Received: 16 July 2021 | Accepted: 10 August 2021

DOI: 10.1002/iid3.517

ORIGINAL ARTICLE

Immunity, Inflammation and Disease Open Access WILEY

Ferritin level: A predictor of severity and mortality in hospitalized COVID-19 patients

Moudhi Alroomi[1] | Rajesh Rajan[2] | Abdulaziz A. Omar[3] | Ahmad Alsaber[4] | Jiazhu Pan[4] | Mina Fatemi[5] | Kobalava D. Zhanna[6] | Wael Aboelhassan[7] | Farah Almutairi[8] | Naser Alotaibi[9] | Mohammad A. Saleh[8] | Noor AlNasrallah[9] | Bader Al-Bader[8] | Haya Malhas[10] | Maryam Ramadhan[11] | Mohammed Abdullah[1] | Hassan Abdelnaby[12,13]

[1]Department of Infectious Diseases, Infectious Diseases Hospital, Shuwaikh Medical Area, Kuwait City, Kuwait

[2]Department of Cardiology, Sabah Al Ahmad Cardiac Centre, Al Amiri Hospital, Kuwait City, Sharq, Kuwait

[3]Department of Medicine, Jaber Al Ahmed Hospital, South Surra, Kuwait

[4]Department of Mathematics and Statistics, University of Strathclyde, Glasgow, United Kingdom

[5]Public Health and Commissioning Manager, Nottinghamshire County Council, Nottingham, United Kingdom

[6]Department of Internal Medicine with the Subspecialty of Cardiology and Functional Diagnostics Named after V.S. Moiseev, Peoples' Friendship University of Russia (RUDN University), Moscow, Russian Federation

[7]Division of Gastroenterology, Department of Medicine, Jaber Al Ahmed Hospital, South Surra, Kuwait

[8]Department of Medicine, Farwaniya Hospital, Farwaniya, Kuwait

[9]Department of Medicine, Al Adan Hospital, Hadiya, Kuwait

[10]Department of Emergency Medicine, Mubarak Al-Kabeer Hospital, Jabriya, Kuwait

[11]Department of Obstetrics and Gynaecology, Maternity Hospital, Shuwaikh Medical Area, Kuwait City, Kuwait

[12]Department of Endemic and Infectious Diseases, Faculty of Medicine, Suez Canal University, Ismailia, Egypt

[13]Division of Gastroenterology, Department of Medicine, Al Sabah Hospital, Shuwaikh Medical Area, Kuwait City, Kuwait

Correspondence
Rajesh Rajan, Department of Cardiology, Sabah Al Ahmed Cardiac Centre, Al Amiri Hospital, Kuwait City 15303, Kuwait.
Email: cardiology08@gmail.com

Abstract

Introduction: This study aims to investigate in-hospital mortality in severe acute respiratory syndrome coronavirus 2 patients stratified by serum ferritin levels.

Methods: Patients were stratified based on ferritin levels (ferritin levels ≤ 1000 or >1000).

Results: Approximately 89% (118) of the patients with ferritin levels > 1000 had pneumonia, and 51% (67) had hypertension. Fever (97, 73.5%) and shortness of breath (80, 61%) were two major symptoms among the patients in this group. Logistic regression analysis indicated that ferritin level (odds ratio

[OR] = 0.36, 95% confidence interval [CI] = 0.21–0.62; $p < .001$), male sex (OR = 2.63, 95% CI = 1.43–5.06; $p = .003$), hypertension (OR = 4.16, 95% CI = 2.42–7.36; $p < .001$) and pneumonia (OR = 8.48, 95% CI = 3.02–35.45; $p < .001$) had significance in predicting in-hospital mortality. Additionally, the Cox proportional hazards analysis and Kaplan–Meier survival probability plot showed a higher mortality rate among patients with ferritin levels > 1000.

Conclusion: In this study, higher levels of serum ferritin were found to be an independent predictor of in-hospital mortality.

KEYWORDS

COVID-19, ferritin, hypertension, in-hospital mortality, male sex, pneumonia, SARS-CoV-2

1 | INTRODUCTION

In severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) risk assessment, ferritin can be used as a biomarker to assess severity and mortality.[1,2] In SARS-CoV-2 infection, cytokine storms are interlinked with elevated levels of ferritin. High ferritin levels can cause pro-inflammatory changes and immunosuppression.[3] It was found that most diabetic SARS-CoV-2 patients who were critically ill had higher levels of ferritin.[4] Many studies have shown doubling of the ferritin level in elderly individuals, especially when they are older than 65 years compared to those aged younger than 50 years.[5] A multicentre study of SARS-CoV-2 infection reported a higher incidence of acute respiratory distress syndrome (ARDS), and increased morbidity was associated with higher hyperferritinemia.[6]

2 | METHODS

This study consisted of confirmed SARS-CoV-2-infected patients, both Kuwaitis and non-Kuwaitis, aged 18 and older. Patients were enrolled in this retrospective cohort study between February 26 and September 8, 2020. All data were obtained from electronic medical records from two tertiary care hospitals in Kuwait: Jaber Al-Ahmed Hospital and Al Adan General Hospital.[7,8]

SARS-CoV-2 infection was confirmed by a positive Reverse Transcription Polymerase Chain Reaction (RT-PCR) swab from the nasopharynx. Care of all patients was standardized according to a protocol established by the Ministry of Health in Kuwait. The standing committee for coordination of health and medical research at the Ministry of Health in Kuwait waived the requirement of informed consent and approved the study (Institutional Review Board number 2020/1422).

The primary outcome measured was SARS-CoV-2 related death as defined by ICD-10 code U07.1. The clinical and laboratory variables collected were as follows: sociodemographic determinants, co-morbidities, clinical presentation, laboratory results, and durations of intensive care unit (ICU) and in-hospital stay. An electronic case-record form (CRF) was used for data entry.

2.1 | Statistical analysis

Descriptive statistics were used to summarize the data in the form of frequency, percentage, mean ± standard deviation (*SD*), and median ± interquartile range (IQR). Differences in patients with respect to study variables in the ferritin group were examined using the Pearson $\chi 2$ test. Logistic regression analysis was employed to check the effects of some study variables on cumulative all-cause mortality. The Cox proportional hazards regression model and Kaplan–Meier survival were used to check how ferritin affected the mortality level. A 5% significance level was used to test the results. Statistical analyses were performed using SPSS version 27 (SPSS) and R software.[9]

3 | RESULTS

The basic characteristics of the patients affected by SARS-CoV-2 are shown in Table 1. A total of 595 patients were considered in the study, among whom 132 had an average age of 56.5 ± 14.8 years and ferritin levels > 1000, and 463 had an average age of 53.3 ± 15.4 years and ferritin levels ≤ 1000. Most of the male (255, 55.1%) and female (208, 44.9%) patients had ferritin levels ≤ 1000. Communities (236, 46.9%) and contacts (232, 46.1%) were two major sources of

TABLE 1 Baseline characteristics of COVID-19 patients stratified by ferritin level

	[ALL] *N = 595*	Ferritin > 1000 *N = 132*	Ferritin ≤ 1000 *N = 463*	*p*	*N*
Age, mean ± SD, years	54.0 (15.3)	56.5 (14.8)	53.3 (15.4)	.029	595
BMI, mean ± SD, kg/m²	29.5 (6.25)	29.3 (6.68)	29.6 (6.12)	.684	408
Sex				<.001	595
Female	233 (39.2%)	25 (18.9%)	208 (44.9%)		
Male	362 (60.8%)	107 (81.1%)	255 (55.1%)		
Smoking				.780	205
Current smoker	21 (10.2%)	6 (9.84%)	15 (10.4%)		
Ex-smoker	25 (12.2%)	6 (9.84%)	19 (13.2%)		
Never smoked	159 (77.6%)	49 (80.3%)	110 (76.4%)		
Source of transmission				.049	503
Community	236 (46.9%)	46 (44.7%)	190 (47.5%)		
Contact	232 (46.1%)	51 (49.5%)	181 (45.2%)		
Healthcare worker	9 (1.79%)	0 (0.00%)	9 (2.25%)		
Hospital acquired	10 (1.99%)	5 (4.85%)	5 (1.25%)		
Imported	16 (3.18%)	1 (0.97%)	15 (3.75%)		
Hypertension	247 (41.5%)	67 (50.8%)	180 (38.9%)	.019	595
DM	260 (43.7%)	49 (37.1%)	211 (45.6%)	.104	595
CVD	56 (9.41%)	17 (12.9%)	39 (8.42%)	.168	595
Chronic lung disease	68 (11.4%)	16 (12.1%)	52 (11.2%)	.898	595
Chronic kidney disease	35 (5.88%)	13 (9.85%)	22 (4.75%)	.047	595
Immunocompromised host	14 (2.35%)	5 (3.79%)	9 (1.94%)	.207	595
Pneumonia	413 (69.4%)	118 (89.4%)	295 (63.7%)	<.001	595
ARDS	126 (21.2%)	57 (43.2%)	69 (14.9%)	<.001	595
ICU admission	135 (22.7%)	67 (50.8%)	68 (14.7%)	<.001	595
ICU duration of stay (number of days) IQR	14.0 [2.00;64.8]	11.0 [2.00;59.0]	16.0 [1.70;74.8]	.058	137
Admission to discharge (number of days) IQR	15.0 [2.00;57.0]	18.0 [2.00;59.5]	14.0 [2.38;51.6]	<.001	587
Mortality	79 (13.3%)	39 (29.5%)	40 (8.64%)	<.001	595

Note: n (%) unless specified otherwise.

Abbreviations: ARDS, acute respiratory distress syndrome; BMI, body mass index; CVD, cardiovascular disease; DM, diabetes mellitus; ICU, intensive care unit; IQR, interquartile range; SD, standard deviation.

transmission of SARS-CoV-2 among patients. Most of the patients with ferritin levels ≤ 1000 had pneumonia (295, 63.7%), followed by hypertension (180, 38.9%), ARDS (69, 14.9%), and chronic kidney disease (22, 4.7%). Among the cohort with ferritin levels > 1000, approximately 67 (50.8%) patients had to be admitted to the ICU, and the median time of discharge of patients in this cohort was 18.0 [2.00; 59.5] days, whereas 68 (14.7%) patients in the cohort with ferritin levels ≤ 1000 had to be admitted to the ICU, and the median time of discharge of patients in this cohort was 14.0 [2.38; 51.6] days. Almost equal numbers of patients died in the cohorts with ferritin levels > 1000 (39, 29.5%) and ferritin levels ≤ 1000 (40, 8.6%).

Most of the patients in the cohort with ferritin levels ≤ 1000 had either asymptomatic infection (41,

8.8%) or had symptoms of fever (287, 62%), shortness of breath (SOB; 182, 39.3%), fatigue or myalgia (137, 29.6%), and headache (61, 13.2%), whereas most of the patients in the cohort with ferritin levels > 1000 had fever (97, 73.5%), followed by SOB (80, 60.6%), fatigue or myalgia (25, 18.9%), and headache (5, 3.7%; Table 2).

Table 3 compares the laboratory parameters among patients with ferritin levels > 1000 or ferritin levels ≤ 1000. Patients with ferritin levels > 1000 had significantly higher counts of white blood cells (9.30 [8.00;10.6], $p < .001$) and neutrophils (7.50 [6.50;8.85], $p < .001$) and higher levels of creatinine (92.0 [85.0;105], $p < .001$), LDH (437 [410;470], $p < .001$), CRP (125 [104;163], $p < .001$), PCT (0.50 [0.30;0.90], $p < .001$), D-dimer (750 [514;1027], $p < .001$), serum troponin HS (22.0 [15.0;39.0], $p < .001$), creatinine kinase (343 [32.0;3147], $p < .037$), ALT (46.5 [40.0;61.8], $p < .001$), AST (55.0 [49.0;61.0], $p < .001$), GGT (68.0 [50.0;90.0], $p < .001$), T. bilirubin (13.6 [12.2;15.6], $p < .001$) and D. bilirubin (4.20 [3.70;5.40], $p < .001$) as compared to the patients with ferritin levels ≤ 1000. Furthermore, patients with ferritin levels ≤ 1000 had significantly higher haemoglobin levels (121 [119;124], $p = .001$), lymphocyte counts (1.30 [1.17;1.40], $p < .001$), vitamin D levels (42.0 [37.0;48.0], $p = .007$) and albumin levels (35.0 [34.0;35.5], $p < .001$) than patients with ferritin levels > 1000.

More patients with ferritin levels ≤ 1000 received antibiotics (252, 54.4%), followed by therapeutic anticoagulation (177, 38.2%), methylprednisolone (88, 19%), Hydroxychloroquine (HCQ; 54, 11.7%), and KALETRA (lopinavir/ritonavir; 61, 13.2%), than patients with ferritin levels > 1000; conversely, more patients with ferritin levels > 1000 received Actemra (Tocilizumab; 10, 7.5%) and azithromycin (8, 6%). Furthermore, it is also noticeable that among the cohort with ferritin levels ≤ 1000, approximately 49% (204) of patients had no requirement for oxygen, 36% (153) had a low oxygen requirement and 15% (64) had a high oxygen requirement, whereas the cohort with ferritin levels > 1000, approximately 14% (18) of patients had no requirement for oxygen, 39% (50) had a low oxygen requirement and 47% (61) had a high oxygen requirement (Table 4).

Logistic regression analysis showed that ferritin level, sex, hypertension, and pneumonia were significant predictors of all-cause cumulative mortality. It is evident that patients with ferritin levels ≤ 1000 (odds ratio [OR] = 0.36, 95% confidence interval [CI] = 0.21–0.62; $p < .001$) were 0.36 times less likely to have all-cause cumulative mortality than patients with ferritin levels > 1000. Additionally, the mortality rate was higher among male patients (OR = 2.63, 95% CI = 1.43–5.06; $p = .003$) and those with hypertension (OR = 4.16, 95% CI = 2.42–7.36; $p < .001$) or pneumonia (OR = 8.48, 95% CI = 3.02–35.45; $p < .001$); Table 5).

A Cox proportional hazards analysis was conducted to determine whether ferritin had a significant effect on the hazard of mortality (Table 6). The findings (LL = 9.85, df = 1, $p = .002$) show that ferritin was able to adequately predict the hazard of mortality. It is evident that at any particular time, patients with ferritin levels ≤ 1000 had a hazard that was 0.49 times as large as that of patients with ferritin levels > 1000 ($B = -0.72$, $SE = 0.23$, $HR = 0.49$, $p = .001$).

TABLE 2 Signs and symptoms of COVID-19 patients stratified by ferritin level

	[ALL]	Ferritin > 1000	Ferritin ≤ 1000		
	N = 595	*N = 132*	*N = 463*	*p*	*N*
Asymptomatic	44 (7.39%)	3 (2.27%)	41 (8.86%)	.018	595
Headache	66 (11.1%)	5 (3.79%)	61 (13.2%)	.004	595
Sore throat	48 (8.07%)	8 (6.06%)	40 (8.64%)	.436	595
Fever	384 (64.5%)	97 (73.5%)	287 (62.0%)	.020	595
Dry cough	322 (54.1%)	67 (50.8%)	255 (55.1%)	.436	595
Productive cough	44 (7.39%)	11 (8.33%)	33 (7.13%)	.781	595
SOB	262 (44.0%)	80 (60.6%)	182 (39.3%)	<.001	595
Fatigue or myalgia	162 (27.2%)	25 (18.9%)	137 (29.6%)	.021	595
Diarrhoea	80 (13.4%)	18 (13.6%)	62 (13.4%)	1.000	595
Nausea	47 (7.90%)	9 (6.82%)	38 (8.21%)	.735	595
Vomiting	49 (8.24%)	8 (6.06%)	41 (8.86%)	.395	595
Change of taste or smell	19 (3.19%)	4 (3.03%)	15 (3.24%)	1.000	595

Note: n (%) unless specified otherwise.

Abbreviation: SOB, shortness of breath.

TABLE 3 Laboratory findings of COVID-19 patients grouped by ferritin level (ng/ml)

	[ALL] *N = 593*	Ferritin > 1000 *N = 132*	Ferritin ≤ 1000 *N = 463*	*p*	*N*
Haemoglobin (g/L)	119 [116;122]	106 [93.0;117]	121 [119;124]	.001	592
Platelets (10^9/L)	257 [242;271]	265 [229;292]	254 [237;271]	.319	592
WBC (10^9/L)	7.00 [6.80;7.40]	9.30 [8.00;10.6]	6.60 [6.20;6.90]	<.001	590
Neutrophils count	4.90 [4.50;5.21]	7.50 [6.50;8.85]	4.20 [4.00;4.70]	<.001	589
Lymphocytes count	1.20 [1.10;1.30]	1.00 [0.80;1.11]	1.30 [1.17;1.40]	<.001	589
Creatinine (μmol/L)	79.0 [76.0;82.0]	92.0 [85.0;105]	76.0 [72.0;79.0]	<.001	593
LDH (IU/L)	320 [304;339]	437 [410;470]	285 [272;306]	<.001	545
CRP (mg/L)	76.0 [69.7;81.0]	125 [104;163]	65.0 [53.0;74.0]	<.001	575
Procalcitonin (ng/ml)	0.16 [0.14;0.20]	0.50 [0.30;0.90]	0.11 [0.09;0.15]	<.001	354
D-Dimer (ng/ml)	388 [337;429]	750 [514;1027]	314 [271;362]	<.001	498
25 (OH) Vitamin D (nmol/L)	38.0 [35.0;45.0]	30.0 [25.0;41.0]	42.0 [37.0;48.0]	.007	130
Troponin I HS (ng/L)	10.0 [8.00;14.0]	22.0 [15.0;39.0]	8.00 [7.00;10.0]	<.001	284
Creatinine kinase (IU/L)	84.5 [56.0;208]	343 [32.0;3147]	59.5 [49.0;101]	.037	26
ALT (IU/L)	35.0 [32.0;37.0]	46.5 [40.0;61.8]	31.0 [29.0;34.0]	<.001	588
AST (IU/L)	39.0 [36.0;42.0]	55.0 [49.0;61.0]	34.0 [32.0;38.0]	<.001	587
ALP (IU/L)	73.0 [70.0;76.0]	77.5 [68.0;89.0]	73.0 [70.0;75.0]	.077	585
GGT (IU/L)	47.0 [42.0;55.0]	68.0 [50.0;90.0]	44.0 [39.0;51.0]	<.001	477
Albumin (g/L)	34.0 [33.2;34.9]	30.0 [28.6;31.7]	35.0 [34.0;35.5]	<.001	587
T. Bilirubin (μmol/L)	11.0 [10.6;11.8]	13.6 [12.2;15.6]	10.4 [9.70;11.0]	<.001	586
D. Bilirubin (μmol/L)	3.00 [2.70;3.10]	4.20 [3.70;5.40]	2.50 [2.30;2.70]	<.001	574

Note: Numerical variables – median ± interquartile range (IQR).

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; D. bilirubin, direct bilirubin; GGT, gamma-glutamyl transferase; HS, high-sensitivity; LDH, lactate dehydrogenase; T. bilirubin, total bilirubin; WBC, white blood cell.

A Kaplan–Meier survival probability plot was also included for ferritin. The plot represents the survival probabilities for different groups over time and shows that in the initial and later periods, the cumulative probability of dying was higher among patients with ferritin levels > 1000, but in the middle period, little difference was observed in the mortality rate of patients in the different ferritin groups (Figure 1).

4 | DISCUSSION

The main finding of our study is that the higher mortality rate among patients having ferritin levels > 1000. Other than ferritin levels gender, hypertension and pneumonia were found to be a predictor of in-hospital mortality. Around 89% of the patients having ferritin levels > 1000 had pneumonia and 51% had hypertension. The mean age of the patients was 54.0 ± 15.3 years and among which the ratio of male to female was 233:362. A male predominance was noted in the group with ferritin levels > 1000. Higher levels of C-Reactive Protein and Procalcitonin were seen in ferritin > 1000.

Serum ferritin was found to be an independent predictor of severe SARS-CoV-2 disease.[10] A study from Indonesia Rasyid et al. documented a mean ferritin level of 1689 in critically ill SARS-CoV-2-infected patients.[11] SARS-CoV-2 patients with cytokine storm were also found to have significantly higher levels of ferritin.[12] Several autopsies of SARS-CoV-2 patients revealed higher ferritin levels.[13] Elderly SARS-CoV-2 patients with elevated ferritin levels showed higher mortality than those with lower ferritin values.[11] In another study, the incidence of ARDS was higher in those with hyperferritinemia.[14]

TABLE 4 Medications taken by the COVID-19 patients stratified by ferritin level

	[ALL] *N = 595*	Ferritin > 1000 *N = 132*	Ferritin ≤ 1000 *N = 463*	*p*	*N*
Antibiotics	359 (60.3%)	107 (81.1%)	252 (54.4%)	<.001	595
Methylprednisolone	128 (21.5%)	40 (30.3%)	88 (19.0%)	.008	595
Dexamethasone	66 (11.1%)	17 (12.9%)	49 (10.6%)	.559	595
Vitamin C effervescent tablets	332 (55.8%)	75 (56.8%)	257 (55.5%)	.866	595
Therapeutic anticoagulation	270 (45.4%)	93 (70.5%)	177 (38.2%)	<.001	595
Azithromycin	12 (2.02%)	8 (6.06%)	4 (0.86%)	.001	595
Vitamin D	184 (30.9%)	43 (32.6%)	141 (30.5%)	.720	595
HCQ	84 (14.1%)	30 (22.7%)	54 (11.7%)	.002	595
KALETRA (lopinavir/ritonavir)	93 (15.6%)	32 (24.2%)	61 (13.2%)	.003	595
Actemra (Tocilizumab)	17 (2.86%)	10 (7.58%)	7 (1.51%)	.001	595
Hydrocortisone	18 (3.03%)	5 (3.79%)	13 (2.81%)	.567	595
a. Receiving ace inhibitors	66 (14.3%)	21 (19.4%)	45 (12.7%)	.109	463
b. Receiving ARBs	83 (18.0%)	16 (15.2%)	67 (18.8%)	.494	462
c. Receiving statin	170 (34.7%)	39 (34.5%)	131 (34.7%)	1.000	490
Oxygen requirements				<.001	550
High oxygen requirement	125 (22.7%)	61 (47.3%)	64 (15.2%)		
Low oxygen requirements	203 (36.9%)	50 (38.8%)	153 (36.3%)		
None	222 (40.4%)	18 (14.0%)	204 (48.5%)		

Note: n (%) unless specified otherwise.

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; HCQ, hydroxychloroquine.

TABLE 5 Multivariate logistic regression analysis of in-hospital death in the overall study cohort

In-hospital mortality		Alive	Dead	Univariate aOR (95% CI, aP-value)	Multivariate logistic regression aOR (95% CI, aP-value)
Ferritin level	≤1000	423 (91.4)	40 (8.6)	0.23 (0.14–0.37, $p < .001$)	0.36 (0.21–0.62, $p < .001$)
Sex	Male	299 (82.6)	63 (17.4)	2.86 (1.65–5.24, $p < .001$)	2.63 (1.43–5.06, $p = .003$)
Hypertension	Yes	191 (77.3)	56 (22.7)	4.14 (2.50–7.07, $p < .001$)	4.16 (2.42–7.36, $p < .001$)
Pneumonia	Yes	337 (81.6)	76 (18.4)	13.46 (4.93–55.44, $p < .001$)	8.48 (3.02–35.45, $p < .001$)

Note: Multivariable analyses were conducted using logistic regression models utilizing the simultaneous method. The models were adjusted for ferritin levels, gender, hypertension, and pneumonia. Percents are row percentages.

Abbreviations: aOR, adjusted odds ratio; a*P*-value, adjusted *p*-value; CI, confidence interval.

TABLE 6 Cox proportional hazards regression coefficients for ferritin

Variable	*B*	*SE*	95% CI	*z*	*p*	*HR*
Ferritin Less than or equal 1000	−0.72	0.23	[−1.17, −0.28]	−3.18	.001	0.49

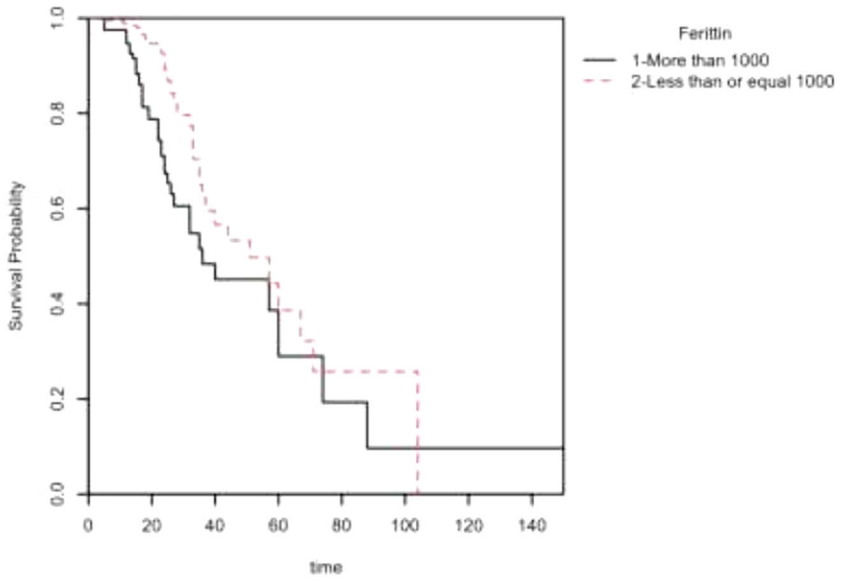

FIGURE 1 Kaplan–Meier survival plot of mortality grouped by fertility

Zhou et al. also reported increased mortality in SARS-CoV-2 patients with higher levels of serum ferritin.[15] Elevated ferritin levels can be used as a biomarker to stratify high-risk patients from low-risk patients, which may in turn help in the early identification and management of SARS-CoV-2 patients.[16] Hyperferritinemia was more common in critically ill and discharged SARS-CoV-2 patients than in stable hospitalized patients.[17]

Unlike our study, hypertensive SARS-CoV-2 patients had lower levels of serum ferritin, as reported by Huang et al.[18] Similar to our study, a study by Phipps et al.[19] showed that the severity of acute liver failure in SARS-CoV-2 patients was more common in patients with hyperferritinemia. The frequency of ICU admission was higher in SARS-CoV-2 patients with hyperferritinemia.[20] Similar findings were also reported in our study. In another study, SARS-CoV-2 patients with cancer had higher serum ferritin levels than those without cancer.[21] The clinical association of hyperferritinemia in SARS-CoV-2 in terms of mortality, comorbidities, and severity was well established in a meta-analysis.[22]

5 | LIMITATIONS

Our study has various limitations. Its retrospective design limits causal inference. Unmeasured confounding factors, such as clinical comorbidities and medications, could have affected the outcomes. This Kuwaiti study included all SARS-CoV-2-positive patients and undoubtedly consisted of mainly milder cases of the disease. However, if it included SARS-CoV-2 patients who typically consist of a significant case mix of mechanically ventilated and critical cases of patients, the findings might have looked different.

6 | CONCLUSIONS

This study demonstrated that hyperferritinemia is an independent predictor of in-hospital mortality in SARS-CoV-2 patients. The incidence of ICU admission was higher with hyperferritinemia. More prospective studies are required to better understand hyperferritinemia and in-hospital mortality in SARS-CoV-2.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Moudhi Alroomi designed the study. Moudhi Alroomi and Rajesh Rajan participated in analysis and manuscript preparation. Ahmad Alsaber, Jiazhu Pan, and Mina Fatemi performed the statistical analysis and reviewed the manuscript. All authors had access to the data and take responsibility for its integrity and the accuracy of the data analysis. All authors have read and approved the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the results of the study are available on request from the corresponding author.

ORCID

Moudhi Alroomi http://orcid.org/0000-0001-6907-011X
Rajesh Rajan http://orcid.org/0000-0002-0249-0440
Ahmad Alsaber https://orcid.org/0000-0001-9478-0404
Jiazhu Pan https://orcid.org/0000-0001-7346-2052
Mina Fatemi http://orcid.org/0000-0002-0208-2498
Kobalava D. Zhanna https://orcid.org/0000-0003-1126-4282

REFERENCES

1. Imran MM, Ahmed U, Usman U, Ali M, Shaukat A, Gul N. Neutrophil/lymphocyte ratio—a marker of COVID-19 pneumonia severity. *Int J Clin Pract*. 2020;75(4):1-15.
2. Li Z, Long F, Yang Y, Chen X, Xu L, Yang M. Serum ferritin as an independent risk factor for severity in COVID-19 patients. *J Infect*. 2020;81(4):647-679.
3. Abbaspour N, Hurrell R, Kelishadi R. Review on iron and its importance for human health. *Res J Med Sci*. 2014;19(2):164-174.
4. Wang Z, Du Z, Zhu F. Glycosylated hemoglobin is associated with systemic inflammation, hypercoagulability, and prognosis of COVID-19 patients. *Diabetes Res Clin Pract*. 2020;164:108214.
5. Ma A, Jia R, Ma X, Sun Y, Zhang H, Ma Y. Iron storage in women is positively correlated with aging and BMI values. *Energy Nutr Metab*. 2016;30(S1):377-382.
6. Wu J, Liu J, Zhao X, et al. Clinical characteristics of imported cases of coronavirus disease 2019 (COVID-19) in Jiangsu Province: a multicenter descriptive study. *Clin Infect Dis*. 2020;71(15):706-712.
7. Al-Jarallah M, Rajan R, Saber AAl, et al. In-hospital mortality in SARS-CoV-2 stratified by hemoglobin levels: a retrospective study. *eJHaem*. 2021:1-5.
8. Al-Jarallah M, Rajan R, Dashti R, et al. In-hospital mortality in SARS-CoV-2 stratified by serum 25-hydroxy-vitamin D levels: a retrospective study. *J Med Virol*. 2021:1-6. https://doi.org/10.1002/jmv.27133
9. Laine T, Reyes EM. Tutorial: survival estimation for Cox regression models with time-varying coefficients using SAS and R. *J Stat Softw*. 2014;61:1-23.
10. Rasyid H, Sangkereng A, Harjianti T, Soetjipto AS. Impact of age to ferritin and neutrophil-lymphocyte ratio as biomarkers for intensive care requirement and mortality risk in COVID-19 patients in Makassar, Indonesia. *Physiol Rep*. 2021;9:e14876.
11. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. HLH across speciality collaboration, UK. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet*. 2020;28395(10229):1033-1034.
12. Fox SE, Akmatbekov A, Harbert JL, et al. Pulmonary and cardiac pathology in Covid-19: the first autopsy series from New Orleans. *medRxiv*. 2020;20050575.
13. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med*. 2020;180(7):934-943.
14. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020 28;395(10229):1054-1062.
15. Sun L, Shen L, Fan J, et al. Clinical features of patients with coronavirus disease 2019 from a designated hospital in Beijing, China. *J Med Virol*. 2020;395(10223):497-506.
16. Cecconi M, Piovani D, Brunetta E, et al. Early predictors of clinical deterioration in a cohort of 239 patients hospitalized for Covid-19 infection in Lombardy, Italy. *J Clin Med*. 2020;9(8):2429.
17. Hou H, Zhang B, Huang H, et al. Using IL-2R/lymphocytes for predicting the clinical progression of patients with COVID-19. *Clin Exp Immunol*. 2020;201:76-84.
18. Huang S, Wang J, Liu F, et al. COVID-19 patients with hypertension have more severe disease: a multicenter retrospective observational study. *Hypertens Res*. 2020;43:824-831.
19. Phipps MM, Barraza LH, LaSota ED, et al. Acute liver injury in COVID-19: prevalence and association with clinical outcomes in a large U.S. cohort. *Hepatology*. 2020;72(3):807-817.
20. Ayanian S, Reyes J, Lynn L, Teufel K. The association between biomarkers and clinical outcomes in novel coronavirus pneumonia in a US cohort. *Biomark Med*. 2020;14(12):1091-1097.
21. Meng Y, Lu W, Guo E, et al. Cancer history is an independent risk factor for mortality in hospitalized COVID-19 patients: a propensity score-matched analysis. *J Hematol Oncol*. 2020;13:75.
22. Cheng L, Li H, Li L, et al. Ferritin in the coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis. *J Clin Lab Anal*. 2020;34:e23618.

How to cite this article: Alroomi M, Rajan R, Omar AA, et al. Ferritin level: A predictor of severity and mortality in hospitalized COVID-19 patients. *Immun Inflamm Dis*. 2021;9:1648-1655. https://doi.org/10.1002/iid3.517