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

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**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...
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
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,

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

| Source of transmission | [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 | | | | | |
| Female | 233 (39.2%) | 25 (18.9%) | 208 (44.9%) | | 595 |
| Male | 362 (60.8%) | 107 (81.1%) | 255 (55.1%) | | |
| Smoking | | | | | .780 |
| Current smoker | 21 (10.2%) | 6 (9.84%) | 15 (10.4%) | | 205 |
| 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 |
| Community | 236 (46.9%) | 46 (44.7%) | 190 (47.5%) | | 503 |
| Contact | 232 (46.1%) | 51 (49.5%) | 181 (45.2%) | | |
| Healthcare worker | 9 (1.79%) | 0 (0.00%) | 9 (2.25%) | | |
| Hospital acquired | 10 (1.9%) | 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 | 11.0 | 16.0 | .058 | 137 |
| Admission to discharge (number of days) IQR | 15.0 | 18.0 | 14.0 | <.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.
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;90.0], 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 [320;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 (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. Furthermore, patients with ferritin levels ≤ 1000 had significantly higher hemoglobin 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] N = 595                  | Ferritin > 1000 N = 132 | Ferritin ≤ 1000 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.
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 3 | Laboratory findings of COVID-19 patients grouped by ferritin level (ng/ml) |
|----------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|          | [ALL] Ferritin > 1000 | Ferritin ≤ 1000   |
|          | N = 593          | N = 132          | N = 463          |
| 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.
### TABLE 4 Medications taken by the COVID-19 patients stratified by ferritin level

|                | [ALL] N = 595 | Ferritin > 1000 N = 132 |
|----------------|---------------|--------------------------|
| **Antibiotics**| 359 (60.3%)   | 107 (81.1%)              |
| **Methylprednisolone** | 128 (21.5%) | 40 (30.3%)          |
| **Dexamethasone** | 66 (11.1%)  | 17 (12.9%)              |
| **Vitamin C effervescent tablets** | 332 (55.8%) | 75 (56.8%)           |
| **Therapeutic anticoagulation** | 270 (45.4%) | 93 (70.5%)           |
| **Azithromycin** | 12 (2.02%)   | 8 (6.06%)                |
| **Vitamin D** | 184 (30.9%)   | 43 (32.6%)               |
| **HCQ** | 84 (14.1%)   | 30 (22.7%)               |
| **KALETRA (lopinavir/ritonavir)** | 93 (15.6%) | 32 (24.2%)           |
| **Actemra (Tocilizumab)** | 17 (2.86%) | 10 (7.58%)            |
| **Hydrocortisone** | 18 (3.03%) | 5 (3.79%)              |
| a. Receiving ace inhibitors | 66 (14.3%) | 21 (19.4%)            |
| b. Receiving ARBs | 83 (18.0%) | 16 (15.2%)           |
| c. Receiving statin | 170 (34.7%) | 39 (34.5%)          |
| **Oxygen requirements** |           |                          |
| High oxygen requirement | 125 (22.7%) | 61 (47.3%)            |
| Low oxygen requirements | 203 (36.9%) | 50 (38.8%)           |
| None | 222 (40.4%) | 18 (14.0%)             |

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 (N=550) | Dead (N=240) | 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, aP < .001)       | 0.36 (0.21–0.62, aP < .001)                             |
| Sex Male              | 299 (82.6%)   | 63 (17.4%)  | 2.86 (1.65–5.24, aP < .001)       | 2.63 (1.43–5.06, aP = .003)                            |
| Hypertension Yes      | 191 (77.3%)   | 56 (22.7%)  | 4.14 (2.50–7.07, aP < .001)       | 4.16 (2.42–7.36, aP < .001)                            |
| Pneumonia Yes         | 337 (81.6%)   | 76 (18.4%)  | 13.46 (4.93–55.44, aP < .001)     | 8.48 (3.02–35.45, aP < .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; aP-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 |
Zhou et al. also reported increased mortality in SARS-CoV-2 patients with higher levels of serum ferritin. 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. Hyperferritinemia was more common in critically ill and discharged SARS-CoV-2 patients than in stable hospitalized patients.

Unlike our study, hypertensive SARS-CoV-2 patients had lower levels of serum ferritin, as reported by Huang et al. Similar to our study, a study by Phipps et al. 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. 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. The clinical association of hyperferritinemia in SARS-CoV-2 in terms of mortality, comorbidities, and severity was well established in a meta-analysis.

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.
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