ORIGINAL RESEARCH

Check for updates

The detrimental impact of elevated Ferritin to Iron ratio on in-hospital prognosis of patients with COVID-19

Vanessa Bianconi^a, Massimo R. Mannarino^a, Filippo Figorilli^a, Elena Cosentini^a, Giuseppe Batori^a, Ettore Marini^a, Maciej Banach ^{b,c}, Amirhossein Sahebkar^{d,e,f} and Matteo Pirro ^a

^aUnit of Internal Medicine, Department of Medicine and Surgery, University of Perugia, Perugia, Italy; ^bDepartment of Hypertension, Wam University Hospital, Medical University of Lodz, Lodz, Poland; ^cDepartment of Cardiology and Adult Congenital Heart Diseases, Polish Mothers Memorial Hospital Research Institute (PMMHRI), Lodz, Poland; ^dBiotechnology Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran; ^eNeurogenic Inflammation Research Center, Mashhad University of Medical Sciences, Mashhad, Iran; ^fSchool of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran

ABSTRACT

Background: Acute viral infections, including coronavirus disease 2019 (COVID-19), are characterized by the dysregulation of iron metabolism, resulting in high serum ferritin and low iron levels.

Research design and methods: This study aimed to evaluate the prospective impact of iron metabolism dysregulation, as expressed by serum Ferritin-to-Iron Ratio (FIR), on the in-hospital prognosis of patients with COVID-19. Serum levels of ferritin and iron, as well as other iron metabolism markers and recognized prognostic indicators of COVID-19 severity, were measured in 362 patients consecutively hospitalized for COVID-19. The prospective relationship between FIR and the risk of the composite outcome of intensive care unit (ICU) admission/in-hospital death was analyzed.

Results: In the population examined (mean age 74 \pm 15 years, males 55%), the rates of radiographic signs of pneumonia, respiratory distress, and the need for noninvasive ventilation were higher in patients with high FIR (\geq 29.2, the 75th percentile) than in those with low FIR (<29.2, the 75th percentile) (p < 0.05 for all comparisons). High FIR was associated with a 1.7-fold (HR 1.709, 95% CI 1.017–2.871, p = 0.043) higher risk of ICU admission/in-hospital death.

Conclusions: Increasing FIR values significantly and independently predicts worse in-hospital prognosis in hospitalized patients with COVID-19.

1. Introduction

Since the start of the SARS-CoV-2 pandemic, hundreds of millions of people have been affected by coronavirus disease 2019 (COVID-19) and over 5 million people have died from this viral disease [1]. SARS-CoV-2-mediated injury of the lower respiratory tract along with the hyperinflammatory state and coagulopathy has a crucial role in the progression toward the most severe and life-threatening complications of COVID-19 (acute respiratory distress syndrome and multi-organ dysfunction) [2-6]. Accordingly, the measurement of circulating levels of different markers of inflammation [7], the detection of laboratory and instrumental anomalies indicative of thrombotic phenomena [8,9], the search for clinical indicators of respiratory distress [10,11] as well as the evaluation of organ dysfunction by means of different scores [12,13], are routinely put into practice during the clinical management of hospitalized patients with COVID-19. However, despite enormous efforts having been made since the beginning of the pandemic in the search for possible prognostic indicators to refine the clinical management and treatment models of COVID-19 [14,15], the in-hospital outcome of this infectious disease is often unfavorable [16-18].

Acute infections, including SARS-CoV-2 infection, are accompanied by a typical acute-phase response that is aimed primarily at eliminating the causative pathogen [19]. Serum ferritin level, a conventional indicator of the adequacy of the body's iron stores, increases during viral infections along with the levels of other acute-phase proteins [20,21]. Such a ferritin increase, beyond being a consequence of the activation of acute inflammation, may itself enhance the inflammatory response, thereby possibly exerting a pathogenic role in viral infections [22]. In addition, hyperferritinemia may be associated with tissue toxicity due to an excessive production of reactive oxygen species and oxidative stress [23–25]; this has been clearly shown in the liver but may also be of importance in the lungs and other organs because of COVID-19. In conjunction with hyperferritinemia, decreased serum iron levels are also observed during acute viral infections because of the hepcidin-mediated inhibition of ferroportin [21,23]. Although the resulting hypoferremia may be protective by subtracting iron from the needs of pathogenic microorganisms [20-24], low iron levels may be harmful; accordingly, hypoferremia may reflect a detrimental intracellular iron overload during inflammatory processes [24] and impair oxygen delivery to peripheral tissues by limiting erythropoiesis [26].

CONTACT Massimo R. Mannarino Samassimo.mannarino@unipg.it Dunit of Internal Medicine. Department of Medicine and Surgery. University of Perugia, Perugia, Italy; Hospital 'Santa Maria della Misericordia'; Piazzale Menghini, 1 - 06129, Perugia, Italy.

B Supplemental data for this article can be accessed here.

 $\ensuremath{\mathbb{C}}$ 2022 Informa UK Limited, trading as Taylor & Francis Group

ARTICLE HISTORY Received 2 July 2021 Accepted 8 March 2022

KEYWORDS COVID-19; ferritin; ferritin to iron ratio; inflammation; iron; SARS-CoV-2



It is important to note that the concomitant presence of high serum ferritin levels and low iron levels can be observed during COVID-19 [26]. Furthermore, despite some inconsistency, many retrospective studies [26-36] and a smaller number of prospective studies [37-40] have shown that either the state of hyperferritinemia or hypoferremia are accompanied by a greater severity/worse prognosis of COVID-19 both in its acute and post-acute phase. In light of the unfavorable prognostic impact of either hyperferritinemia or hypoferremia in COVID-19, we may hypothesize that our ability to stratify the prognosis of hospitalized patients with COVID-19 might be further increased by integrating the value gathered from these individual variables (serum ferritin and iron levels) into a combined index, that is the Ferritin-to-Iron Ratio (FIR). Furthermore, given the biological plausibility of a pathogenic link between iron metabolism and COVID-19 severity, it is possible that the putative negative impact of elevated FIR on the clinical outcome of patients with COVID-19 might be independent of that of established indicators of poor prognosis, such as comorbidities [e.g. Charlson Comorbidity Index, CCI)], markers of inflammation [e.g. erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)] and organ damage [e.g. Sequential Organ Failure Assessment (SOFA)].

The objective of this prospective study was to evaluate the ability of elevated FIR, as the expression of a possible unfavorable interaction between hyperferritinemia and hypoferremia, to predict the in-hospital prognosis of COVID-19 patients.

2. Patients and methods

2.1. Study population

In this prospective study, hospitalized COVID-19 patients referring to the Internal Medicine and Infectious Diseases wards of the 'Santa Maria della Misericordia Hospital' of Perugia (Italy) from December 2020 to February 2021, mainly coming from the Umbria region of central Italy, were consecutively enrolled. The study protocol was developed in accordance with the principles of the Helsinki Declaration and was approved by the local ethics committee (Comitato Etico Regionale Umbria). Inclusion criteria were the following ones: 1) age \geq 18 years; 2) a positive result on real-time reverse-transcriptase-PCR (RT-PCR) assays testing for SARS-CoV-2 on nasal or pharyngeal swab specimens at hospital admission; 3) informed written consent. The estimated study sample size was of 308 patients by assuming the type I error = 0.05, the type II error = 0.1, the ratio of the unexposed group (FIR \leq the 75th percentile) to the exposed group (FIR > the 75th percentile) = 3, the probability of event (ICU admission/inhospital death) in the unexposed group = 0.25, and the probability of event in the exposed group = 0.45. Noteworthy, the composite endpoint of ICU admission/in-hospital death was a priori selected to ensure the observation of a sufficient number of events providing an acceptable statistical power to the analyses. In addition, the probabilities of the event (ICU admission/in-hospital death) were arbitrarily established for this pilot study, as no previous literature data on the association between FIR and in-hospital outcomes in COVID-19 patients were available. Also, given the absence of literature data reporting a preferable/universally accepted cutoff for high FIR, the 75th

percentile was arbitrarily chosen as the cutoff for high FIR, in that it was hypothesized to provide the best dichotomy for FIR values.

2.2. Data collection

For each patient data on demographic characteristics, coexisting medical conditions, current treatments, laboratory tests as well as physical and instrumental examinations performed within 48 hours since hospital admission were collected and registered in medical records. Tests for SARS-CoV-2 on nasal or pharyngeal swab specimens were performed through RT-PCR assays (Allplex 2019-nCoV Assay, Seegene, Seoul, South Korea or the Xpert Xpress SARS-CoV-2, Cepheid, Sunnyvale, USA). Arterial and venous blood samples were collected at hospital admission and processed according to standard laboratory techniques in order to determine the following laboratory variables: blood gas parameters (ABL90 FLEX blood gas analyzer, Radiometer, Brønshøj, Denmark), leukocytes, platelets, hemoglobin, and red blood cell count (Sysmex XT-2000i, Dasit, Milano, Italy), D-dimer (BCS XP Coagulation Analyzer, Siemens, Munich, Germany), highsensitivity cardiac troponin (hs-cTn) (UniCel Dxl 800 analyzer, Beckman Coulter, Brea, USA), C-reactive protein (CRP), blood urea nitrogen (BUN), creatinine, lactate dehydrogenase (LDH), bilirubin, ferritin, serum iron, total iron-binding capacity (TIBC), and fasting glucose (AU5800 Clinical Chemistry System, Beckman Coulter, Brea, USA). Transferrin was calculated according to the following formula: transferrin = (0.8 X TIBC) - 43. Transferrin saturation was calculated as serum iron/TIBC X 100. Estimated glomerular filtration rate (eGFR) was calculated through the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Radiological diagnosis of pneumonia was made based on the presence of at least one of the following radiographic signs in either chest X-ray or high-resolution computed tomography: mono or bilateral consolidations, ground glass opacities, and crazy paving pattern. Respiratory insufficiency was defined as the presence of peripheral oxygen saturation (SpO2) ≤90% and/or arterial partial pressure of oxygen (PaO2) ≤60 mmHg and/or need of oxygen support at admission. Calculated PaO2/fraction of inspiration oxygen ratio (PaO2/ FiO2) ≤300 was used to define the presence of respiratory distress. The SOFA score was estimated for each patient by integrating six clinical/laboratory data at admission [i.e. 1- PaO2/FiO2; 2 platelets; 3 - bilirubin; 4 - mean arterial pressure as the compositum of systolic and diastolic blood pressures assessed through sphygmomanometer; 5 - creatinine; 6 - Glasgow Coma Scale] [41–43]. The CCI was calculated for each patient by integrating information on coexisting medical conditions [44]. Data on clinical course [in-hospital medical treatments and need of noninvasive ventilation (NIV)] and in-hospital outcomes (ICU admission, in-hospital death or hospital discharge) were collected and registered in medical records.

2.3. Statistical analysis

The SPSS statistical package, release 24.0 (SPSS Inc, Chicago, IL), was used for all statistical analyses. The Shapiro test was used to verify the normality of the study variables. Categorical

variables were expressed as percentages, while continuous variables were expressed as mean ± standard deviation (SD) or median and interquartile ranges. The independent samples t-test, the Mann-Whitney U-test, and the chi-squared test were used for two-group comparisons. Correlation analyses between the study variables were performed using the Pearson's and Spearman's coefficients of correlation. Time-to-event analyses were performed to assess the association between FIR and the composite endpoint of ICU admission/inhospital death. For six patients, who did not meet the composite endpoint and were still hospitalized at the time of analysis, the event date was censored on 28 April 2021.

Multivariable linear regression analyses were performed to determine the independent predictors of FIR. The association between either serum iron, ferritin, or both serum iron and ferritin and the composite endpoint of ICU admission/inhospital death was investigated through three different Cox proportional Hazard models including multiple potential confounders. The Chi squared test was performed to assess the association between high FIR (FIR ≥the 75th percentile) and the composite endpoint of ICU admission/in-hospital death, as well the sensitivity, specificity, positive predictive value, and negative predictive value of high FIR (FIR \geq the 75th percentile) toward the same endpoint. In order to assess the risk of the composite endpoint of ICU admission/in-hospital death according to high versus low FIR (FIR ≥the 75th percentile versus FIR 75th percentile], both in the entire study population and in the severe COVID-19 subgroup, a Kaplan-Meier plot was run and the Log-rank test was performed. The association between FIR, either as continuous or categorical variable (FIR quartiles and high FIR), and the composite endpoint of ICU admission/in-hospital death was further evaluated through three Cox proportional Hazard models including multiple potential confounders, both in the entire study population and in the severe COVID-19 subgroup. The following exploratory analyses were also performed: 1) multi-adjusted Cox regression analyses to assess the association between FIR, either as continuous or categorical variable, and either ICU admission or in-hospital death as single endpoints; 2) a multiadjusted Cox regression analysis to assess the association between FIR ≥the median value and the composite endpoint of ICU admission/in-hospital death; 3) univariate Cox regression analyses to assess the association between Ferritin-to-Transferrin Ratio (FTR) and either ICU admission or inhospital death as single endpoints, in analogy with a previous study [45]. Statistical significance was assumed if a null hypothesis could be rejected at p ≤ 0.05 .

3. Results

3.1. Baseline characteristics of the study population

Three hundred and sixty-two COVID-19 patients were enrolled (mean age 74 \pm 15 years, males 55%). The characteristics of the study population categorized according to FIR \geq 29.2 (FIR \geq the 75th percentile) *versus* FIR < 29.2 (FIR <the 75th percentile) are reported in Table 1, while the characteristics of the study population dichotomized according to the occurrence

Table 1. Base	line characteristic	s of COVID-	19 patients acc	cording to FIR \geq	29.2 (i.
$e. \geq the 75^{th}$	percentile) versus	5 FIR <29.2 ((i.e. < the 75 th	percentile) .	

	FIR < 29.2	FIR ≥ 29.2	
	n = 272	n = 90	р
Age, years	72 (16)	76 (13)	0.170
Male gender, %	53	63	0.085
BMI, kg/m ²	26.3 (4.3)	25.8 (4.5)	0.227
Current smoking, %	18	20	0.705
Hypertension, %	63	68	0.400
Type 2 diabetes, %	20	24	0.441
CKD, %	13	11	0.662
Previous CV event, %	19	20	0.976
Active cancer, %	11	9	0.506
Previous VTE, %	29	78	0.046
AF, %	19	13	0.212
COPD, %	14	8	0.123
Obesity, %	33	23	0.079
CCI	4 (3–6)	5 (4–6)	0.125
ACE inhibitors, %	25	32	0.239
ARBs, %	14	18	0.431
Statins, %	15	15	1.000
DOACs, %	12	10	0.647
VKAs, %	2	4	0.370
LMWH, %	17	25	0.085
Anti-platelets, %	28	34	0.318
BBs, %	30	31	0.915
CCBs, %	23	21	0.740
Diuretics, %	39	32	0.277
Insulin, %	12	14	0.584
Oral hypoglycemic agents, %	10	12	0.609
SBP, mmHg	132 (20)	127 (24)	0.036
DBP, mmHg	77 (11)	73 (12)	0.014
Leukocytes, X 10 ³ /µL	7.6 (5.4–10.6)	7.9 (5.4–11.6)	0.396
Platelets, X 10 [°] /µL	211 (160-269)	19/(141-259)	0.111
Hb, g/dL	13.2 (11./-14.4)	12.7 (10.7-14.4)	0.254
Red blood cells, X 10%µL	4.4 (3.9–4.9)	4.3 (3.6–4.8)	0.071
D-dimer, ng/mL	844 (533-1538)	1405 (600-2799)	0.002
HS-CIN, NG/L	13 (7-30)	27 (14-44)	<0.001
CRP, mg/dL	5.8 (2.8-9.5)	11.9 (5.7–17.1)	<0.001
ESR, mm/n	52 (34-79)	68 (51-94)	< 0.001
Fasting glucose, mg/dL	120 (102-145)	127 (105-162)	0.222
Albumin a/dl	/ I (2/) 2 5 (2 2 2 7)	01 (20) 2 2 (2 7 2 5)	0.032
Albumin, g/al	2.2 (3.2-3./) 200 (225 207)	3.2 (2.7-3.3)	< 0.001
	200 (225-30/)	304 (20/-400)	< 0.001
	200 (195-310)	197 (126-276)	<0.001
SOLA SCOLE	Z (Z-4)	4 (2-5)	< 0.001

ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers; AF, atrial fibrillation; BBs, beta-blockers; BMI, body mass index; CCBs, calcium channel blockers; CCI, Charlson Comorbidity Index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CV, cardiovascular; DBP, diastolic blood pressure; DOACs, direct oral anticoagulants; eGFR, estimated glomerular filtration rate; ESR, erythrocyte sedimentation rate; FiO2, fraction of inspiration oxygen; FIR, ferritin to iron ratio; Hb, hemoglobin; hs-cTn, high sensitivity cardiac troponin; LDH lactate dehydrogenase; LMWH, low molecular weight heparin; NLR, neutrophil-to-lymphocyte ratio; PaO2, arterial partial pressure of oxygen; SBP, systolic blood pressure; SOFA, Sequential Organ Failure Assessment; VKAs, vitamin-K antagonists; VTE, venous thromboembolism.

of the composite outcome of ICU admission/in-hospital death are described in Table 2. Hyperferritinemia (ferritin >300 ng/ mL, the upper limit of the normal range) was found in 64% of the enrolled patients, while hypoferremia (serum iron <80 µg/ dL in males or serum iron <60 µg/dL in females) was detected in 86/80% of males/females, respectively. Noteworthy, only 3 out of 362 patients had extremely high ferritin levels (ferritin >4420 ng/mL), which are compatible with the macrophage activation syndrome [46]. Patients who were admitted to ICU/ died had reduced serum iron levels, TIBC, transferrin, and

Table 2. Baseline characteristics of COVID-19	patients according to	the composite endp	point of ICU	admission/in-hospit	tal death
---	-----------------------	--------------------	--------------	---------------------	-----------

		ICU admitted/	
	Non-ICU admitted/Discharged alive	Non-survivors	
	n = 261	n = 101	р
Age, years	72 (16)	79 (12)	< 0.001
Male gender, %	53	62	0.103
BMI, kg/m ²	26.6 (4.5)	25.7 (4.1)	0.128
Current smoking, %	19	18	0.762
Hypertension, %	62	68	0.297
Type 2 diabetes, %	20	26	0.227
CKD. %	10	18	0.053
Previous CV event, %	18	25	0.126
Active cancer, %	11	10	0.739
Previous VTF. %	5	3	0.486
AF. %	16	22	0.203
COPD %	12	14	0.608
Obesity %	32	26	0.000
	4 (2-6)	5 (4-7)	0.001
ACE inhibitors %	27	29	0.001
ABBs %	14	17	0.732
Stating %	15	13	0.505
	15	15	0.836
VKAs %	2	5	0.000
IMWH %	10	21	0.107
Anti-platelets %	24	21	0.005
	27	21	0.075
	10	30	0.994
Diuretics %	25	42	0.037
Inculin %	10	42	0.173
Oral hypoglycomic agents %	12	15	0.433
CPD mmHa	10 (21)	12	0.072
	132 (21) 77 (11)	72 (11)	0.019
Loukocutos $X = 10^3/m$	77 (11) 77 (5 2 10 9)	75 (11)	0.007
$\frac{1}{10} \frac{1}{10} \frac$	7.7 (3.2-10.8)	7.0 (J.0-11.1) 195 (144, D25)	0.043
μ		10.7 (10.9 14.2)	0.003
ND, g/uL Red blood cells, V 10 ⁶ /ul	15.2 (11.7 - 14.4)	12.7 (10.0-14.3)	0.102
Red blood cells, X TO /μL	4.4 (3.9–4.9) 960 (E6E 1760)	4.5 (5.5-4.6)	0.042
D-aimer, ng/mL		1150 (555-1605)	0.205
	12.5 (0.0-27.5)	20.0 (17.0-51.9)	< 0.001
CRP, mg/dL	6.1 (2.8-10.8)	9.2 (4.5-15.7)	< 0.001
ESR, mm/n	54 (30-83) 120 (102 146)	05 (47-88) 121 (105-160)	0.100
Fasting glucose, mg/dL	120 (102–146)	131 (105-160)	0.282
	73 (20)	58 (27) 2 2 (2 - 2 C)	< 0.001
	3.4 (3.1-3./) 201 (224 205)	3.3 (3-3.0) 266 (202, 460)	0.010
	281 (224-385)	300 (283-408)	<0.001
	2/1 (206-312)	161 (114–261)	<0.001
SUFA score	2 (2-3)	4 (2–5)	<0.001

ACE, angiotensin converting enzyme; ARBs, angiotensin II receptor blockers; AF, atrial fibrillation; BBs, beta-blockers; BMI, body mass index; CCBs, calcium channel blockers; CCI, Charlson Comorbidity Index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CV, cardiovascular; DBP, diastolic blood pressure; DOACs, direct oral anticoagulants; eGFR, estimated glomerular filtration rate; ESR, erythrocyte sedimentation rate; FiO2, fraction of inspiration oxygen; Hb, hemoglobin; hs-cTn, high sensitivity cardiac troponin; ICU, intensive care unit; LDH lactate dehydrogenase; LMWH, low molecular weight heparin; NLR, neutrophil-to-lymphocyte ratio; PaO2, arterial partial pressure of oxygen; SBP, systolic blood pressure; SOFA, Sequential Organ Failure Assessment; VKAs, vitamin-K antagonists; VTE, venous thromboembolism.

 Table 3. Baseline iron metabolism parameters according to the composite endpoint of ICU admission/in-hospital death.

	Non-ICU admitted/ Discharged alive n = 261	ICU admitted/ Non-survivors n = 101	р
Serum iron, µg/dL	35 (23–58)	26 (17–37)	<0.001
Ferritin, ng/mL	402 (185–790)	772 (313–1375)	< 0.001
FIR	10 (5–24)	27 (11–56)	< 0.001
TIBC, μg/dL	213 (184–250)	195 (156–219)	< 0.001
Transferrin, mg/dL	130 (104–157)	113 (82–133)	< 0.001
Transferrin saturation, %	16 (10–29)	13 (8–20)	0.008
FTR	3 (1–6)	8 (2–14)	<0.001

FIR, Ferritin to Iron Ratio; FTR, Ferritin-to-Transferrin Ratio; ICU, intensive care unit; TIBC, total iron binding capacity.

transferrin saturation, and increased ferritin levels and FIR as compared to those who were not admitted to ICU/were discharged alive (Table 3).

3.2. Clinical course and in-hospital outcomes

At hospital admission, 25 (7%), 59 (16%), and 278 (77%) patients had mild COVID-19 (signs and symptoms of COVID-19 without shortness of breath, dyspnea, or abnormal chest imaging), moderate COVID-19 (lower respiratory disease during clinical assessment or imaging and SpO2 \geq 94% on room air at sea level) and severe COVID-19 (SpO2 < 94% on room air at sea level, PaO2/FiO2 < 300 mmHg, respiratory frequency >30 breaths/min, or lung infiltrates >50%), respectively, according to the National Institutes of Health (NIH) classification of COVID-19 severity [47]. Mild (200< PaO2/FiO2 \leq 300), moderate (100< PaO2/FiO2 \leq 200), and severe respiratory distress (PaO2/FiO2 \leq 100) were documented in 141 (39%), 91 (25%) and 24 (7%) patients, respectively. During the hospital stay, the therapeutic management of patients followed the



Figure 1. Cumulative hazard of ICU admission/in-hospital death according to low *versus* high FIR (*i.e.* FIR \geq 29.2 *versus* FIR <29.2, the 75th percentile) at hospital admission in the entire study population (panel A) and in the severe COVID-19 subgroup (panel B).

scientific recommendations formulated during the pandemic evolution. Thirty-five patients (10%) underwent ICU admission, 66 (18%) patients died, and 101 patients (28%) met the composite endpoint of ICU admission/in-hospital death. The median time from in-hospital admission to ICU admission was 2 (2–5) days, while the median time from in-hospital admission to death was 10 (6–16) days. **Supplementary Table 1** shows the main medical therapies and clinical complications that were recorded in the study population during the hospital stay according to the composite outcome of ICU admission/in-hospital death.

3.3. Serum iron, ferritin, FIR, and their covariates

Serum iron levels were negatively associated with age (rho = -0.242, p < 0.001), CCI (rho = -0.225, p < 0.001), ESR (rho = -0.166, p = 0.009), SOFA score (rho = -0.198, p < 0.001), and hs-cTn (rho = -0.238, p < 0.001), whereas they were positively associated with LDH (rho = 0.125, p = 0.018), albumin (rho = 0.121, p = 0.022), eGFR (rho = 0.203, p < 0.001), TIBC (rho = 0.159, p = 0.003), ferritin (rho = 0.120, p = 0.022), transferrin saturation (rho = 0.923, p < 0.001), red blood cells (rho = 0.169, p = 0.001), and hemoglobin (rho = 0.199, p = 0.199)p < 0.001). Ferritin was higher in males than females (p < 0.001). In addition, it correlated positively with ESR (rho = 0.239, p < 0.001), CRP (rho = 0.451, p < 0.001), SOFAscore (rho = 0.191, p > 0.001), LDH (rho = 0.402, p < 0.001), hscTn (rho = 0.165, p = 0.005), serum iron (rho = 0.120, p = 0.022), transferrin saturation (rho = 0.282, p < 0.001), hemoglobin (rho = 0.144, p = 0.006), leukocytes (rho = 0.115, p = 0.029), and D-dimer (rho = 0.114, p = 0.047), whereas it was negatively associated with PaO2/FiO2 (rho = -0.275, p < 0.001), albumin (rho = -0.173, p = 0.001) and TIBC (rho = -0.468, p < 0.001). FIR was higher in men than in women (p < 0.001). In addition, it correlated positively with ESR (rho = 0.328, p < 0.001), CRP (rho = 0.409, p < 0.001), SOFA score (rho = 0.294, p < 0.001), LDH (rho = 0.274, p < 0.001), hscTn (rho = 0.292, p < 0.001), and D-dimer (rho = 0.159, p = 0.005), whereas it was negatively associated with albumin (rho = -0.222, p < 0.001), eGFR (rho = -0.194, p < 0.001), TIBC

(rho = -0.526, p < 0.001), transferrin saturation (rho = -0.254, p < 0.001), and PaO2/FiO2 (rho = -0.293, p < 0.001).

In a multivariable linear regression analysis including logarithmic (LG)-FIR as the dependent variable and non-iron metabolismrelated FIR covariates (sex, either LG-ESR or LG-CRP, LG-SOFA score, LG-LDH, LG-hs-cTn, LG-D-dimer, LG-albumin, and eGFR) as the independent variables, inflammatory markers (LG-ESR and LG-CRP, which were included one at time) were independent predictors of LG-FIR (β = 0.262 and p < 0.001 for LG-ESR, β = 0.279 and p < 0.001 for LG-CRP, in models including either LG-ESR or LG-CRP, respectively).

3.4. Association between iron metabolism parameters and the composite endpoint of ICU admission/in-hospital death

Six models of Cox regression analysis were plotted to explore the association between iron metabolism parameters and risk of ICU admission/in-hospital death. In a model in which serum iron was included as an independent variable, the latter one was associated with an increased risk of worse in-hospital prognosis independently of confounders (age, sex, CCI, red blood cell count, platelet count, hs-cTn, albumin, CRP, SOFA score, LDH, and D-dimer) (Table 4, Model 1). In another model, in which the independent variable serum iron was replaced by ferritin (Table 4, Model 2), the latter one was significantly associated with the in-hospital outcome. Upon the inclusion in the same model of both serum iron and ferritin (Table 4, Model 3), both these independent variables were able to predict in-hospital prognosis irrespective of confounders.

A significant association emerged between high FIR (FIR \geq 29.2, the 75th percentile) and the composite endpoint of ICU admission/in-hospital death (p < 0.001), with a 45.5% sensitivity, 83.1% specificity, 51.1% positive predictive value, and 79.8% negative predictive value of high FIR (FIR \geq 29.2, the 75th percentile) in the prediction of the same endpoint. Figure 1 shows the Kaplan-Meier analysis stratified according to high *versus* low FIR (FIR \geq 29.2 or <29.2, the 75th percentile) in the entire study population (Panel A) (Log-rank p < 0.001)

Table 4. Association between iron metabolism parameters (*i.e.* serum iron, ferritin, and FIR) and the composite endpoint of ICU admission/in-hospital death in the entire study population.

Serum Iron 0.988 0.978-0.989 0.07 0.72 Agc 1.004 0.971-2.053 0.332 Sec 1.201 0.971-2.053 0.332 Gishood cell count 0.999 0.997-1.001 0.232 Har.Site count. 0.999 0.997-1.001 0.232 Har.Site count. 0.999 0.997-1.001 0.0371 Abumin 1.155 0.72-2.019 0.807 Abumin 1.001 0.001 0.001 0.001 Abumin 1.001 0.001 0.001 0.001 0.001 Adder 1.001 0.001 0.001 0.001 0.001 <	Model 1	Variables	HR	95% Cl	р
Age 1.094 0.981-1.027 0.745 Sec 1.281 0.771-2655 0.338 Ged bladt clount 0.999 0.995-1.001 0.235 Hart-Tn 1.000 0.999-1.001 0.735 Mburnin 1.163 0.672-2.019 0.8897 CRP 1.002 0.997-1.057 0.8897 CRP 1.002 1.001-1.003 0.017 Delmer 1.002 1.000-1.003 0.017 Delmer 1.002 0.001-1.001 0.001 Delmer 1.001 0.001-1.001 0.001 Delmer 1.001 0.001-1.001 0.001 Model 2 Method cell count 1.063 0.044-1.201 0.000 Method cell count 1.063 0.044-1.201 0.001 0.001 0.001 Method cell count 1.002 0.997-1.002 0.897 0.031 0.997 Model 3 Method cell count 1.001 0.001-1.001 0.001 0.001 0.001 0.001 0.001		Serum iron	0.988	0.978-0.998	0.017
Sex1.2h10.711-20650.335Grid bod cell count0.9940.9595-10010.235Hatelet count0.9990.9595-10010.235Herfa1.0000.999-10010.235Alburnin1.1050.672-2.0190.507Alburnin1.0250.672-2.0190.507SOFA Kore1.2881.122-1.4790.000SOFA Kore1.2881.122-1.4790.001Jore1.0001.000-1.0000.037-1Model 2VarablesHE95%-GPFerlinin1.0010.034-1.0340.484Age1.0010.034-1.0340.484Jore1.0020.997-1.0120.021Hatelet count0.9990.977-1.0220.445His-Cin1.0000.999-1.0010.959Joren1.0250.998-1.0010.959Joren1.0260.999-1.0020.959Joren1.0260.999-1.0020.959Joren1.0000.999-1.0010.959Joren1.0260.999-1.0010.959Joren1.0000.999-1.0010.959Joren1.0260.999-1.0010.959Joren1.0000.999-1.0010.959Joren1.0260.999-1.0010.959Joren1.0000.999-1.0010.959Joren1.0270.951-1.3530.454Joren1.0010.999-1.0010.959Joren1.0020.9990.964-0.999<		Age	1.004	0.981-1.027	0.745
CC1 1.032 0.919-11.00 0.535 He dianad cell count 0.949 0.053-13.00 0.535 He cfn 1.000 0.999-1001 0.755 Hubminn 1.165 0.622-2019 0.557 CRP 1.026 0.997-1037 0.800 SCRA core 1.288 1.122-1479 0.0001 LDH 1.000 0.998-1.031 0.017 Herritin 1.001 1.000-1.003 0.017 Herritin 1.001 1.000-1.001 0.010 CC 1.133 0.674-1.841 0.675 CC 1.133 0.674-1.841 0.675 CC 1.028 0.966-1.060 0.996 CRP 1.028 0.966-1.060 0.996 SCRA score 1.288 0.906-1.001 0.028 Albumin 1.028 0.906-1.060 0.996 SCRA score 1.288 0.906-1.060 0.996 SCRA score 1.286 0.996-1.060 0.996 SCRA scor		Sex	1.261	0.771–2.065	0.356
Nodel 4: 1.948 0.053-1.380 0.054 Nodel 5: 0.007 0.007 0.007 Alburnin 1.165 0.077-2.019 0.080 SQFA Score 1.288 0.1722 4.000 SQFA Score 1.288 0.1221 4.79 <-0.001			1.032	0.919–1.160	0.592
Nodel 2 Institution 1.000 0.0399 1.001 0.0399 Alkornin 1.155 0.027-1.037 0.080 GPA score 1.286 1.12-1.479 0.000 LDH 1.002 1.000-1.003 0.017 Define 1.001 1.001 0.01 0.017 Herrin 1.001 1.005 0.041 0.010 0.017 Herrin 1.001 1.005-1.001 0.010<		Red blood cell count	0.944	0.655-1.360	0./56
Albumin11650.072-2.0190.597GP10260.072-2.0190.001SOTA score1.2881.122-14.910.001Definer1.0001.000-1.0030.017Petter1.0001.000-1.0030.017Petter1.0001.000-1.0030.017Petter1.0001.000-1.0030.017Petter1.0000.094-1.0210.038Petter1.0090.994-1.0210.038Petter0.9990.994-1.0210.038Petter0.9990.997-1.0020.038Petter0.9990.997-1.0020.038Petter0.0990.997-1.0020.938Petter1.0000.999-1.0020.938Petter1.0000.999-1.0020.938Petter1.0000.999-1.0020.938Petter1.0000.999-1.0020.938Petter1.0000.999-1.0020.938Petter1.0000.999-1.0020.938Petter1.0010.999-1.0020.938Petter1.0010.999-1.0020.938Petter1.0010.999-1.0020.938Petter1.0010.999-1.0020.938Petter1.0010.999-1.0020.938Petter1.0010.999-1.0020.938Petter1.0010.999-1.0020.938Petter1.0010.999-1.0010.938Petter1.0010.999-1.0010.938Petter <td< td=""><td></td><td></td><td>1 000</td><td>0.990-1.001</td><td>0.265</td></td<>			1 000	0.990-1.001	0.265
Addel 2CipP10.260.997-10.270.000Model 21.2671.2881.12.21-14/9-0.001Polmer1.0001.000-1.0000.371Polmer1.0001.000-1.0010.031Polmer1.0011.000-1.001-0.001Polmer1.0010.001-1.001-0.001Polmer1.0010.001-1.001-0.001Polmer1.0010.07/1-1.8110.07/1-1.811Polmer1.0010.0570.97/1-1.520.7/11Polmer1.0000.999-1.0010.592Polmer1.0000.999-1.0010.592Polmer1.0000.999-1.0020.593Polmer1.0000.999-1.0020.593Polmer1.0001.000-1.0010.001Polmer1.0011.000-1.0010.001Polmer1.0010.009-1.0020.593Polmer1.0010.001-1.0010.001Polmer1.0010.001-1.0010.001Polmer1.0010.001-1.0010.001Polmer1.0010.009-1.0020.593Polmer1.0010.001-1.0010.001Polmer1.0010.001-1.0010.001Polmer1.0010.001-1.0010.001Polmer1.0010.001-1.0010.001Polmer1.0010.001-1.0010.001Polmer1.0010.001-1.0010.001Polmer1.0010.001-1.0010.001Polmer1.002		Albumin	1.000	0.672-2.019	0.779
Addel 2SDFA score1.281.122-1479<0.0001DeH1.0001.000-1.0030.0171Pedmer1.0011.000-1.0030.0171Permin1.0011.000-1.0030.0171Age1.0011.000-1.0010.0401SGE1.0050.994-1.0310.0441SGE1.0050.994-1.0310.0383SGE1.0050.994-1.0310.308SGE1.0050.994-1.0310.308SGE1.0070.9990.997-1.0230.686SGE1.2860.128-1.4090.6081SGE Ascore1.2860.128-1.4090.6081SGE Ascore1.2860.128-1.4090.001SGE Ascore1.2860.128-1.4090.001SGE Ascore1.2860.998-0.9090.002Model 3507 Ascore1.2840.689-1.6030.026Ferritin1.0011.000-1.0010.001Age1.0330.979-1.0230.808Ferritin1.0130.099-1.0020.218Model 41.0740.999-1.0020.218Fist Timmer1.0530.994-1.0570.113SGE Ascore1.2861.108-1.4080.696Fist Timmer1.0010.097-1.0230.638Fist Timmer1.0010.099-1.0020.216Fist Timmer1.0030.994-1.0570.011SGE Ascore1.2861.097-1.0280.696Fist Timmer1.0010.092-1.0100.696<		CRP	1.026	0.997-1.057	0.080
Ddf1.0021.000-1.0030.017Model 2VariablesHR95% CIPFerrine1.0010.002-1.001C.000Age1.0010.002-1.001C.000Age1.0010.002-1.001C.000Age1.0010.002-1.001C.000CI0.0010.002-1.001C.000Nodel 30.94-1.4210.0020.959Nodel 50.0010.9590.0010.959Nodel 50.0010.0590.0010.0592Nodel 50.0010.0590.0010.0592Nodel 50.0010.0010.0010.001Nodel 50.0010.0010.0010.001Nodel 50.0010.0010.0010.001Nodel 50.0010.0010.0010.001Nodel 50.0010.0010.0010.001Nodel 50.0010.0010.0010.001Nodel 50.0010.0010.0010.001Nodel 50.0010.0010.0010.001Nodel 4N0.0020.00210.002Nodel 4N0.0030.009-1.0010.001Nodel 4N0.0030.009-1.0010.001Nodel 4N0.0030.009-1.0010.001Nodel 50.0010.0010.0010.001Nodel 4N0.0010.0010.001Nodel 50.0010.0010.0010.001Nod		SOFA score	1.288	1.122-1.479	< 0.001
Addel 2D-dimer1.0001.00010.0010.071Ferritin1.0011.00011.0001<0.001		LDH	1.002	1.000-1.003	0.017
Model 2VariablesHR95% ClpAge1.0070.004-1.0240.0001Age1.0070.0674-1.8340.0481Age1.0030.074-1.5250.741Patcles count0.9630.074-1.5250.741Natcles count0.9690.099-1.0020.485Hasch0.0000.999-1.0020.686Albumin1.1270.631-2.0120.686CRP1.2680.966-1.0600.884Definer1.0000.999-1.0020.539Model 3VariablesHR95% ClpAlbumin0.0010.001-1.0000.023Agein0.0030.999-1.0020.023Model 3VariablesHR95% ClpAgein0.0030.999-1.0010.680Agein1.0030.999-1.0010.680Agein1.0030.999-1.0010.680Agein1.0030.999-1.0010.680Agein1.0030.999-1.0010.680Agein1.0030.999-1.0010.680Albumin1.150.644-1.9310.666Albumin1.150.644-1.9310.666Albumin1.0710.099-1.0010.201Agein1.0070.999-1.0010.202Agein1.0070.999-1.0010.202Agein1.0070.999-1.0010.202Agein1.0070.999-1.0010.202Agein1.0070.999-1.0010.202<		D-dimer	1.000	1.000-1.000	0.371
Herritin1.0011.0041.0000.00441.0340.0484Sec1.1050.0674-1.5150.741Patclet count1.0630.741-1.5250.741Hs-GT1.0000.999-1.0010.485Hs-GT1.0000.999-1.0010.485Albumin1.1270.631-2.0120.686JOFA Score1.2861.126-1.4690.000D-dimer1.0000.999-1.0010.081JOFA Score1.2861.126-1.4690.000JOFA Score1.2860.999-1.0020.559D-dimer0.0011.000-1.0010.001Age1.0010.999-1.0020.228Scrum iron0.9980.996-1.0020.021Age1.0010.999-1.0020.228Pateler count0.9990.996-1.0020.021Age1.0010.997-1.0230.026Red bloot cell count0.9990.996-1.0020.245Pateler count0.9990.996-1.0020.245Pateler count0.9990.996-1.0020.314Hs-GT1.0010.999-1.0020.314Pateler count0.9990.998-1.0020.314Pateler count0.9990.998-1.0020.314Pateler count0.9990.998-1.0020.314Pateler count0.9990.998-1.0020.314Pateler count0.9990.998-1.0020.314Pateler count0.9990.998-1.0020.998Pateler count0.999 </td <td>Model 2</td> <td>Variables</td> <td>HR</td> <td>95% Cl</td> <td>р</td>	Model 2	Variables	HR	95% Cl	р
Nodel 31030.6740.6310.639Red bload cell count1.0630.7410.308Red bload cell count0.9690.9971.0020.445Harcler count0.9690.9970.0010.592Harcler count0.9690.9971.0020.868Abburnin1.1270.6310.1020.532CR1.0280.9961.0001.0000.001Differ1.0000.9990.0010.011Differ1.0001.0001.0001.0001.000Differ1.0000.0010.0010.001Age1.0030.9790.0010.001Age1.0030.9790.0010.001Age1.0330.9790.0010.001Age1.0330.9790.0010.001Age1.0330.9790.0010.001Age1.0330.9790.0010.001Age1.0330.9790.0010.001Age1.0330.9790.0010.001Age1.0350.9990.0010.001Age1.0270.9990.9960.001Age1.0070.9990.9960.001Age1.0070.9990.9960.001Age1.0070.9990.9960.001Age1.0070.9990.9960.001Age1.0070.9990.9960.002Age1.007		Ferritin	1.001	1.000-1.001	< 0.001
AddAddAddAddRed blodCl0.9990.997-10020.495Hs-Crh1.0000.999-10010.592Albumin1.1270.631-20120.686CRP1.2861.126-1.4690.000D-dimer1.0000.999-1.0010.832Model 30.947-1.0000.999-1.0020.559Model 41.0001.000-1.0000.382P-dimer1.0000.999-1.0020.559D-dimer1.0010.0010.001Age1.0010.0010.001Age1.0010.0010.001Age1.0010.099-1.0020.262CC0.0730.955-1.3050.026Age1.0010.095-1.1030.026Pateler count0.9990.908-1.0020.246Hs-Crh1.0010.995-1.1030.026Age1.0010.995-1.0020.246Hs-Crh1.0010.996-1.0020.245Hs-Crh1.0010.999-1.0020.245Hs-Crh1.0010.999-1.0020.245Hs-Crh1.0010.999-1.0020.245Hs-Crh1.0010.999-1.0020.245Hs-Crh1.0010.999-1.0020.245Hs-Crh1.0010.999-1.0020.245Hs-Crh1.0010.999-1.0020.314Hs-Crh1.0010.999-1.0020.314Hs-Crh1.0010.999-1.0020.314Hs-Crh1.0010.999-1.002		Age	1.009	0.984-1.034	0.484
Red block cell count10630741-15320741Na cell0.9990.0997-1.0010.992Hardet count1.0000.9997-1.0020.686(RP1.0280.999-1.0020.686(RP1.0280.999-1.0020.539Dedmer1.0000.999-1.0020.539Polmer1.0000.999-1.0020.539Polmer1.0000.999-1.0020.538Polmer1.0011.000-1.0010.001Polmer1.0011.000-1.0010.001Polmer1.0011.000-1.0010.001Set1.1240.682-1.6330.646Set1.1240.682-1.6330.646Patelet count1.0740.935-1.1230.646Patelet count1.0740.935-1.0210.466Alburnin1.1150.644-1.9310.656Alburnin1.1150.644-1.9310.656Alburnin1.1150.644-1.9310.656Alburnin1.0150.994-1.0270.031Alburnin1.0150.994-1.0370.134Alburnin1.0150.994-1.0370.134Alburnin1.0250.994-1.0370.355Set1.1790.715-1.9420.351Alburnin1.0260.997-1.0010.326Set1.0260.997-1.0010.326Set1.0270.999-1.0010.326Set1.0260.999-1.0010.331Alburnin1.0260.999-1.0010.331			1.065	0.944-1.201	0.308
Model 3Platelet count0.9990.997-1.0020.485Nis-Tin1.000.999-1.0010.592Alburnin1.1270.631-2.1020.686SOFA score1.2860.128-1.499-0.001DH1.0000.099-1.0010.032D-dimer1.0001.000-1.0000.332P-dimer1.0011.000-1.0010.332Ferritin0.9890.980-0.9990.028Sex1.0230.977-1.0280.806Sex1.0330.977-1.0280.806CCI1.0730.955-1.2060.236Sex1.1240.682-1.8370.686Sex1.1230.6450.999Platelet count0.9990.999-1.0020.428Alburnin1.1150.444-1.3310.666Sex1.2661.108-1.4470.001Alburnin1.1150.444-1.3310.666Alburnin1.1350.99-1.1020.231Datel1.0070.999-1.0010.911Alburnin1.1350.444-1.9310.661Alburnin1.2650.7020.591Alburnin1.2650.7020.591Alburnin1.2650.702-2.2800.434Alburnin1.2650.702-2.2800.434Alburnin1.2650.702-2.2800.434Alburnin1.2650.702-2.2800.434Alburnin1.2650.702-2.2800.434Alburnin1.2650.702-2.2800.434 </td <td></td> <td>Red blood cell count</td> <td>1.063</td> <td>0.741-1.525</td> <td>0.741</td>		Red blood cell count	1.063	0.741-1.525	0.741
Hs-Tn1.0000.999-1.0010.592Ardel 30.56F score1.280.996-1.6000.086LDH1.0280.999-1.6020.539Dedmer1.0000.999-1.0020.539Ser score1.280.996-0.9990.282Ferntin1.0011.000-1.0000.001Age1.0311.000-1.0010.001Ser score1.1250.980-0.9990.980-0.999Ferntin1.0011.000-1.0010.001Age1.0330.979-1.0230.886Ser score1.1270.682-1.8360.648Ser score1.1270.682-1.8360.648Ferntin1.0010.979-1.0230.486Age1.0370.989-1.0020.486Ser score1.2661.108-1.4470.001His-Ch1.0001.009-1.0000.285SiFA score1.2661.081-1.4470.001DH1.0010.099-1.0020.234Age1.0070.983-1.0310.593Sex core1.0600.997-1.0010.255Sex core1.0600.997-1.0010.235His-Ch1.0000.999-1.0010.236Sex core1.0670.999-1.0010.236Sex core1.0670.999-1.0010.235His-Ch1.0000.999-1.0010.236Sex core1.0270.999-1.0010.236Sex core1.0270.999-1.0010.247His-Ch1.0000.999-1.001 <t< td=""><td></td><td>Platelet count</td><td>0.999</td><td>0.997-1.002</td><td>0.485</td></t<>		Platelet count	0.999	0.997-1.002	0.485
Abumin1.1270.6381-20120.6865CRP1.2860.996-1.6600.084SOFA score1.2861.126-1.4690.001D-dimer1.0000.999-1.0020.5382D-dimer1.0000.999-1.0020.5382Serum iron0.9890.989-0.9990.0283Serum iron0.9890.989-0.9990.0283Serum iron0.9890.989-0.9990.0283Serum iron0.9890.989-1.0020.0865Sex1.1240.6852-1.3530.0695Sex1.1270.985-1.2050.1285Red blood cell count1.0730.959-1.0210.286Plateter count0.9890.999-1.0010.666Affarmin1.1050.699-1.0010.668Affarmin1.1050.699-1.0010.699JDFA score1.0010.099-1.0020.0314D-dimer1.0011.000-1.0000.2255Sex1.0790.715-1.9420.519Affarmin1.2550.724-1.4750.838Sex1.0610.099-1.0020.959CCI0.0511.000-1.0000.925Sex1.0250.724-1.4750.838Plateter count0.9990.999-1.0010.745Age1.0011.000-1.0020.926Sex1.0260.722-2.2800.434CRP1.0250.999-1.0100.745Sex1.0410.0010.0020.931Age1.0410.001		Hs-cTn	1.000	0.999–1.001	0.592
GRP 1.028 0.098-1.060 0.0084 LDH 1.000 0.999-1.022 0.559 Dedimer 1.000 1.000-1.000 0.332 Setum iron 0.98 0.999-1.022 0.0559 Ferritin 1.001 1.000-1.001 0.032 Age 1.033 0.979-1.022 0.0261 Sex 1.124 0.682-1.833 0.645 CCI 1.073 0.935-1.266 0.226 Red blood cell count 1.074 0.750-1.536 0.698 Platelet count 0.999 0.996-1.002 0.424 Abumin 1.115 0.644-1.931 0.696 CRP 1.025 0.999-1.002 0.214 Abumin 1.115 0.644-1.931 0.696 CRP 1.025 0.999-1.002 0.214 Dedimer 1.000 1.000-1.000 0.255 SoFA score 1.225 0.999-1.022 0.514 LDH 1.001 0.999-1.022 0.514 Model		Albumin	1.127	0.631–2.012	0.686
Model 3SDF A SCOPE1,2861,149-1,4920,0001D-dimer1,0000,999-1,0020,332Permi iron0,9890,999-0,9990,028Serum iron0,9890,999-0,10010,006Age1,0030,979-1,0280,806Serum iron0,9890,999-1,0280,806Serum iron0,9790,999-1,0280,906Red blood cell count1,0730,955-1,2660,236Red blood cell count0,7301,3550,696Hes-Tin0,0000,999-1,0010,680Albumin1,1150,644-1,9310,696CIP1,2661,9990,996-1,0020,314Albumin1,1150,644-1,9310,696CIP1,2661,999-1,0020,314Model 40,6970,993-1,0130,595CID-dimer1,0000,999-1,0020,314D-dimer1,0000,999-1,0020,315Sex1,1790,975-1,3220,519CCI1,0510,942-1,1560,325Red blood cell count0,3330,774-1,4750,585Age1,0710,999-1,0020,591Sex1,1790,975-1,3220,519CCI1,0010,001-1,0000,033Hos-Tin1,0000,999-1,0010,475Albumin1,2650,702-2,7280,434Hos-Tin1,0000,999-1,0010,475Albumin1,2740,966-1,3600,984 <td< td=""><td></td><td>CRP</td><td>1.028</td><td>0.996-1.060</td><td>0.084</td></td<>		CRP	1.028	0.996-1.060	0.084
LDn 1,000 0.999-1,002 0.332 Model 3 Variable HR 95% Cl p Arge 0,038 0,080-059 0,023 Ferritin 1,001 1,000-1,001 0,001 Arge 1,003 0,975-1,028 0,080 Set 1,124 0,052-1,833 0,046 CG 1,073 0,955-1,206 0,226 Ret blood cell count 1,074 0,730-1,336 0,696 Hatelet count 0,999 0,999-1,001 0,606 Albomin 1,115 0,444-1,357 0,608 Albomin 1,001 0,999-1,001 0,608 CAF 1,025 0,994-1,037 0,011 Daff 1,001 0,999-1,001 0,021 Daff 1,001 0,999-1,001 0,021 Daff 1,007 0,999-1,001 0,021 Albomin 1,007 0,999-1,001 0,021 Age 1,007 0,999-1,001 0,021 Age<		SUFA score	1.286	1.126-1.469	<0.001
Model 3 Variables IR 99% C 0000 0000 Serum Iron 0.989 0.9300-0.999 0.038 Ferntin 1.001 1.000-1.001 0.001 Age 1.031 0.0379-1.028 0.045 Serut 1.124 0.032-1.853 0.045 CG 1.073 0.355-1.206 0.226 Red blood cell count 1.074 0.730-1.356 0.039 Machel 4 0.899 0.999-1.002 0.428 His-Crin 1.000 0.999-1.002 0.234 Alburnin 1.115 0.644-1.931 0.668 Alburnin 1.015 0.994-1.037 0.113 SOFA score 1.266 0.029-1.010 0.265 LDH 1.001 0.099-1.002 0.314 D-dimer 1.007 0.838-1.031 0.578 Sex 1.079 0.715-1.942 0.519 Sex 1.079 0.999-1.002 0.591 Hacel count 0.999 0.997-1.02 <t< td=""><td></td><td>LDH D-dimer</td><td>1.000</td><td>1 000-1 000</td><td>0.559</td></t<>		LDH D-dimer	1.000	1 000-1 000	0.559
Serum iron 0.89 0.89–0.39 0.58 Ferritin 0.01 1.002–1.031 0.001 Age 1.031 0.377–1.028 0.806 Set 1.124 0.622–1.833 0.645 CG 0.073 0.355–1.206 0.236 Red blood cell count 1.074 0.750–1.336 0.696 Patelet count 0.999 0.996–1.002 0.426 Hot Ch 1.001 0.999–1.001 0.686 Albumin 1.115 0.644–1.931 0.696 CRP 1.025 0.994–1.037 0.131 D-dimer 1.000 1.000-1.000 0.265 Model 4 Variables HR 95% CI p Patelet count 0.031 0.742+1.475 0.835 Model 4 Variables HR 95% CI p Red blood cell count 1.033 0.724-1.475 0.835 Model 5 Age 1.007 0.997-1.002 0.591 CCI 1.061 1.000	Model 3	Variables	HR	95% CI	0.302 n
Ferritin1.011.000-1.0010.001Age1.0130.979-1.0280.806Sex1.1240.682-1.8330.645CCI1.0740.955-1.2060.0236Ret blood cell count1.0740.750-1.3360.989Plateler count1.0790.999-1.0010.806Alburnin1.1050.994-1.0570.113SOFA score1.2650.994-1.0570.011Doffer1.0010.999-1.0010.025VariablesHR95% CIpFIR1.0070.024-1.0140.001Doffer1.0010.999-1.0020.314Age1.0070.999-1.0020.314Age1.0070.999-1.0020.315Sex1.1790.715-1.9420.519Sex1.1790.715-1.9420.519Sex1.1790.724-1.4750.838Sex1.1790.975-1.4260.002Hacter count0.9990.997-1.0020.991Model 5Ners1.0250.722-2.8000.434CRP1.0250.722-2.8000.983Jaburnin1.2250.994-1.0570.991Doffer1.0011.000-1.0000.002Doffer1.0310.6630.983Alburnin1.2250.924-1.4750.637CI1.0340.697-1.4260.692Doffer1.0300.000-1.0000.001Doffer1.0311.006-1.0020.997Doffer<		Serum iron	0.989	0.980-0.999	0.028
Age1.030.979-1.0280.806Sex1.1240.682-1.8530.6455CCI1.0730.955-1.2060.236Red blaod cell count0.9990.996-1.0020.426Hs-CTn1.0090.996-1.0020.426Notel A1.0150.644-1.9310.689Albumin1.1150.644-1.9310.689Albumin1.0250.994-1.0570.113SOFA score1.2661.108-1.4470.001D-dimer1.0001.000-1.0000.265Model 4VariablesHR95% CLpFIR1.0990.997-1.0220.519Age1.0770.715-1.9420.519Age1.0790.993-1.0310.598Pielet count0.9990.997-1.0020.591Hs-CTn1.0610.942-1.1960.236Pielet count0.9990.997-1.0020.591Hs-CTn1.0611.067-1.4260.002Offer score1.2650.702-2.2800.434Hs-CTn1.0611.007-1.0000.331Offer score1.2650.996-1.0010.597Albumin1.2650.996-1.0010.597GCI1.0840.657-1.7890.577GCI1.0840.657-1.7890.577GCI1.0840.657-1.7890.577GCI1.0840.657-1.7890.577GCI1.0840.657-1.7890.577GCI1.0840.657-1.7890.577<		Ferritin	1.001	1.000-1.001	0.001
Sex 1,124 0.682-1,833 0.645 CCI 1.073 0.955-1,206 0.236 Red blood cell count 1.074 0.750-1,336 0.698 Plateler count 0.999 0.966-1,002 0.426 Hs-CTn 1.001 0.999-1,001 0.680 Albumin 1.125 0.994-1,057 0.113 SOFA score 1.266 1.186-1,447 0.001 DH 1.001 0.999-1,002 0.234 Dedimer 1.001 0.999-1,002 0.235 Model 4 Variables HR 95% C P FIR 1.007 0.981-1.031 0.593 Sex 1.179 0.972-1.942 0.519 Sex 1.179 0.972-1.942 0.531 Sex 1.179 0.972-1.942 0.951 Hacler count 1.033 0.724-1.475 0.838 GCI 1.011 0.000 0.331 Dedimer 1.027 0.999-1.001 0.434 <		Age	1.003	0.979-1.028	0.806
CCl 1.073 0.955-1.206 0.236 Red blood cell count 0.999 0.996-1.002 0.426 Hs-cTn 1.000 0.999-1.001 0.680 Albumin 1.115 0.644-1.931 0.696 CRP 1.226 1.108-1.447 0.001 SOFA score 1.266 1.108-1.447 0.001 D-dimer 1.000 1.000-1.000 0.265 D-dimer 1.000 1.000-1.000 0.265 GC P P P P Age 1.007 0.983-1.031 0.593 Sex 1.179 0.715-1.942 0.519 GC 1.061 0.942-1.196 0.326 Red blood cell count 0.999 0.997-1.002 0.591 GC 1.061 0.942-1.196 0.326 Red blood cell count 0.999 0.997-1.002 0.591 Hactert count 0.999 0.997-1.002 0.591 Model 5 CCP 1.245 0.022-2.201 0.43		Sex	1.124	0.682-1.853	0.645
Model 5 Nodel Cell Countt 1.0194 0.750-1.536 0.6989 Hastelit countt 0.999 0.999-1.002 0.626 Hs-CTn 1.000 0.999-1.001 0.680 Albumin 1.115 0.644-1.931 0.696 CRP 1.025 0.994-1.007 0.314 D-dimer 1.000 1.000-1.000 0.266 D-dimer 1.001 0.999-1.002 0.263 Model 4 Variables HR 95% CI p FiR 1.007 0.083-1.031 0.593 Age 1.007 0.983-1.031 0.593 Sex 1.179 0.715-1.942 0.519 CCI 1.061 0.942-1.196 0.326 Red blood cell count 0.939 0.997-1.002 0.591 Model 5 Order 1.000 0.099-1.002 0.591 KCI 1.061 1.002-1.002 0.591 Model 5 Order 1.002 0.331 Model 6 Variables HR		CCI	1.073	0.955-1.206	0.236
Model 4 0.999 0.999-1.002 0.420 Albumin 1.115 0.644-1.931 0.680 Albumin 1.115 0.644-1.931 0.696 SOFA score 1.266 1.108-1.447 0.001 LOH 1.001 0.999-1.002 0.314 Dedimer 1.000 1.000-1.000 0.265 Model 4 Variables H 95% CI p FIR 1.009 1.004-1.014 0.001 Age 1.007 0.983-1.031 0.533 Sex 1.179 0.715-1.942 0.519 CCI 1.061 0.942-1.196 0.326 Red blood cell count 1.033 0.724-1.475 0.858 Platelet count 0.399 0.997-1.002 0.591 Hs-CTn 1.000 0.099-1.001 0.745 Albumin 1.265 0.702-2.280 0.434 CRP 1.027 0.996-1.001 0.321 D-dimer 1.001 1.000-1.002 0.321		Red blood cell count	1.074	0.750-1.536	0.698
Abumin 1.000 0.644-1.331 0.6690 ARbumin 1.115 0.644-1.331 0.6960 CRP 1.025 0.994-1.057 0.113 SOFA score 1.266 1.1148-1.447 0.001 L0H 1.001 0.999-1.002 0.2314 D-dimer 1.000 1.000-1.000 0.265 Model 4 Variables HR 95% CI p FIR 1.009 1.004-1.014 0.001 Age 1.007 0.383-1.031 0.593 Sex 1.179 0.715-1.942 0.519 Red blood cell count 1.033 0.724-1.475 0.858 Plateele count 0.999 0.997-1.002 0.591 Hs-CTn 1.000 0.999-1.001 0.445 Albumin 1.265 0.702-2.280 0.434 CRP 1.027 0.996-1.060 0.888 SOFA score 1.245 1.087-1.426 0.002 LDH 1.001 1.000-1.000 0.311 <t< td=""><td></td><td></td><td>1 000</td><td>0.990-1.002</td><td>0.420</td></t<>			1 000	0.990-1.002	0.420
CRP 1.025 0.994-1.057 0.113 SOFA score 1.266 1.108-1.447 0.001 LDH 1.000 1.099-1.002 0.314 D-dimer 1.000 1.000-1.000 0.265 FIR 1.009 1.004-1.014 0.001 Age 1.007 0.938-1.031 0.593 Sex 1.179 0.715-1.942 0.519 CCI 1.061 0.942-1.196 0.326 Red blood cell count 1.033 0.724-1.475 0.858 Platelet count 0.999 0.997-1.002 0.591 Has-CTn 1.000 0.999-1.01 0.745 Albumin 1.265 0.702-2.280 0.434 CRP 1.027 0.996-1.060 0.088 D-dimer 1.001 1.000-1.000 0.331 Model 5 Variables HR 95% CI p Fit quartiles 1.418 1.062 0.002 Albumin 1.265 0.702-5.2180 0.751		Albumin	1.115	0.644–1.931	0.696
SOFA score1.2661.108-1.4470.001LDH1.0010.999-1.0020.314D-dimer1.0001.000-1.0000.265Model 4VariablesHR95% CIPFIR1.0070.983-1.0310.593Sev1.0770.933-1.0310.593Sev1.0770.933-1.0310.593CCI1.0610.942-1.1960.326Red blood cell count0.9930.997-1.0020.591Hs-CTn1.0000.999-1.0100.745Hs-CTn1.0000.999-1.0100.745Kodel 5OFA score1.2451.007-1.0220.092D-dimer1.0001.000-1.0020.092LDH1.0011.000-1.0020.092LDH1.0011.000-1.0020.092LDH1.0011.000-1.0020.092LDH1.0011.000-1.0020.092LDH1.0141.000-1.0020.092LDH1.0140.001-1.0020.931Red blood cell count0.9990.996-1.0110.371CCI1.0450.929-1.1750.467Sex1.0840.657-1.7890.751CCH1.0250.994-1.0570.116Sex1.0250.994-1.0570.116SoFA score1.011.003-1.0020.231D-dimer1.0010.0010.021LDH1.0250.994-1.0570.116SoFA score1.011.131-1.494<0.001		CRP	1.025	0.994–1.057	0.113
Model 41.0010.999-1.0020.314 0.2655Model 4VariablesHR95% ClpFIR1.0091.004-1.0140.001 0.935Age1.0070.983-1.0310.593 0.582Sex1.1790.715-1.9420.519 0.932CCl1.0610.942-1.1960.326 0.999-1.002Red blood cell count1.0330.724-1.4750.858 0.832Platelet count0.9990.997-1.0020.591 		SOFA score	1.266	1.108-1.447	0.001
Dedimer1.0001.000-1.0000.265Model 4VariablesHR95% ClpFiR1.0091.004-1.0140.001Age1.0070.983-1.0310.593Sex1.1790.715-1.5420.519CCI1.0610.942-1.1960.326Red blood cell count0.3310.724-1.4750.858Platelet count0.9990.997-1.0020.591Hs-cTn1.0000.999-1.0010.745Albumin1.2650.702-2.2800.434CRP1.0270.996-1.0600.088SDFA score1.2451.087-1.4260.002D-dimer1.0011.000-1.0020.0331Model 5VariablesHR95% ClpFiR quartiles1.4811.162-1.8880.002Age1.0070.983-1.0310.587Sex1.0840.657-1.7890.751CCI1.0450.929-1.1750.467Red blood cell count0.9990.996-1.0010.537Sex1.0810.1330.9740.474Nodel 5CP1.0010.999-1.0010.643Red blood cell count0.9990.996-1.0010.537Nodel 6HR95% ClPHigh FiR (FIR ≥2.2)1.0070.984-1.0310.164Age1.0070.994-1.0510.434Age1.0070.994-1.0310.585Sex1.0970.996-1.0010.541D-dimer1.		LDH	1.001	0.999-1.002	0.314
Model 4 Variables HR 95% Cl p FIR 1009 1004-1014 0.001 Age 1.079 0.983-1031 0.593 Sex 1.179 0.715-1942 0.519 CCI 1.061 0.942-1.196 0.326 Red blood cell count 1.033 0.724-1.1475 0.858 Platelet count 0.999 0.979-1.002 0.519 Has-CTn 1.000 0.999-1.001 0.745 Albumin 1.265 0.722-2.280 0.0434 CRP 1.027 0.996-1.060 0.088 SOFA score 1.245 1.087-1.426 0.002 D-dimer 1.000 1.000-1.000 0.331 Model 5 Variables HR 95% Cl p Fliq quarities 1.481 1.162-1.888 0.002 Age 1.007 0.983-1.031 0.587 Sex 1.084 0.657-1.789 0.751 CCI 1.045 0.929-1.175 0.467 </td <td></td> <td>D-dimer</td> <td>1.000</td> <td>1.000-1.000</td> <td>0.265</td>		D-dimer	1.000	1.000-1.000	0.265
HR 1.009 1.004-1.014 0.001 Age 1.007 0.983-1.031 0.593 Sex 1.179 0.715-1.942 0.519 CCI 1.061 0.942-1.196 0.326 Red blood cell count 1.033 0.724-1.475 0.858 Platelet count 0.999 0.997-1.002 0.591 Hs-cTn 1.000 0.999-1.001 0.745 Albumin 1.265 0.702-2.280 0.434 CRP 1.027 0.996-1.060 0.088 SOFA score 1.245 1.087-1.426 0.002 LDH 1.001 1.000-1.002 0.092 D-dimer 1.001 1.000-1.002 0.092 Age 1.007 0.983-1.031 0.587 Sex 1.084 0.657-1.789 0.751 CCI 1.045 0.929-1.175 0.467 Red blood cell count 0.942 0.663-1.340 0.741 Platelet count 0.9999 0.996-1.001 0.370	Model 4	Variables	HR	95% Cl	р
Age 1.07 0.935-1.031 0.335 Sex 1.179 0.715-1.942 0.519 CCI 1.061 0.942-1.196 0.326 Red blood cell count 1.033 0.724-1.475 0.858 Platelet count 0.999 0.997-1.002 0.591 Hs-CTn 1.000 0.999-1.001 0.745 Albumin 1.265 0.702-2.280 0.434 CRP 1.027 0.996-1.060 0.088 SOFA score 1.245 1.087-1.426 0.002 LDH 1.001 1.000-1.002 0.092 D-dimer 1.001 1.000-1.002 0.031 Model 5 HR 95% CI p Fl quartiles H.481 1.162-1.888 0.002 Age 1.007 0.933-1.031 0.587 Sex 1.084 0.657-1.789 0.751 CCI 1.045 0.929-1.175 0.467 Hystelt count 0.949 0.996-1.001 0.331 Hystelf cou		FIR	1.009	1.004-1.014	0.001
Action 1.061 0.942-1.96 0.335 Red blod cell count 1.033 0.724-1.475 0.888 Platelet count 0.999 0.997-1.002 0.591 Hastelet count 0.000 0.999-1.001 0.745 Albumin 1.265 0.702-2.280 0.434 CRP 1.001 1.000-1.002 0.092 D-dimer 1.001 1.000-1.002 0.092 D-dimer 1.001 1.000-1.002 0.092 Age 1.001 1.000-1.002 0.031 Age 1.001 0.000-1.000 0.331 Sex 1.084 0.657-1.789 0.751 CCI 1.045 0.929-1.175 0.467 Red blood cell count 0.999 0.996-1.001 0.3370 Hs-CTn 1.000 0.999-1.001 0.633-1.340 Albumin 1.214 0.637-1.789 0.751 CCI 1.045 0.929-1.175 0.467 Red blood cell count 0.999 0.996-1.001 0.3370 <td></td> <td>Age Sex</td> <td>1.007</td> <td>0.983-1.031 0.715-1.942</td> <td>0.593</td>		Age Sex	1.007	0.983-1.031 0.715-1.942	0.593
Red blood cell count 1.033 0.724-1.475 0.858 Platelet count 0.999 0.997-1.002 0.591 Hs-CTn 1.000 0.999-1.001 0.745 Albumin 1.265 0.702-2.280 0.434 CRP 1.027 0.996-1.060 0.088 SOFA score 1.245 1.087-1.426 0.002 LDH 1.001 1.000-1.002 0.092 D-dimer 1.000 1.000-1.002 0.092 D-dimer 1.000 1.000-1.002 0.092 Age 1.481 1.62-1.888 0.002 Age 1.007 0.933-1.031 0.587 Sex 1.084 0.657-1.789 0.751 CCI 1.045 0.929-1.175 0.467 Red blood cell count 0.942 0.663-1.340 0.741 Platelet count 0.942 0.663-1.340 0.741 Platelet count 0.999 0.996-1.001 0.370 HS-CTn 1.000 0.099-1.011 0.643 <td></td> <td></td> <td>1.061</td> <td>0.942-1.196</td> <td>0.375</td>			1.061	0.942-1.196	0.375
Platelet count 0,999 0,997-1.002 0,591 Hs-CTn 1.000 0,999-1.001 0,745 Albumin 1.265 0,702-2.280 0,434 CRP 1.027 0,996-1.060 0.088 SOFA score 1.245 1.087-1.426 0.002 D-dimer 1.001 1.000-1.000 0.331 Model 5 Variables HR 95% CI p If quartiles 1.481 1.162-1.888 0.002 Age 1.007 0.983-1.031 0.587 Sex 1.084 0.657-1.789 0.751 GCI 1.045 0.592-1.175 0.467 Red blood cell count 0.942 0.663-1.340 0.741 Platelet count 0.942 0.663-1.340 0.741 D-Grome 1.000 0.999-1.001		Red blood cell count	1.033	0.724–1.475	0.858
Hs-CTn 1.000 0.999-1.001 0.745 Albumin 1.265 0.702-2.280 0.434 CRP 1.027 0.996-1.060 0.088 SOFA score 1.245 1.087-1.426 0.002 LDH 1.001 1.000-1.002 0.092 D-dimer 1.000 1.000-1.000 0.331 FIR quartiles HR 95% CI p Fix quartiles 1.481 1.162-1.888 0.002 Age 1.007 0.983-1.031 0.587 Sex 1.084 0.657-1.789 0.751 CCI 1.045 0.929-1.175 0.467 Red blood cell count 0.942 0.663-1.340 0.741 Hatelet count 0.999 0.996-1.001 0.370 Hs-CTn 1.000 0.999-1.001 0.643 Albumin 1.214 0.693-2.128 0.498 Albumin 1.214 0.693-2.128 0.498 Model 6 Variables HR 95% CI p <		Platelet count	0.999	0.997-1.002	0.591
Albumin 1.265 0.702-2.280 0.434 CRP 1.027 0.996-1.060 0.088 SOFA score 1.245 1.087-1.426 0.002 LDH 1.001 1.000-1.002 0.092 D-dimer 1.000 1.000-1.000 0.331 Model 5 HR 95% CI p FIR quartiles 1.481 1.162-1.888 0.002 Age 1.007 0.983-1.031 0.587 Sex 1.084 0.657-1.789 0.751 CCI 1.045 0.929-1.175 0.467 Red blood cell count 0.942 0.663-1.340 0.741 Platelet count 0.942 0.663-1.340 0.741 O.643 1.000 0.999-1.001 0.635 <td></td> <td>Hs-cTn</td> <td>1.000</td> <td>0.999–1.001</td> <td>0.745</td>		Hs-cTn	1.000	0.999–1.001	0.745
CRP 1.027 0.996-1.060 0.088 SOFA score 1.245 1.087-1.426 0.002 LDH 1.001 1.000-1.002 0.992 D-dimer 1.001 1.000-1.000 0.331 Model 5 Variables HR 95% Cl p FlR quartiles 1.481 1.162-1.888 0.002 Age 1.007 0.983-1.031 0.587 Sex 1.084 0.657-1.789 0.751 CCI 1.045 0.929-1.175 0.467 Red blood cell count 0.942 0.663-1.340 0.741 Platelet count 0.999 0.996-1.001 0.370 Hs-CTn 1.000 0.999-1.001 0.643 Albumin 1.214 0.693-2.128 0.498 CRP 1.025 0.994-1.057 0.116 SOFA score 1.301 1.133-1.494 <0.001		Albumin	1.265	0.702–2.280	0.434
SOFA score 1.245 1.087-1.426 0.002 LDH 1.001 1.000-1.002 0.992 D-dimer 1.000 1.000-1.000 0.331 Model 5 Variables HR 95% Cl p FIR quartiles 1.481 1.162-1.888 0.002 Age 1.007 0.983-1.031 0.587 Sex 1.084 0.657-1.789 0.751 CCI 1.045 0.929-1.175 0.467 Red blood cell count 0.942 0.663-1.340 0.741 Platelet count 0.999 0.999-1.001 0.643 Model 6 CRP 1.025 0.994-1.057 0.116 SOFA score 1.301 1.133-1.494 <0.001		CRP	1.027	0.996-1.060	0.088
D-dimer 1.001 1.000-1.002 0.031 Model 5 Variables HR 95% Cl p FIR quartiles 1.481 1.162-1.888 0.002 Age 1.007 0.983-1.031 0.587 Sex 1.084 0.657-1.789 0.751 CCI 1.045 0.929-1.175 0.467 Red blood cell count 0.942 0.663-1.340 0.741 Platelet count 0.999 0.996-1.001 0.370 Hs-CTn 1.000 0.999-1.001 0.643 Albumin 1.214 0.693-2.128 0.498 CRP 1.025 0.994-1.057 0.116 SOFA score 1.301 1.133-1.494 <0.001			1.245	1.087-1.426	0.002
Model 5 Variables HR 95% Cl p FIR quartiles 1.481 1.162–1.888 0.002 Age 1.007 0.983–1.031 0.587 Sex 1.084 0.657–1.789 0.751 CCI 1.045 0.999–1.175 0.467 Red blood cell count 0.942 0.663–1.340 0.741 Platelet count 0.999 0.996–1.001 0.370 Hs-CTn 1.000 0.999–1.075 0.163 Albumin 1.214 0.693–2.128 0.498 CRP 1.025 0.994–1.057 0.116 SOFA score 1.301 1.133–1.494 <0.001		D-dimer	1.001	1.000-1.002	0.092
FIR quartiles 1.481 1.162-1.888 0.002 Age 1.007 0.983-1.031 0.587 Sex 1.084 0.657-1.789 0.751 CCI 1.045 0.929-1.175 0.467 Red blood cell count 0.942 0.663-1.340 0.741 Platelet count 0.999 0.996-1.001 0.370 Hs-cTn 1.000 0.999-1.001 0.643 Albumin 1.214 0.693-2.128 0.498 CRP 1.025 0.994-1.057 0.116 SOFA score 1.301 1.133-1.494 <0.001	Model 5	Variables	HR	95% CI	a
Age1.007 $0.983-1.031$ 0.587 Sex1.084 $0.657-1.789$ 0.751 CCI1.045 $0.929-1.175$ 0.467 Red blood cell count 0.942 $0.663-1.340$ 0.741 Platelet count 0.999 $0.996-1.001$ 0.370 Hs-CTn1.000 $0.999-1.001$ 0.643 Albumin1.214 $0.693-2.128$ 0.498 CRP1.025 $0.994-1.057$ 0.116 SOFA score1.301 $1.133-1.494$ <0.001		FIR quartiles	1.481	1.162–1.888	0.002
Sex 1.084 $0.657-1.789$ 0.751 CCI 1.045 $0.929-1.175$ 0.467 Red blood cell count 0.942 $0.663-1.340$ 0.741 Platelet count 0.999 $0.996-1.001$ 0.370 Hs-cTn 1.000 $0.999-1.001$ 0.643 Albumin 1.214 $0.693-2.128$ 0.498 CRP 1.025 $0.994-1.057$ 0.116 SOFA score 1.301 $1.133-1.494$ <0.001 LDH 1.001 $1.000-1.002$ 0.131 D-dimer 1.000 $1.000-1.002$ 0.241 Model 6VariablesHR 95% ClpHigh FIR (FIR ≥ 29.2) 1.709 $1.017-2.871$ 0.043 Age 1.007 $0.984-1.031$ 0.558 Sex 1.095 $0.655-1.829$ 0.730 CCI 1.031 $0.916-1.160$ 0.611 Red blood cell count 0.929 $0.996-1.001$ 0.351		Age	1.007	0.983-1.031	0.587
CCI 1.045 0.929-1.175 0.467 Red blood cell count 0.942 0.663-1.340 0.741 Platelet count 0.999 0.996-1.001 0.370 Hs-cTn 1.000 0.999-1.001 0.643 Albumin 1.214 0.693-2.128 0.498 CRP 1.025 0.994-1.057 0.116 SOFA score 1.301 1.133-1.494 <0.001		Sex	1.084	0.657–1.789	0.751
Red blood cell count 0.942 $0.663-1.340$ 0.741 Platelet count 0.999 $0.996-1.001$ 0.370 Hs-cTn 1.000 $0.999-1.001$ 0.643 Albumin 1.214 $0.693-2.128$ 0.498 CRP 1.025 $0.994-1.057$ 0.116 SOFA score 1.301 $1.133-1.494$ <0.001 LDH 1.001 $1.000-1.002$ 0.131 D-dimer 1.000 $1.000-1.000$ 0.241 Model 6VariablesHR 95% ClpHigh FIR (FIR $\ge 29.2)$ 1.709 $1.017-2.871$ 0.043 Age 1.007 $0.984-1.031$ 0.558 Sex 1.095 $0.655-1.829$ 0.730 CCl 1.031 $0.916-1.160$ 0.611 Red blood cell count 0.929 $0.966-1.001$ 0.351		CCI	1.045	0.929–1.175	0.467
Mateliet count 0.999 0.996-1.001 0.370 Hs-cTn 1.000 0.999-1.001 0.643 Albumin 1.214 0.693-2.128 0.498 CRP 1.025 0.994-1.057 0.116 SOFA score 1.301 1.133-1.494 <0.001		Red blood cell count	0.942	0.663-1.340	0.741
Albumin 1.000 0.999-1.001 0.0493 Albumin 1.214 0.693-2.128 0.498 CRP 1.025 0.994-1.057 0.116 SOFA score 1.301 1.133-1.494 <0.001			0.999	0.996-1.001	0.370
GRP 1.025 0.994 -1.057 0.116 SOFA score 1.301 1.133-1.494 <0.001		Albumin	1.000	0.693-2.128	0.043
SOFA score 1.301 1.133-1.494 <0.001 LDH 1.001 1.000-1.002 0.131 D-dimer 1.000 1.000-1.000 0.241 Model 6 Variables HR 95% Cl p High FIR (FIR ≥29.2) 1.709 1.017-2.871 0.043 Age 1.007 0.984-1.031 0.558 Sex 1.095 0.655-1.829 0.730 CCl 1.031 0.916-1.160 0.611 Red blood cell count 0.929 0.966-1.001 0.351		CRP	1.025	0.994-1.057	0.116
LDH 1.001 1.000-1.002 0.131 D-dimer 1.000 1.000-1.000 0.241 Model 6 Variables HR 95% Cl p High FIR (FIR ≥29.2) 1.709 1.017-2.871 0.043 Age 1.007 0.984-1.031 0.558 Sex 1.095 0.655-1.829 0.730 CCl 1.031 0.916-1.160 0.611 Red blood cell count 0.929 0.966-1.001 0.351		SOFA score	1.301	1.133–1.494	<0.001
D-dimer 1.000 $1.000-1.000$ 0.241 Model 6VariablesHR 95% ClpHigh FIR (FIR ≥ 29.2) 1.709 $1.017-2.871$ 0.043 Age 1.007 $0.984-1.031$ 0.558 Sex 1.095 $0.655-1.829$ 0.730 CCl 1.031 $0.916-1.160$ 0.611 Red blood cell count 0.929 $0.966-1.335$ 0.691 Platelet count 0.999 $0.996-1.001$ 0.351		LDH	1.001	1.000-1.002	0.131
Model 6VariablesHR95% ClpHigh FIR (FIR \geq 29.2)1.7091.017–2.8710.043Age1.0070.984–1.0310.558Sex1.0950.655–1.8290.730CCI1.0310.916–1.1600.611Red blood cell count0.9290.646–1.3350.690Platelet count0.9990.996–1.0010.351		D-dimer	1.000	1.000-1.000	0.241
High FIR (FIR ≥ 29.2)1.7091.017-2.8710.043Age1.0070.984-1.0310.558Sex1.0950.655-1.8290.730CCI1.0310.916-1.1600.611Red blood cell count0.9290.646-1.3350.690Platelet count0.9990.996-1.0010.351	Model 6	Variables	HR	95% CI	р
Age 1.007 0.984–1.031 0.558 Sex 1.095 0.655–1.829 0.730 CCI 1.031 0.916–1.160 0.611 Red blood cell count 0.929 0.646–1.335 0.690 Platelet count 0.999 0.996–1.001 0.351		High FIK (FIR ≥29.2)	1.709	1.017-2.871	0.043
Image: Non-State Image: Non-State<		Age Sav	1.007	0.984-1.031 0.655-1.820	0.558
Red blood cell count 0.929 0.646–1.335 0.690 Platelet count 0.999 0.996–1.001 0.351			1.035	0.029	0.750
Platelet count 0.999 0.996–1.001 0.351		Red blood cell count	0.929	0.646–1.335	0.690
		Platelet count	0.999	0.996-1.001	0.351

(Continued)

Table 4. (Continued).				
Model 1	Variables	HR	95% CI	р
	Hs-cTn	1.000	0.999–1.001	0.691
	Albumin	1.186	0.671-2.097	0.558
	CRP	1.027	0.997-1.059	0.082
	SOFA score	1.319	1.149–1.515	< 0.001
	LDH	1.001	1.000-1.002	0.071
	D-dimer	1.000	1.000-1.000	0.370

CCI, Charlson comorbidity index; CI, confidence interval; CRP, C-reactive protein; hs-cTn, high-sensitivity cardiac troponin; FIR, ferritin to iron ratio; LDH, lactate dehydrogenase; HR, hazard ratio; SOFA, Sequential Organ Failure Assessment.

and in the severe COVID-19 subgroup (Panel B) (Log-rank p < 0.001). In three Cox regression analyses (Table 4, **Models 4–6**) including FIR, either as continuous variable (FIR) or categorical variable [either FIR quartiles (1st FIR <5.9, 2nd 5.9 \leq FIR >13.9, 3rd 13.9 \leq FIR >29.2, 4th FIR \geq 29.2) or high FIR], FIR, FIR quartiles, and high FIR were able to predict the in-hospital prognosis of COVID-19 patients regardless of confounders (age, sex, CCI, red blood cell count, platelet count, hs-cTn, albumin, CRP, SOFA score, LDH, and D-dimer). Similarly, FIR, FIR quartiles, and high FIR were able to predict the in-hospital prognosis of patients with severe COVID-19 regardless of confounders (age, sex, CCI, red blood cell count, platelet count, hs-cTn, albumin, CRP, SOFA score, LDH, and D-dimer). Similarly, FIR, FIR quartiles, and high FIR were able to predict the in-hospital prognosis of patients with severe COVID-19 regardless of confounders (age, sex, CCI, red blood cell count, platelet count, hs-cTn, albumin, CRP, SOFA score, LDH, and D-dimer) (**Supplementary Table 2**).

3.5. Exploratory analyses

At multi-adjusted Cox regression analysis, a significant association emerged between either FIR quartiles or high FIR and ICU admission as single endpoint, while the association between FIR as continuous variable and ICU admission as single endpoint was not significant (**Supplementary Table 3**). In addition, a significant association emerged between either FIR, FIR quartiles or high FIR and in-hospital death as single endpoint (**Supplementary Table 4**). At the same multi-adjusted model, FIR \geq 13.9 (the median value) was independently associated with the composite endpoint of ICU admission/in-hospital death (**Supplementary Table 5**). At univariate Cox regression analysis, FTR as continuous variable was significantly associated with the single endpoint of in-hospital death (HR 1.037, 95%CI 1.027– 1.046, p < 0.001), but not with the single endpoint of ICU admission (HR 1.015, 95% CI 0.997–1.034, p = 0.102).

4. Discussion

Three main results of this study deserve discussion: 1) hyperferritinemia and hypoferremia were prevalent conditions in hospitalized COVID-19 patients; 2) both ferritin and serum iron levels were associated with the composite endpoint of ICU admission/in-hospital death in hospitalized COVID-19 patients; 3) high FIR, as an integrated marker of ferritin and iron status, was an independent predictor of in-hospital prognosis in COVID-19 patients.

The high prevalence of hyperferritinemia (ferritin >300 ng/mL) [48] and hypoferremia (serum iron <80 μ g/dL in males or serum iron <60 μ g/dL in females) [49] which emerged in this study strongly suggests that iron metabolism is dysregulated in

COVID-19. Consistently, previous studies have shown significantly higher ferritin levels and reduced serum iron levels in hospitalized COVID-19 patients as compared to COVID-19 negative subjects [50-52]. From a biological perspective, different mechanisms might explain the derangement of iron metabolism occurring in COVID-19. First, inflammatory response may mediate both the increase of ferritin levels and the decrease of serum iron levels in COVID-19 patients. Indeed, ferritin is a well-known acute-phase protein, whose expression may be induced by proinflammatory cytokines during infections [53]. Also, hypoferremia occurs during infections due to the hepcidin-mediated inhibition of ferroportin and subsequent iron retention in the intracellular compartment [54]. In agreement with this, different markers of inflammation were independent predictors of FIR, as the compositum of ferritin and serum iron levels, in the present study. Second, it has been speculated that SARS-CoV -2 may directly affect iron metabolism. Indeed, SARS-CoV-2 has been shown to exhibit hepcidin-like properties, potentially contributing to reduce serum iron availability, independently from the inflammatory response, through the inhibition of ferroportin activity [55,56]. Also, SARS-CoV-2, by promoting the disruption of hemoglobin 1-beta chain and the dissociation of porphyrins from iron, has been speculated to increase ferritin expression [57].

In this study a significant prospective association emerged between both ferritin and serum iron and COVID-19 prognosis. This result supports previous literature data, mainly derived from retrospective analyses, showing a significant association between either hyperferritinemia or hypoferremia, and COVID-19 severity/prognosis [26–40].

As an unprecedented finding, the present study showed a significant and independent association between FIR, either as continuous or categorical variable, and in-hospital prognosis of patients with COVID-19. Indeed, to the best of our knowledge, the association of the high ferritin/low iron binomial with COVID-19 prognosis has never been explored so far. A plausible biological explanation of this result may rely on the possible pathogenic role, either individual or synergistical, of the two elements combined in FIR, in the context of COVID-19. In this regard, there is evidence suggesting that both hyperferritinemia and hypoferremia, beyond being induced by COVID-19, may themselves promote some pathophysiological mechanisms leading to the most severe clinical manifestations of COVID-19 (enhanced inflammatory response and multi-organ dysfunction) [23,58]. Supporting this notion, ferritin stimulates intracellular proinflammatory pathways culminating in the activation of NF-KB and in the increased expression of pro-inflammatory mediators [23,58]. In addition, iron excess bound to ferritin within the intracellular compartment may promote the generation of reactive oxygen species and oxidative damage, ultimately leading to ferroptosis (the programmed cell death induced by iron-dependent peroxidation mechanisms) [59]. Finally, hypoferremia may impair tissue oxygen supply, thereby affecting negatively COVID-19 outcome [26]. Overall, these processes are likely to be implicated in the onset of multi-organ damage in COVID-19.

From a clinical perspective, the existence of a significant and independent association between FIR and COVID-19 prognosis may have important implications: 1) the utility of FIR measurement in the prognostic stratification of COVID-19 patients; 2) the need of a better understanding of FIR as a possible therapeutic target in COVID-19. Regarding the first issue, it should be emphasized that FIR is an inexpensive and easily available laboratory parameter, which can be rapidly obtained from venous blood samples at hospitalization. Regarding the second issue, it should be considered that, although different therapeutic strategies targeting iron metabolism have been proposed in patients with COVID-19 (iron chelation, therapeutic plasma exchange, iron depletion) [60], there is no evidence from randomized controlled trials of the impact of this therapeutic approach on COVID-19 outcomes.

Some limitations of this study, mainly considering its observational character, should be acknowledged. First, this is a single-center prospective study enrolling patients from a quite restricted Italian region, in a short period of time, and with variable COVID-19 severity. A multi-center design with an extended enrollment period might have allowed for the evaluation of a greater number of participants from different geographical areas and in different seasons, potentially overcoming geographical and seasonal variations of iron parameters, which have been reported in previous studies [61,62]; in addition, it might have allowed for sub-group analyses. Second, due to the study design, comparison of ferritin, iron, and FIR values between COVID-19 cases and COVID-19 negative controls was not possible; a case-control analysis could have strengthened the study results. Third, the observation lasted until the occurrence of the composite endpoint of ICU admission/death or hospital discharge; this did allow for the investigation of the association between FIR and in-hospital prognosis but not the association between FIR and long-term prognosis. Fourth, the possible residual confounding effect due to unmeasured variables cannot be ruled out. To this regard, it should be considered that serum hepcidin levels were not measured, although they could have displayed a high informative value in support of the hypothetical pathophysiological mechanisms underlying iron metabolism derangement in COVID-19; therefore, future studies exploring this issue are warranted. Fifth, as in the nature of observational analysis, our study did suggest but not prove any causality between iron metabolism derangement and COVID-19 severity/prognosis. Finally, as a possible methodological limitation of the study, blood samples were not performed in the same daytime hours; therefore, possible diurnal variations of serum iron levels, which have been extensively recognized [63],

may compromise, at least partially, the reliability of the observed results.

5. Conclusions

This study shows that FIR directly correlates with COVID-19 severity and predict worse in-hospital clinical outcomes in COVID-19 patients. Accordingly, FIR, as an integrated parameter of iron metabolism derangement, may be worthy of attention to refine the prognostic stratification of COVID-19 patients at hospital admission. Potential therapeutic strategies aimed at restoring iron homeostasis are worthy of being investigated to prevent the most severe complications of COVID-19.

Author contributions

Conception and design: V.B and M.P.; analysis and interpretation of the data: V.B., M.R.M., F.F., E.C., G.B., E.M., M.B., A.S., and M.P.; the drafting of the paper or revising it critically for intellectual content: V.B., M.R.M., M.B., A.S., and M.P.; final approval of the version to be published: V.B., M.R.M., F. F., E.C., G.B., E.M., M.B., A.S., and M.P. All authors agree to be accountable for all aspects of the work.

Data availability statement

The data that support the findings of this study are available from the corresponding author, [M.R.M.], upon reasonable request.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants, or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

ORCID

Maciej Banach () http://orcid.org/0000-0001-6690-6874 Matteo Pirro () http://orcid.org/0000-0002-5527-4821

References

- 1. Coronavirus disease (COVID-19) pandemic. World Health Organization. Available from: https://www.who.int/emergencies/dis eases/novel-coronavirus-2019. Accessed on November 30 2021.
- Bohn MK, Hall A, Sepiashvili L, et al. Pathophysiology of COVID-19: mechanisms underlying disease severity and progression. Physiology (Bethesda). 2020;35(5):288–301.
- Romanova ES, Vasilyev VV, Startseva G, et al. Cause of death based on systematic post-mortem studies in patients with positive SARS-CoV-2 tissue PCR during the COVID-19 pandemic. J Intern Med. 2021;290(3):655–665.
- Gao YM, Xu G, Wang B, et al. Cytokine storm syndrome in coronavirus disease 2019: a narrative review. J Intern Med. 2021;289(2):147–161.
- Bhaskar S, Sinha A, Banach M, et al. Cytokine storm in COVID-19immunopathological mechanisms, clinical considerations, and therapeutic approaches: the REPROGRAM consortium position paper. Front Immunol. 2020;11:1648.

- Petrovic V, Radenkovic D, Radenkovic G, et al. Pathophysiology of cardiovascular complications in COVID-19. Front Physiol. 2020;11:575600.
- Ji P, Zhu J, Zhong Z, et al. Association of elevated inflammatory markers and severe COVID-19: a meta-analysis. Medicine (Baltimore). 2020;99 (47):e23315.
- Juneja GK, Castelo M, Yeh CH, et al. COVID-BEACONS investigators. Biomarkers of coagulation, endothelial function and fibrinolysis in critically-ill patients with COVID-19: a single-centre prospective longitudinal study. J Thromb Haemost. 2021;19(6):1546–1557.
- 9. Alfageme M, González Plaza J, Méndez S, et al. Venous doppler ultrasound in critically ill COVID-19 patients: game changer in anticoagulation therapy. Ultrasound J. 2020;12(1):54.
- 10. Balfanz P, Hartmann B, Müller-Wieland D, et al. Early risk markers for severe clinical course and fatal outcome in German patients with COVID-19. PLoS One. 2021;16(1):e0246182.
- 11. Pennica A, Conforti G, Falangone F, et al. Clinical management of adult coronavirus infection disease 2019 (COVID-19) positive in the setting of low and medium intensity of care: a short practical review. SN Compr Clin Med. 2020;2(6):694–699.
- 12. Raschke RA, Agarwal S, Rangan P, et al. Discriminant accuracy of the SOFA score for determining the probable mortality of patients with COVID-19 pneumonia requiring mechanical ventilation. JAMA. 2021;325(14):1469–1470.
- Fan G, Tu C, Zhou F, et al. Comparison of severity scores for COVID-19 patients with pneumonia: a retrospective study. Eur Respir J. 2020;56(3):2002113.
- Bianconi V, Mannarino MR, Figorilli F, et al. Prevalence of vitamin D deficiency and its prognostic impact on patients hospitalized with COVID-19. Nutrition. 2021;91-92:111408.
- Bianconi V, Mannarino MR, Figorilli F, et al. Low brachial artery flow-mediated dilation predicts worse prognosis in hospitalized patients with COVID-19. J Clin Med. 2021;10(22):5456.
- Madahar P, Wunsch H, Jha P, et al. Trends in COVID-19-related in-hospital mortality: lessons learned from nationwide samples. Lancet Respir Med. 2021;9(4):322–324.
- Bellan M, Patti G, Hayden E, et al. Fatality rate and predictors of mortality in an Italian cohort of hospitalized COVID-19 patients. Sci Rep. 2020;10(1):20731.
- Bianconi V, Violi F, Fallarino F, et al. Is acetylsalicylic acid a safe and potentially useful choice for adult patients with COVID-19 ? Drugs. 2020;80(14):1383–1396.
- 19. Azkur AK, Akdis M, Azkur D, et al. Immune response to SARS-CoV-2 and mechanisms of immunopathological changes in COVID-19. Allergy. 2020;75(7):1564–1581.
- 20. Wang W, Knovich MA, Coffman LG, et al. Serum ferritin: past, present and future. Biochim Biophys Acta. 2010;1800(8):760–769.
- 21. Drakesmith H, Prentice A. Viral infection and iron metabolism. Nat Rev Microbiol. 2008;6(7):541–552 .
- 22. Ruscitti P, Berardicurti O, Barile A, et al. Severe COVID-19 and related hyperferritinaemia: more than an innocent bystander? Ann Rheum Dis. 2020;79(11):1515–1516.
- Gomes AC, Moreira AC, Mesquita G, et al. Modulation of iron metabolism in response to infection: twists for all tastes. Pharmaceuticals (Basel). 2018 Sep 1;11(3):84 .
- Galaris D, Barbouti A, Pantopoulos K. Iron homeostasis and oxidative stress: an intimate relationship. Biochim Biophys Acta Mol Cell Res. 2019;1866(12):118535.
- Ruddell RG, Hoang-Le D, Barwood JM, et al. Ferritin functions as a proinflammatory cytokine via iron-independent protein kinase C zeta/nuclear factor kappaB-regulated signaling in rat hepatic stellate cells. Hepatology. 2009;49(3):887–900.
- Hippchen T, Altamura S, Muckenthaler MU, et al. Hypoferremia is associated with increased hospitalization and oxygen demand in COVID-19 patients. Hemasphere. 2020;4(6):e492.
- In this retrospective study, low serum iron levels predicted hospitalization due to COVD-19.
- 27. Zhao K, Huang J, Dai D, et al. Serum iron level as a potential predictor of coronavirus disease 2019 severity and mortality: a retrospective study. Open Forum Infect Dis. 2020;7(7):ofaa250.

- In this retrospective study, low serum iron levels predicted COVID-19 severity and mortality.
- Lino K, Guimarães GMC, Alves LS, et al. Serum ferritin at admission in hospitalized COVID-19 patients as a predictor of mortality. Braz J Infect Dis. 2021;25(2):101569.
- In this retrospective study, high ferritin levels predicted COVID-19 mortality.
- Taneri PE, Gómez-Ochoa SA, Llanaj E, et al. Anemia and iron metabolism in COVID-19: a systematic review and meta-analysis. Eur J Epidemiol. 2020;35(8):763–773.
- In this meta-analysis of 189 studies (57,563 COVID-19 patients), severe COVID-19 cases had higher ferritin levels as compared to moderate cases; in addition, serum ferritin levels were significantly lower in survivors as compared to non-survivors.
- Ashktorab H, Pizuorno A, Aduli F, et al. Elevated liver enzymes, ferritin, C-reactive protein, D-dimer, and age are predictive markers of outcomes among African American and Hispanic patients with coronavirus disease 2019. Gastroenterology. 2021;161(1):345–349.
- Zeng HL, Yang Q, Yuan P, et al. Associations of essential and toxic metals/metalloids in whole blood with both disease severity and mortality in patients with COVID-19. FASEB J. 2021;35(3):e21392.
- Bia Biamonte F, Botta C, Mazzitelli M, et al. Combined lymphocyte/ monocyte count, D-dimer and iron status predict COVID-19 course and outcome in a long-term care facility. J Transl Med. 2021;19(1):79.
- 33. Shah A, Frost JN, Aaron L, et al. Systemic hypoferremia and severity of hypoxemic respiratory failure in COVID-19. Crit Care. 2020;24 (1):320.
- In this retrospective study, serum iron levels were significantly lower in patients with severe hypoxemia as compared to patients with non-severe hypoxemia.
- Deng F, Zhang L, Lyu L, et al. Increased levels of ferritin on admission predicts intensive care unit mortality in patients with COVID-19. Med Clin (Engl Ed). 2021;156(7):324–331.
- In this retrospective study, ferritin levels were positively associated with mortality in patients with COVID-19 admitted to Intensive Care Unit.
- Nai A, Lorè NI, Pagani A, et al. Hepcidin levels predict COVID-19 severity and mortality in a cohort of hospitalized Italian patients. Am J Hematol. 2021;96(1):E32–E35.
- 36. Bozkurt FT, Tercan M, Patmano G, et al. Can ferritin levels predict the severity of illness in patients with COVID-19? Cureus. 2021;13 (1):e12832.
- 37. Sonnweber T, Boehm A, Sahanic S, et al. Persisting alterations of iron homeostasis in COVID-19 are associated with non-resolving lung pathologies and poor patients' performance: a prospective observational cohort study. Respir Res. 2020;21(1):276.
- In this prospective multicentre study, alterations of iron homeostasis were shown to persist for at least two months after the onset of COVID-19 and to be closely associated with nonresolving lung pathologies and impaired physical performance.
- Arnold DT, Attwood M, Barratt S, et al. Predicting outcomes of COVID-19 from admission biomarkers: a prospective UK cohort study. Emerg Med J. 2021;21:emermed-2020-210380.
- Elhadi M, Alsoufi A, Abusalama A, et al. Epidemiology, outcomes, and utilization of intensive care unit resources for critically ill COVID-19 patients in libya: a prospective multi-center cohort study. PLoS One. 2021;16(4):e0251085.
- Al Sulaiman KA, Aljuhani O, Eljaaly K, et al. Clinical features and outcomes of critically ill patients with coronavirus disease 2019 (COVID-19): a multicenter cohort study. Int J Infect Dis. 2021;105:180–187.
- 41. Schillaci G, Mannarino MR, Pucci G, et al. Age-specific relationship of aortic pulse wave velocity with left ventricular geometry and function in hypertension. Hypertension. 2007;49(2):317–321.
- Schillaci G, Pirro M, Ronti T, et al. Prognostic impact of prolonged ventricular repolarization in hypertension. Arch Intern Med. 2006;166(8):909–913.

- Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA. 2016;315(8):801–810.
- Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373–383.
- 45. Bellmann-Weiler R, Lanser L, Barket R, et al. Prevalence and predictive value of anemia and dysregulated iron homeostasis in patients with COVID-19 infection. J Clin Med. 2020 Jul 29;9(8):2429.
- 46. Giamarellos-Bourboulis EJ, Netea MG, Rovina N, et al. Complex immune dysregulation in COVID-19 patients with severe respiratory failure. Cell Host Microbe. 2020;27(6):992–1000.e3.
- 47. COVID-19 treatment guidelines. National Institute of Health. Available from: https://www.covid19treatmentguidelines.nih.gov/ overview/clinical-spectrum/. Accessed on November 30 2021.
- Lee J, Park HK, Kwon MJ, et al. Decreased lung function is associated with elevated ferritin but not iron or transferrin saturation in 42,927 healthy Korean men: a cross-sectional study. PLoS One. 2020;15(4):e0231057.
- 49. Pagana KD, Pagana TJ, Pagana TN. Mosby's diagnostic and laboratory test reference. 14th ed. St Louis (MO): Elsevier; 2019.
- Banchini F, Cattaneo GM, Capelli P. Serum ferritin levels in inflammation: a retrospective comparative analysis between COVID-19 and emergency surgical non-COVID-19 patients. World J Emerg Surg. 2021;16(1):9.
- 51. Gharamti AA, Mei F, Jankousky KC, et al. Diagnostic utility of a ferritin-to-procalcitonin ratio to differentiate patients with COVID-19 from those with bacterial pneumonia: a multicenter study. medRxiv. 2020;2020.10.20.20216309.
- 52. Tapan OO, Gursoy C, Dogan E, et al. Evaluation of iron deficiency in COVID-19 pneumonia. Authorea. 2021.

- 53. Kernan KF, Carcillo JA. Hyperferritinemia and inflammation. Int Immunol. 2017;29(9):401–409.
- 54. Rivera S, Nemeth E, Gabayan V, et al. Synthetic hepcidin causes rapid dose-dependent hypoferremia and is concentrated in ferroportin-containing organs. Blood. 2005;106(6):2196–2199.
- 55. Habib HM, Ibrahim S, Zaim A, et al. The role of iron in the pathogenesis of COVID-19 and possible treatment with lactoferrin and other iron chelators. Biomed Pharmacother. 2021;136:111228.
- Ehsani S. COVID-19 and iron dysregulation: distant sequence similarity between hepcidin and the novel coronavirus spike glycoprotein. Biol Direct. 2020;15(1):19.
- 57. Liu W, Li H. COVID-19: attacks the 1-beta chain of hemoglobin and captures the porphyrin to inhibit human heme metabolism. ChemRxiv 2020.
- Shoenfeld Y. Corona (COVID-19) time musings: our involvement in COVID-19 pathogenesis, diagnosis, treatment and vaccine planning. Autoimmun Rev. 2020;19(6):102538.
- Edeas M, Saleh J, Peyssonnaux CI. Innocent bystander or vicious culprit in COVID-19 pathogenesis? Int J Infect Dis. 2020;97:303–305.
- Menshawey R, Menshawey E, Alserr AHK, et al. Low iron mitigates viral survival: insights from evolution, genetics, and pandemics a review of current hypothesis. Egypt J Med Hum Genet. 2020;21 (1):75.
- Rodrigues PCO, Ignotti E, Hacon SS. Association between weather seasonality and blood parameters in riverine populations of the Brazilian amazon. J Pediatr (Rio J). 2017;93(5):482–489.
- 62. Nicolau GY, Haus E, Lakatua DJ, et al. Chronobiology of serum iron concentration in subjects of different ages at different geographic locations. Endocrinologie. 1987;25(2):63–82.
- Nguyen LT, Buse JD, Baskin L, et al. Influence of diurnal variation and fasting on serum iron concentrations in a community-based population. Clin Biochem. 2017;50(18):1237–1242.