able to reveal the severity of COVID-19.

3.4 Diagnostic ability of ferritin

The AUC of ROC plot for ferritin was 0.873 (95% *CI*: 0.798–0.954), larger than that of age (0.697, 95% *CI*: 0.567–0.828), CRP (0.730, 95% *CI*: 0.602–0.859) and lymphocytes% (LYM%, 0.717, 95% *CI*: 0.586–0.847), indicating ferritin possesses a considerable diagnostic value for severity of patients on admission. The best cutoff value of ferritin was 272.5 ng/mL, with a sensitivity of 96% and specificity of 70% (Fig. 3A). Furthermore, we established a multivariable diagnostic model incorporating sex, age, ferritin, LYM% and CRP (n = 69, 0.862 (95% *CI*: 0.761–0.962), sensitivity 77%, specificity 87%) (Fig. 3B). It is interesting to find that the diagnostic ability of integrated model showed the

similar value as ferritin alone with the AUC showing (n = 69, 0.861 (95% *CI*: 0.773–0.949), sensitivity 95%, specificity 68%) (p = 0.981). These results suggest that ferritin may act as an independent risk factor on COVID-19 patients.

In addition, we employed logistic regression analysis to assess the risk factors related with severity illness (Fig. 3C). The results showed that a 100 ng/mL increase in serum ferritin, the odds ratio (OR) of severity illness was 1.17 (95% *CI*: 1.03–1.33, p = 0.014). After adjusted for sex, age, CRP or LYM%, the OR of severity illness was 1.20 (95% *CI*: 1.02–1.41, p = 0.014). Moreover, Fig. 3D showed that the OR of severity illness for serum ferritin was 10.78 (95% *CI*: 1.13-102.73, p = 0.039) when serum ferritin was calculated as categorical variable (> 200 ng/mL vs ≤ 200 ng/mL) in crude model. After adjusted for age, sex, CRP and LYM%, the OR of severity illness for patients with elevated ferritin level (> 200 ng/mL) was 18.75 (95% *CI*: 1.28, 275.41, p = 0.032), as compared with patients with normal ferritin level (≤ 200 ng/mL). Therefore, we established a nomogram based on the above risk factors to improve the availability in clinical practice (Fig. 4).

3.5 Prognostic ability of ferritin

Median duration of viral clearance was 6 days (IQR 2–25) in normal ferritin group (≤ 200 ng/mL, but elevation ferritin group (> 200 ng/mL) was 16 days (IQR 2–47). The viral clearance events in in normal group and elevation ferritin group by using Kaplan-Meier survival analysis were displayed in Fig. 5A (p < 0.001).

Besides, we recorded the length of hospitalization of all patients except 2 deceased ones and 8 patients that transferred to other hospitals. Our result showed that patients with higher ferritin levels on admission stayed in hospital for a longer time (18 days, IQR 3–47), when compared with the ones with normal ferritin levels (10 days, IQR 5–29). The discharge events in in normal group and elevation ferritin group by using Kaplan-Meier survival analysis are displayed in Fig. 5B (p < 0.001).

4. Discussion

The number of diagnosed COVID-19 patients worldwide is increasing rapidly every day. Until now, there is no effective medicine available to treat COVID-19. Medical resources in every country are in shortage or even overdrawn, so there is an urgent need of identifying severe cases and poor prognosis cases at early stage of disease. Only in this way, can medical staffs make greater use of limited medical resources and reduce mortality. Recent clinical data have indicated that lymphocyte [9, 10], CRP [11] and other factors may be related to the severity of COVID-19 [6]. However, the role of ferritin seems to be ignored even though clinical observation has discovered the abnormal ferritin levels in severe COVID-19 patients [6]. For the first time, the present study shows the relationships between ferritin and severity and viral clearance in COVID-19 patients.

Herein, the data of 79 patients with COVID-19 pneumonia were analyzed, the baseline characteristics of patients in the severe and non-severe groups were described and compared, and the dynamic changes of ferritin and imaging were demonstrated. Our results showed that ferritin levels differed significantly between severity and non-severity illness. Ferritin variations were also consistent with CT manifestation, presenting the ability to act as a sensitive and accurate indicator. Then, the diagnostic value of ferritin for the incidence of severe illness was compared to that of age, sex, CRP and LYM%, which had been recognized as the risk factors of COVID-19 [9, 12–14]. Our results showed that the AUC of ferritin ROC were significantly larger than other risk factors, and the multivariable combined model manifested similar ability compared with ferritin alone, demonstrating that ferritin was an independent easy-to-use predictor. In addition, we compared the viral clearance rate and in-hospital length between elevation ferritin group and normal group, finding that ferritin was also a discriminated indictor for prognosis of COVID-19 patients. Viral clearance is the golden standard for defining the recovery of COVID-19 infections and predicting in-hospital length is extremely vital in COVID-19 pandemic due to the lack of medical resource [15]. Thus, we suppose ferritin could act as both an effective discriminator for severity illness and a predictor for prognosis.

Ferritin is an acute phase protein which can be released from damaged hepatocytes [16]. Hyperferritinemia has been previously recognized in abnormal liver function conditions or metabolic syndrome [5, 17, 18]. In our study, the severe patients on admission manifested slight risk of liver injury and dyslipidemia. Other observations also find that liver injury is prevalent in severe cases of COVID-19 [19]. Therefore, we recommend that patients should pay close attention to the risk of developing secondary liver diseases or metabolic syndrome after they are discharged. Intensive surveillance and regular comprehensive medical examination are necessary, especially for the severe patients.

However, there were some limitations in the study. First, this was a single-center retrospective study with limited size. Second, some cases had incomplete biochemistry determinations. Third, the present study failed to predict the mortality of COVID-19 patients due to the insufficient number of deaths.

In summary, the findings indicate that early examination of ferritin in COVID-19 patients could effectively discriminate severity illness and predict the prognosis. Therefore, ferritin could act as a simple complementary tool to help guiding clinical decision and facilitating appropriate treatment. Patients with elevated admission ferritin level should be provided with strengthened attention and treatment. More

studies are needed to confirm these findings and to explore exact pathological mechanisms. Further understanding of pathological significance of serum ferritin elevation in severe COVID-19 patients is warranted to help clinicians make reasonable decisions to decrease the risks of adverse outcome.

5. Conclusion

In conclusion, serum ferritin might be an independent risk factor for severity illness and predictor for prognosis of COVID-19 patients.

Abbreviations

ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; AUC: area under the curve; CK: creatine kinase; COVID-19: coronavirus disease 2019; Cre: creatinine; CRP: C-reactive protein; CT: computerized tomography; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; ESR: erythrocyte sedimentation rate; FBG: fasting blood glucose; FDP: fibrinogen degradation product; FIB: fibrinogen; HDL-c: high-density lipoprotein cholesterol; IL-6: interleukin-6; IQR: Inter Quartile Range; LDH: lactate dehydrogenase; NK-cell: natural kill-cell; NLR: neutrophils and neutrophil-to-lymphocyte ratio; OR: odds ratio; ROC: receiver operating curve; SAA: amyloid A protein; SBP: systolic blood pressure; SD: standard deviation; TG: triglyceride; TNI: troponin; TT: thrombin time; γ-GT: γ-glutamyl transferase

Declarations

Conflicts of interest

The authors declare no conflicts of interest.

Consent for publication

Not applicable.

Availability of data and materials

The raw data required to reproduce these findings cannot be shared at this time as the data also forms part of an ongoing study.

Author contributions

Peng Cao: Data collection, Writing-Original draft preparation, Conceptualization; **Yuanjue Wu:** Data analysis, manuscript revision; **Sanlan Wu:** Data collection; **Tingting Wu:** Data collection; **Rui Zhang:** Data collection; **Qilin Zhang:** Data collection; **Yu Zhang:** Supervision.

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Ethics approval and consent to participate

This study had been approved by the Ethics Committee of the Union Hospital, Tongji Medical College, Huazhong University of Science and Technology (Review date: March 24, 2020) and was exempted from the need for informed consent from patients because it was a retrospective assessment. All procedures followed the instructions of local ethic committee (approval 2020 NO. 0134).

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Tables

Table 1. Demographic and characteristics of COVID-19 patients [a]

	Total	Normal ferritin group （≤200 ng/mL）	Elevation ferritin group（>200 ng/mL）	p-value
	n=79	n=35	n=44	
Severe patient	23 (29.1%)	1 (2.9%)	22 (50.0%)	<0.001
Baseline				
Age (years)	44.1 ± 14.4	36.8 ± 12.6	49.9 ± 13.1	<0.001
Sex (male)	36 (45.6%)	6 (17.1%)	30 (68.2%)	<0.001
Days from illness onset to admission, day	8.5 (5.0-15.0)	10.0 (5.0-15.0)	7.0 (5.5-14.5)	0.324
SBP (mmHg)	126.5 ± 16.0	122.5 ± 15.9	130.5 ± 15.3	0.048
DBP (mmHg)	79.2 ± 10.4	77.6 ± 9.4	80.7 ± 11.2	0.244
Respire (breaths per min)	20.1 ± 1.0	20.1 ± 1.1	20.1 ± 0.9	0.894
Pulse (beats per min)	84.7 ± 10.7	84.0 ± 9.8	85.4 ± 11.7	0.602
Smoking (yes)	3 (3.8%)	3 (8.6%)	0 (0.0%)	0.048
Disease severity status				<0.001
Severe	23 (29.1%)	1 (2.9%)	22 (50.0%)	
Non-severe	56 (70.9%)	34 (97.1%)	22 (50.0%)	
Comorbidities				
Diabetes	9 (11.4%)	5 (14.3%)	4 (9.1%)	0.470
Hypertension	14 (17.7%)	7 (20.0%)	7 (15.9%)	0.636
Others	27 (34.2%)	9 (25.7%)	18 (40.9%)	0.157
Symptoms				
Fever	59 (74.7%)	23 (65.7%)	36 (81.8%)	0.102
Cough	39 (49.4%)	17 (48.6%)	22 (50.0%)	0.900
Fatigue	20 (25.3%)	8 (22.9%)	12 (27.3%)	0.654
Sore muscle	8 (10.1%)	6 (17.1%)	2 (4.5%)	0.065
Diarrhea	2 (2.5%)	0 (0.0%)	2 (4.5%)	0.201
Chest distress	11 (13.9%)	6 (17.1%)	5 (11.4%)	0.461
Expectoration	6 (7.6%)	4 (11.4%)	2 (4.5%)	0.251
Sore throat	5 (6.3%)	3 (8.6%)	2 (4.5%)	0.465
Headache	4 (5.1%)	2 (5.7%)	2 (4.5%)	0.814
Anhelation	15 (19.0%)	5 (14.3%)	10 (22.7%)	0.342
Drug Treatment				
Antivirus	76 (96.2%)	33 (94.3%)	43 (97.7%)	0.427
Antibacteria	67 (84.8%)	28 (80.0%)	39 (88.6%)	0.288
Expectorant	30 (38.0%)	11 (31.4%)	19 (43.2%)	0.285
Hormone	13 (16.5%)	3 (8.6%)	10 (22.7%)	0.092
Hepatinica	18 (22.8%)	6 (17.2%)	12 (27.3%)	0.286
Chinese medicine	16 (20.3%)	5 (14.3%)	11 (25.0%)	0.239
Immune Globulin	19 (24.1%)	8 (22.9%)	11 (25.0%)	0.825
Outcome				0.011
Discharged	69 (87.3%)	35 (100.0%)	34 (77.3%)	
Death	2 (2.5%)	0 (0.00%)	2 (4.5%)	
Transfer to other hospital	8(10.1%)	0 (0.00%)	8 (18.2%)	

[a] Continuous variable was presented as mean ± SD or median (IQR), categorical variables were showed as n (%). p-values were from *t* test for normally distributed continuous data and from Mann-Whitney U test for abnormally distributed continuous data. p-values were from χ^2 test for categorical data.

Figures

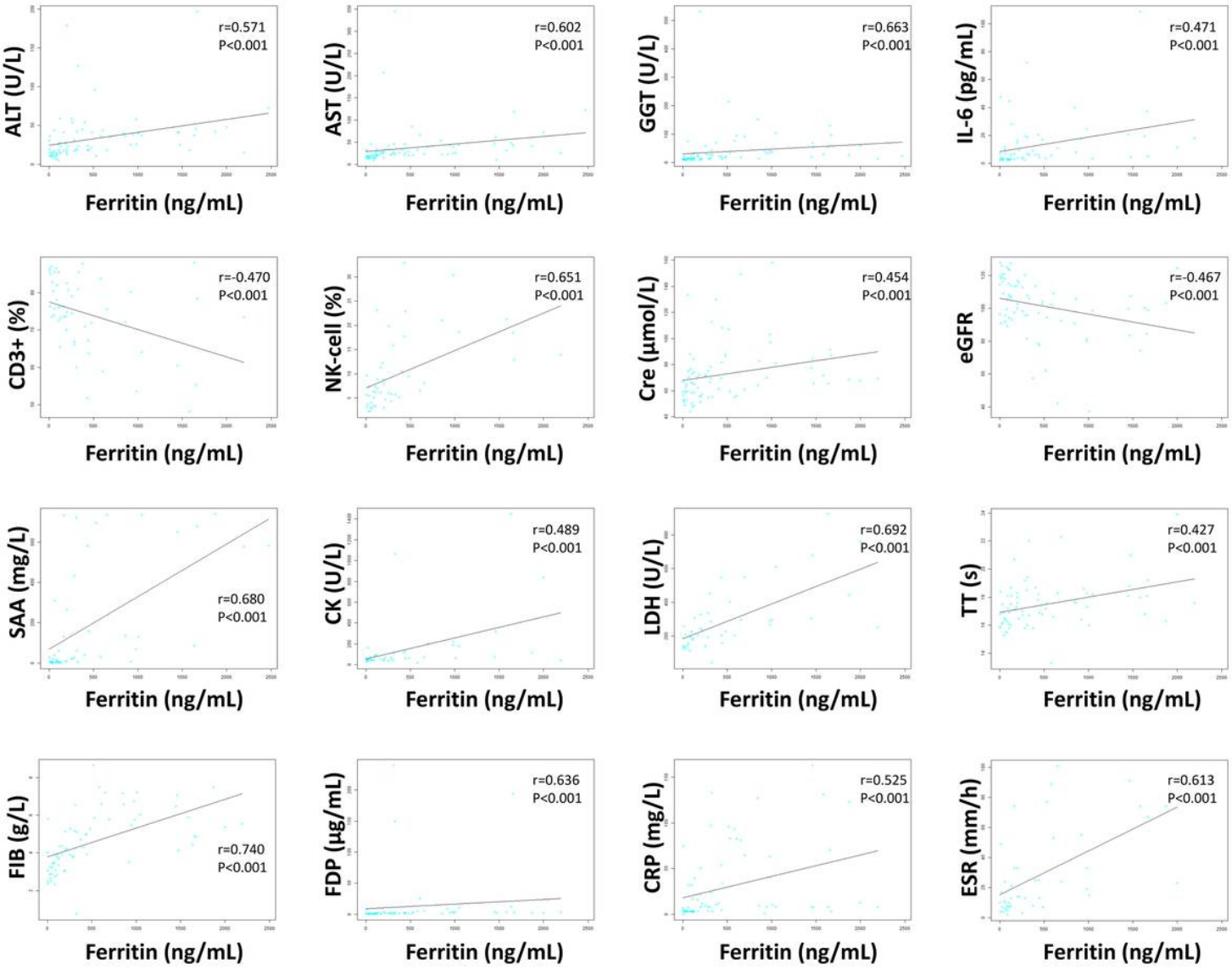

Figure 1

Correlation between ferritin and other serum biomarkers.

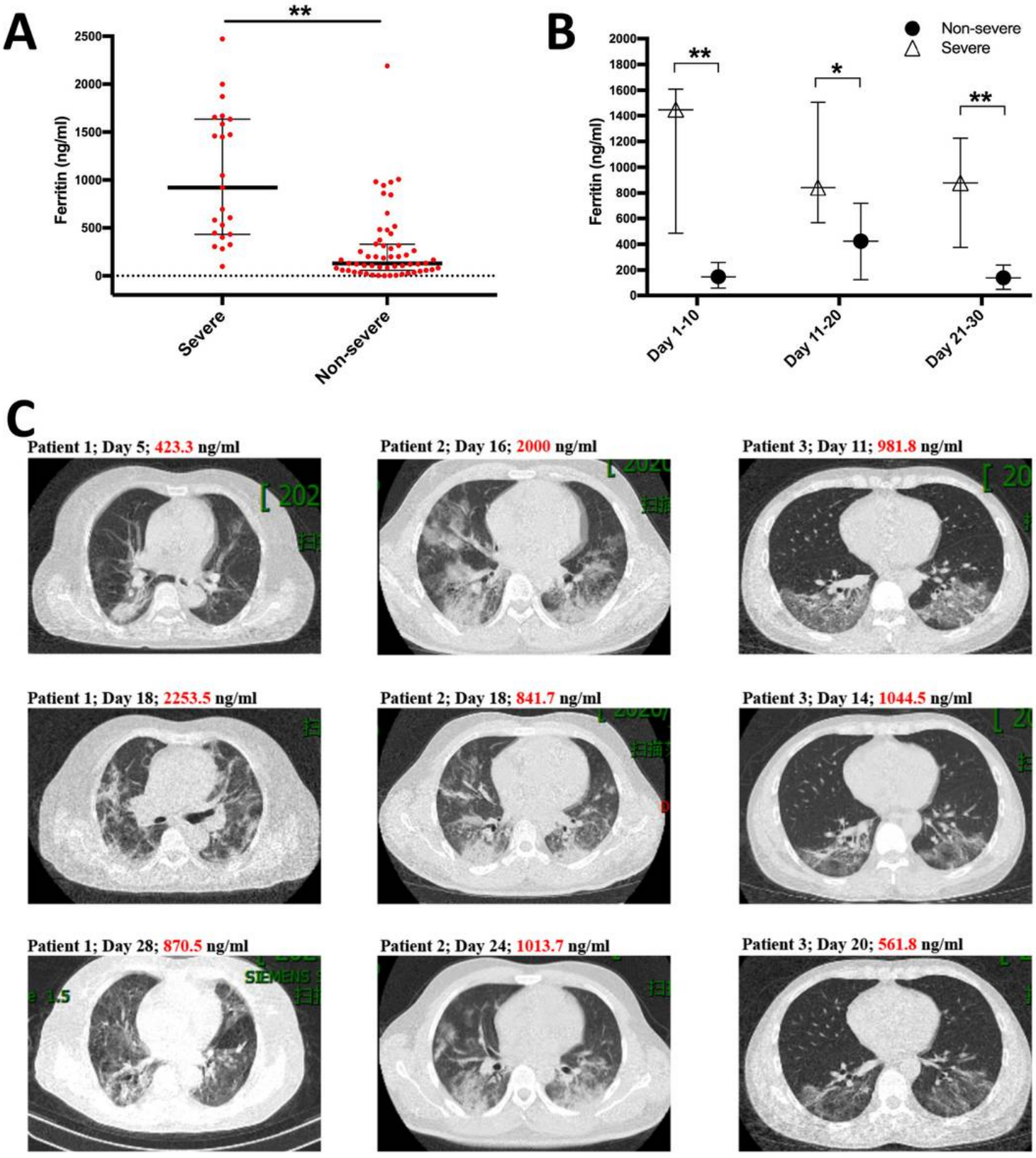

Figure 2

(A) The levels of ferritin in severe and non-severe patients on admission; (B) The monitor of ferritin calculated from the onset of symptom; (C) CT manifestation of severe (patient 1&2) and non-severe (patient 3) cases (the corresponding ferritin levels and time points are displayed on the top of each image). The data are shown as median (IQR); ** p<0.001, * p<0.01.

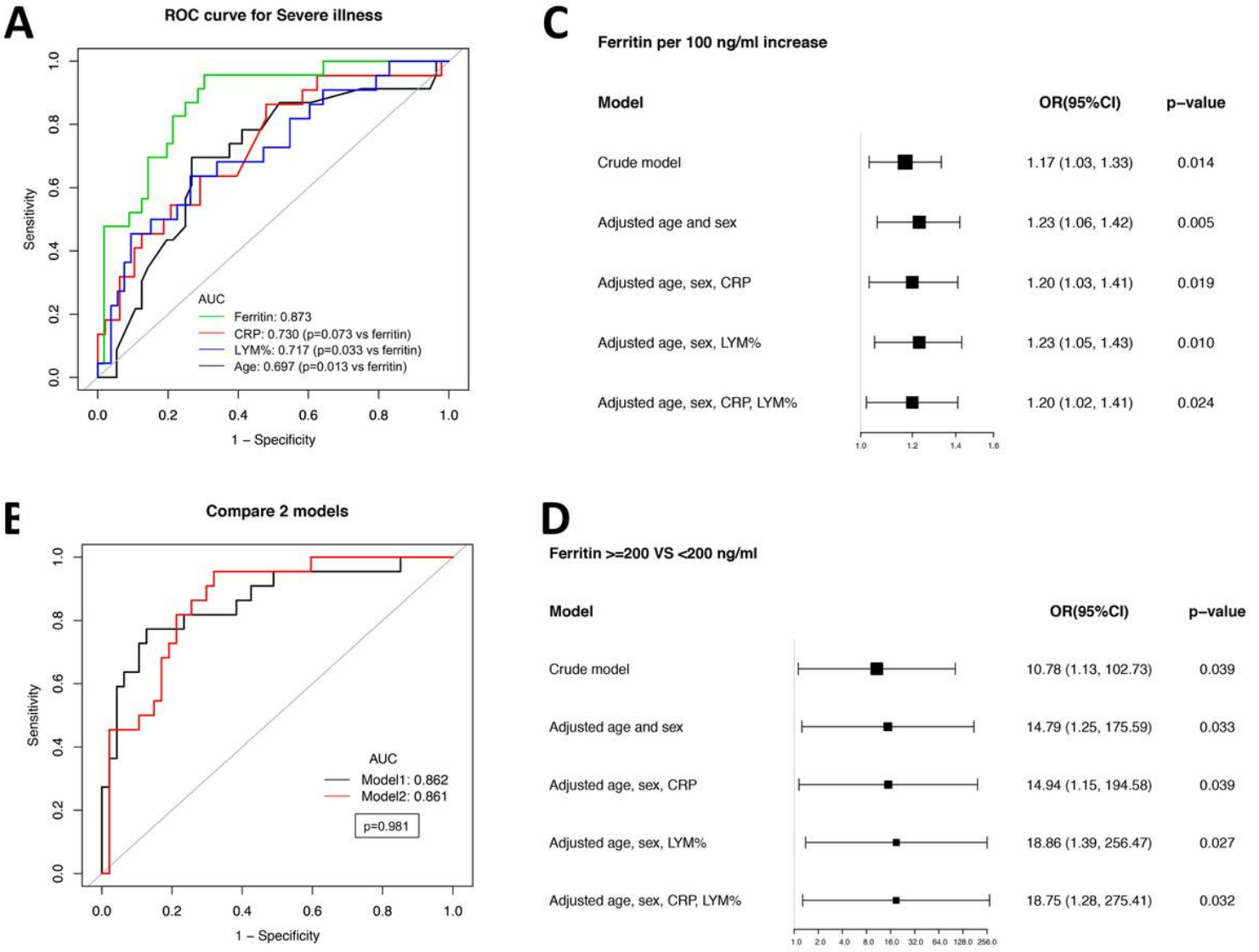

Figure 3

(A) ROC curves of potential risk factors (n=79 for age and ferritin, n=75 for LYM%, n=70 for CRP); (B) The comparison of ROC curves between ferritin alone and multivariable model (n=69, Model 1: ferritin independent factor, Model 2: multiple factors integrating gender, age, ferritin, LYM% and CRP); (C) Forest plots of logistic regression analysis between serum ferritin (assessed as a continuous variable, per 100 ng/mL) and the risk of severity illness; (D) Forest plots of logistic regression analysis between serum ferritin (assessed as a categorical variable, ≤200 ng/mL and >200 ng/mL) and the risk of severity illness.

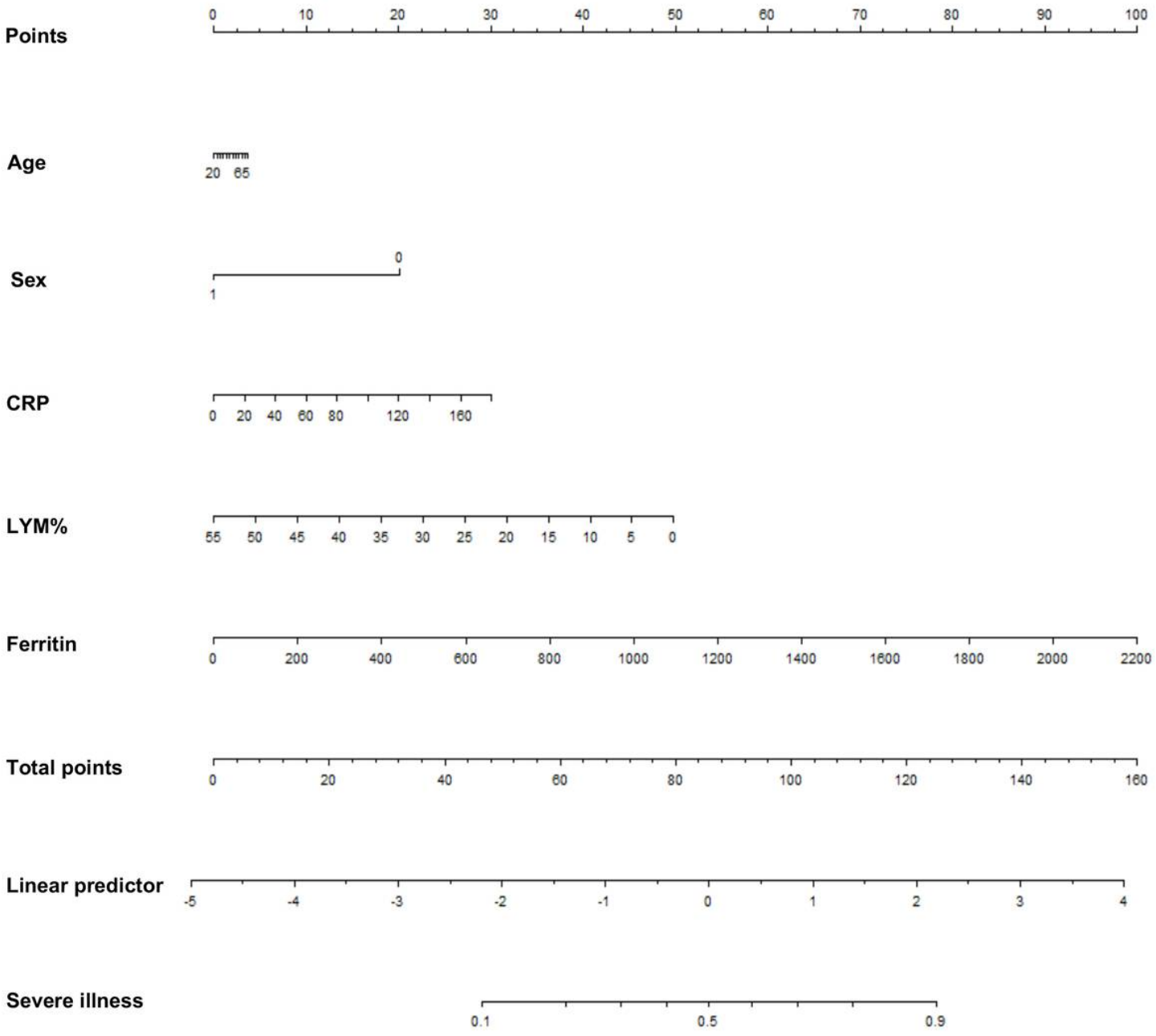

Figure 4

Nomogram incorporating risk factors.

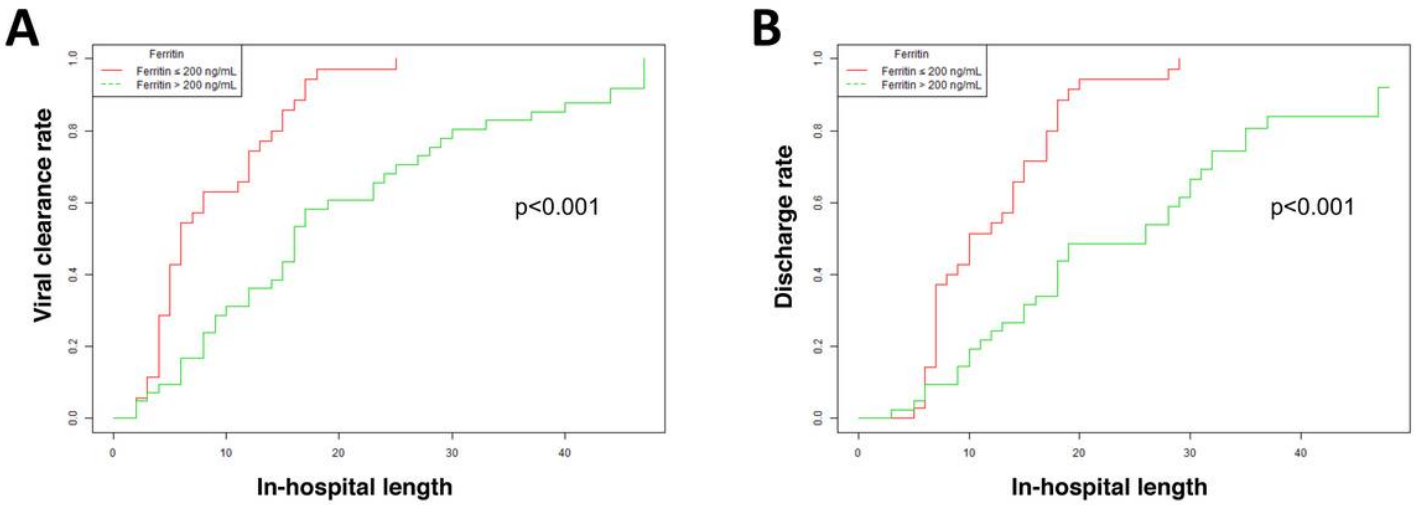

Figure 5

Kaplan Meier estimates of viral clearance rate (A) and inpatient discharge rate (B) over time stratified by serum ferritin levels. (77 patients were included except 2 deceased ones)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementalTable.docx