Research Article

Revealing ferritin's significance: A prognostic marker in COVID-19 at a tertiary care hospital in Rawalpindi

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Abstract

Amid the global COVID-19 crisis with over 762 million cases by 2023, reaching 775 million by 2024, this study examines the critical role of ferritin in diagnosing and managing COVID-19, emphasizing its correlation with disease severity and patient outcomes, especially in Pakistan, where data is scarce. At Benazir Bhutto Hospital in Rawalpindi, this study analyzed medical records of 376 COVID-19 patients aged 25-87 between April 2020 to August 2021, categorizing them by severity. Biochemical parameters, as well as ferritin, AST, ALT, urea, creatinine, and LDH, be assessed using Beckman Coulter AU480, with group differences analyzed via nonparametric tests and SPSS 25. Among 376 patients, predominantly aged 45-65 with a male majority (56.6%), 88.2% had comorbidities and 34.8% deceased during hospitalization. Elevated levels of ferritin, AST, urea, creatinine, and LDH were strongly linked to mortality ($p < 0.001$). The patients in the 66-90 age group had significantly increased risk of death from COVID-19 than those aged 45-65, by an adjusted odds ratio (AOR = 4.973; 95% CI: 2.517, 9.826; $p = 0.0001$). Additionally, individuals in the upper ferritin tertile were more susceptible to death, with an AOR of 3.443(95% CI: 2.012, 5.892; $p = 0.0001$) in contrast to those in middle and lower ferritin tertiles. These findings underscore the predictive value of age and ferritin levels in COVID-19 mortality. Increased ferritin levels stand out as a vital indicator, along with age, for forecasting mortality in COVID-19 patients, highlighting the pressing need for prompt intervention and customized treatment approaches.

Keywords: Corona virus, Hyperferritinemia, Ferritin; mortality, infectious diseases, SARS-CoV-2, Comorbidities.

Article History: **Received:** 13 June 2024, **Revised:** 09 August 2024, **Accepted**: 16 August 2024, **Published:** 23 September 2024.

Introduction

The outbreak of the novel corona virus disease 2019 (COVID-19) in December 2019 in Wuhan (Hubei, China) has resulted in a significant worldwide spread [1]. Despite continued unpredictability in clinical progression and symptoms, patients affected by severe acute respiratory syndrome corona virus 2

(SARS-CoV-2) often exhibit severe pneumonia and targeted organ damage involving the liver, heart, and kidneys [2].

Human ferritin comprises a protein shell enclosing iron in its core [3]. This protein is composed of varying proportions of two subunits: ferritin light chain (FTL) and ferritin heavy chain (FTH) [4]. The body regulates this ratio, with FTH subunits increasing amid inflammatory reactions, particularly in the heart and kidneys, assisting in the transformation of ferrous iron to its ferric state. On the other hand, the FTL subunit, which is further prevalent in the liver and spleen, primarily facilitates iron storage [3, 5].

Various biochemical indicators are linked to forecasting the severity of corona virus disease. Ferritin, an acute phase reactant, is produced during inflammatory conditions such as infectious, malignant, hematologic, and rheumatologic diseases. Increased serum ferritin levels can be observed in individuals with elevated pathogen burdens, as ferritin restricts iron availability to pathogens [6]. Ferritin also plays a role in regulating cytokine synthesis and release, thereby contributing to the inflammatory cytokine storm, which is the primary factor driving severity and mortality. This storm involves the abrupt and excessive release of pro-inflammatory cytokines, including interleukins IL-6, IL-10, and tumor necrosis factor (TNF-α), by macrophages [7, 8]. Understanding this crucial event in the pathophysiological mechanism, analyzing plasma inflammatory markers and acute phase reactants like ferritin could aid in predicting disease progression [9].

Numerous regulatory and functional proteins in the severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) depend on iron [10]. Ferritin levels show a robust correlation with COVID-19 severity [11, 12] with hyperferritinemia independently linked to elevated mortality rates in COVID-19 infections [13, 14]. A study in China involving twenty COVID-19 cases revealed a significant association between elevated serum ferritin concentrations and severe disease, with a significant distinction between severe and mild cases [15]. Conversely, a separate study using records from multiple hospitals in New York City found serum ferritin to have limited predictive value for mortality [16].

Although hyperferritinemia is strongly linked to mortality, it remains uncertain whether it serves as a biomarker of disease progression or plays a crucial role in its pathogenesis [17]. Despite the accessibility and affordability of the ferritin tests, they are frequently overlooked as a tool for forecasting the prognosis of COVID-19 [12]. Given the sparse literature on ferritin's role and the inconsistent findings regarding its link to disease severity and mortality, we aimed to evaluate its link with disease severity among hospitalized COVID-19 patients. This study aimed to evaluate the practical value of ferritin as a serum indicator in COVID-19, assisting in patient triage upon admission. Additionally, it will address the gap in data regarding ferritin’s use among COVID-19 patients.

Methodology

Ethical statement

This cross-sectional study received approval from the Ethical Review Committee, Department of Pathology, Benazir Bhutto Hospital Rawalpindi, Pakistan.

Study subjects

This retrospective cohort study involved 376 COVID-19 patients of both genders aged 25 and above with ferritin levels recorded at first presentation to Outpatients Department, Benazir Bhutto

Hospital Rawalpindi after infection. All patients had a confirmed positive polymerase chain reaction (PCR) test for SARS-CoV-2 and were initially categorized as mild to moderate or severe. Patients with underlying medical conditions such as Cardiovascular disorders (CVD), Diabetes Mellitus (DM), Hypertension (HTN), Respiratory disorder (RD), and chronic kidney disease (CKD) were included**,** while children, pregnant women, and those unable to give consent were excluded.

Data collection

Data including demographic, clinical, and disease outcomes (recovered or expired), ferritin levels, and comorbidities like type 2 diabetes mellitus (DM), hypertension (HTN), and chronic kidney disease (CKD), were obtained from electronic medical records as well as from patient's files. Due to the constraints of retrospective data analysis, ferritin levels from within 48 hours of admission were utilized, with the closest measurement recorded if multiple were available.

Statistical analysis

The distribution of the data was assessed using the Shapiro-Wilk test. Data with non-normal distribution were presented as the median (minimum and maximum). Patients were categorized into three age groups: 25-45, 46-65, and 66–90 years. Patients were categorized into ferritin tertiles based on their ferritin levels; lower, middle, and upper tertile. Biochemical parameters ALT, AST, LDH, urea, and creatinine, were log-transformed to achieve the parametric distribution. The median ferritin levels between the groups were compared using the Mann-Whitney U test and Kruskal-Walli's test. Multivariate Cox regression analysis was performed to identify the risk factors affecting COVID-19 mortality, with age, gender, comorbidities, and biochemical parameters included as confounding variables. Odds ratios (OR, 95% CI) were calculated for each variable, with significance defined at $p < 0.05$. Receiver operating characteristic (ROC) curves defined ferritin level cut offs for recovered and dead. Data analysis was conducted with SPSS version 25.

Results

Comparative analysis of baseline laboratory findings among ferritin tertile-based COVID-19 groups

Among 376 patients, 213 patients (56.6%) were male and females (43.4%). The median (min-max) age of the participants was 58 (25-87) years. Overall, comorbidities were present in 88.2% of patients. Specifically, Diabetes Mellitus was present in 95 (25.3%) patients, hypertension in 80 (21.3%), coronary heart disease in 55 (14.6%), chronic kidney disease in 71 (18.9%), and respiratory disorder in 27 (7.2%). The median (min-max) ferritin level was 396 (15-1500) ng/mL.

Patients with markedly elevated median ferritin levels upon admission tended to be in the (66-90) followed by 46-65 years age groups (Table 1). Biochemical parameters, the median LDH U/L, ALT U/L, creatinine mg/dL, and urea mg/ml were notably elevated in the upper ferritin tertile group ($p < 0.001$ for all) except AST as depicted in Table 1.

Factors influencing disease outcome in COVID-19 patients

Patients in the age group 66-90 showed higher odds of dying of COVID-19 (AOR = 4.973; 95% CI: 2.517, 9.826; $p = 0.0001$) compared to those aged 45-65(AOR 1.24787; 95% CI: .624, 2.614; $p = 0.503$). Both groups were compared with the reference age group, which is 25-45 years. Additionally, patients in upper.

Table 1: Baseline characteristics of the study participants at presentation

Ferritin Tertile					
Variables	Lower tertile 102(15,193) ng/ml	Middle tertile 396(209, 692) ng/ml	Upper tertile 1000 (696, 1500) ng/ml	Total	p-value
Sex n (%)					
Female	62(49.2)	56(44.8)	45(36)	163(43.4)	0.525#
Male	64(50.8)	69(55.2)	80(64)	213(56.6)	
Age Groups years					
25-45	45 (51.1)	24(27.3)	19(21.6)	88(23.40)	0.001#
45-65	51 (277)	66 (35.9)	67 (36.4)	184(48.93)	
65-90	30(28.8)	35 (33.7)	39(37.5)	104(27.65)	
Comorbidities n (%)					
Diabetes Mellitus	29(23)	33(26.4)	33(26.4)	95(25.3)	0.0001 #
Hypertension	29(23)	39(31.2)	12(9.8)	80(21.3)	
Coronary heart disease	9(7.1)	17 (13.6)	29 (23.2)	55(14.6)	
Chronic kidney disease	3(2.4)	10 (8)	14(11.2	71(18.9)	
Respiratory disorder	22(17.5)	19 (15.2)	30(24)	27(7.2)	
No comorbidity	34(27)	7 (5.6)	7(5.6)	48 (12.8)	
Clinical findings, Median IQR					
Aspartate aminotransferase, U/L	52(35-91)	54(35-83)	52(37-82)	53(36-85)	0.919*
Alanine aminotransferase, U/L	34(20-50)	38(24-67)	44(26-72)	38(23-66)	0.011*
Lactate dehydrogenase, U/L	389(264-565)	496(335-702)	539(391-850)	460(331-704)	0.001*
Creatinine, mg/dL	0.85(0.70-1.10)	1.0(0.7-1.2)	1.0(0.8-1.4)	0.9(0.7_1.2)	0.039*
Urea mg/dl	42(25-75)	49 (35-76)	66(47-97)	53(34-83)	0.011*

* Kruskal Wallice test, # Chi-Square test

ferritin tertile are more likely to succumb to death (AOR = 3.443; 95% CI: 2.0121, 5.892; p = 0.0001) than patients in middle and lower ferritin tertile. No significant association was observed between gender and mortality. Furthermore, chemistry parameters such as AST, LDH, ALT, urea, and creatinine showed insignificant association in multivariate analysis. Adjusted odds ratios for each variable are given in Table 2.

Table 2: Multivariate cox regression analysis

Variables	B	SE	AOR	95.0% CI for Exp(B)		p-value
				Lower	Upper	
Age groups (years) #	-0.06	0.194	0.942	0.644	1.377	0.757
45-65	0.245	0.365	1.278	0.624	2.614	0.503
66-90	1.604	0.347	4.973	2.517	9.826	0
Ferritin tertiles, median (min, max) ng/ml*						
Middle 396(209,692)	0.407	0.296	1.503	0.842	2.683	0.168
Upper 879(696,1500)	1.236	0.274	3.443	2.012	5.892	0
Log Alanine transaminase U/L	0.031	0.287	1.031	0.587	1.811	0.915
Log Aspartate transaminase U/L	0.091	0.279	1.096	0.634	1.894	0.744
Log Lactate dehydrogenase U/L	-0.144	0.318	0.866	0.464	1.616	0.651
Log Creatinine mg/dl	0.189	0.424	1.207	0.525	2.774	0.657
Log Urea mg/dl	0.331	0.407	1.393	0.628	3.09	0.415

*Reference category; lower tertile range, # 25-45 years.

Assessment of mortality rates across age, gender, comorbidities, and ferritin level

The highest mortality rate was observed in the (66-90) years age group (p = 0.0001), where among 104,80 (76.92%) patients died of COVID-19. Similarly, in the upper ferritin tertile group, 75(60%) out of 125 patients were expired (p = 0.0001) as depicted in Figure 1. Regarding comorbidities, the highest proportion of patients with respiratory disorders expired 19(70%) out of 27. Additionally, half of the COVID-19 patients with CHD 28 out of 56 expired followed by CKD patients 35 out of 71 (49.29%).

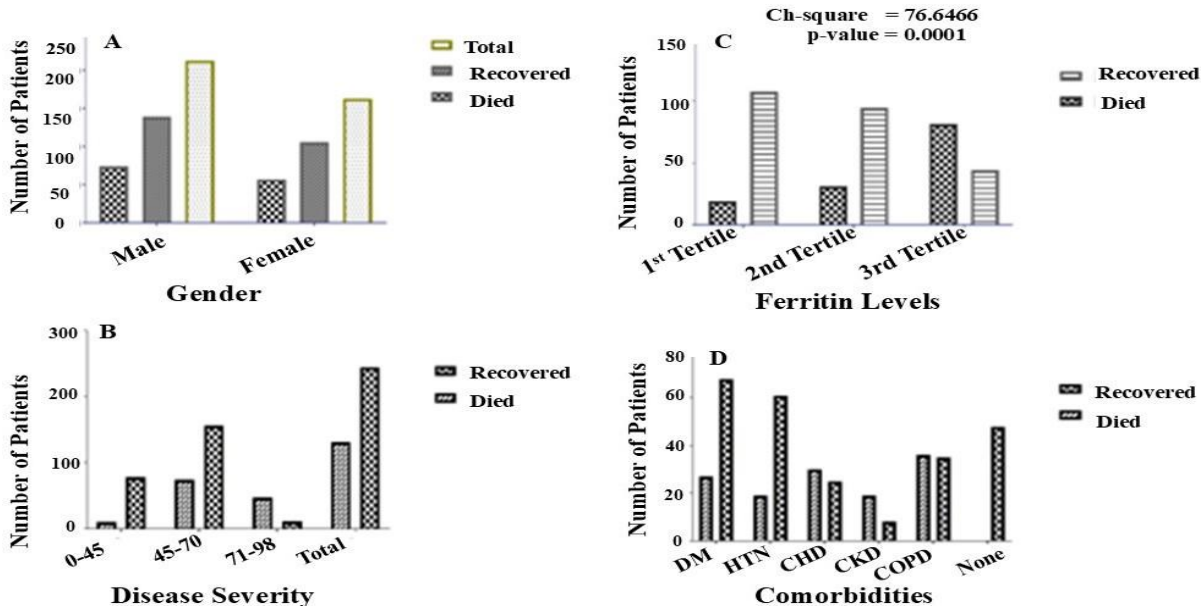

Figure 1: Mortality rates across various parameters

Almost one-quarter of patients with DM and HTN expired 24(25.24%) out of 95 and 19(23.75%) out of 80, respectively. A non-significant difference was observed in the mortality rates between males and females 56.5% vs 43.6% (p=0.525) as shown in Figure 1.

A. Bar charts illustrate mortality rates among different age groups, with 231 males and 163 females exhibiting significantly different mortality rates. The X-axis illustrates gender, and the Y-axis indicates the total number of patients. **B.** Mortality rates were significantly different across age groups 0-45, 46-70, and 71-90 between the recovered and deceased groups. The X-axis indicates age group severity, and the Y-axis illustrates the total number of patients. **C.** A comparison of mortality rates between the recovered and deceased groups across different ferritin tertiles revealed significant differences. The X-axis illustrates ferritin level tertiles, and the Y-axis indicates the total number of patients. **D.** Mortality rates varied across different ferritin tertiles among various comorbidities. A significant difference in mortality among ferritin tertiles with comorbidities was observed. The X-axis illustrates the comorbidities of the recovered and deceased groups, and the Y-axis indicates the total number of patients.

Ferritin levels as prognostic indicator among COVID-19 patients

Ferritin concentrations were significantly high in died patients compared to recovered as depicted in Figure 2. Ferritin concentrations in ferritin tertile are shown in Figure 2.

A. Ferritin levels were analyzed in COVID-19-infected individuals categorized as recovered and died. The X-axis represents the COVID-infectedgroups, while the Y-axis displays ferritin level values. Statistical significance was assessed using a student's t-test.

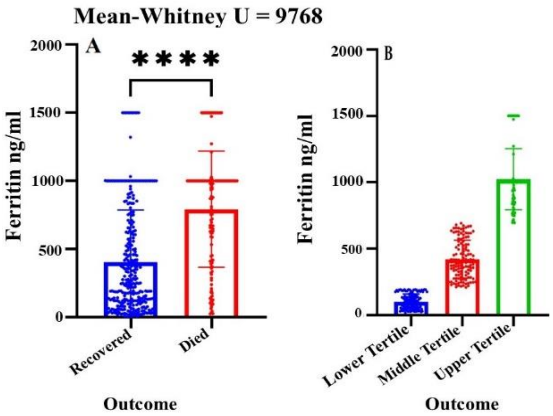

Figure 2: Ferritin levels analysis in COVID-19 infected individuals.

B. Analysis of recovered and died subjects across ferritin tertiles revealed a significant association between high ferritin levels and mortality (p = 0.0001***). The X-axis represents ferritin tertiles, while the Y-axis displays ferritin values. Statistical significance was evaluated using a student t-test.

Ferritin as a predictor of mortality in COVID-19 patients

Ferritin was identified as a significant predictor of mortality, with an Area under the curve (AUC) of 0.78 (95% CI: 0.729-0.832), as demonstrated in Figure 3.

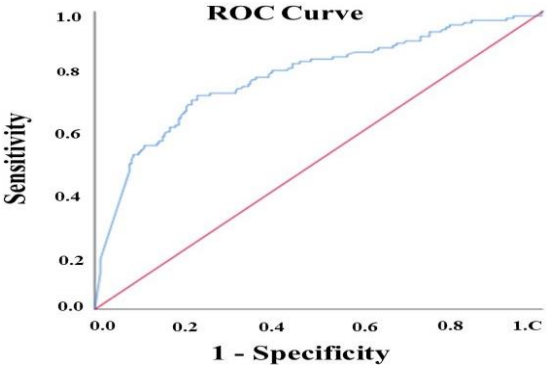

Figure 3: ROC analysis for ferritin's Predictive Ability for Mortality in COVID-19.

The optimal cut-off for predicting mortality was 506 ng/mL with a sensitivity of 72.5% and specificity of 72.7%. Receiver operating characteristic (ROC) curve analysis was conducted to evaluate ferritin's prognostic capability for mortality in COVID-19. Ferritin levels were examined in COVID-19-infected individuals classified as recovered and died.

Discussion

Rasyid et al. conducted study on 1689 SARS-CoV-2 patients, serum ferritin levels were identified as a sole predictor of COVID-19 severity [18, 19]. Those experiencing a cytokine storm demonstrated notably elevated ferritin levels [20]. Raised levels of serum ferritin were observed in the Autopsies of SARS-CoV-2 patients [21]. Additionally, Elevated ferritin correlated with higher mortality rates, especially among elderly patients [19]. Hyperferritinemia was linked with a higher incidence of ARDS and higher rate of mortality [22]. This biomarker can assist in categorizing high-risk patients for timely detection and intervention. [23]. Studies have shown that hyperferritinemia was more prevalent in critically ill than in stable hospitalized ones [24]. A recent systematic review of one sixty-three studies validated the association between elevated serum ferritin levels and disease severity [4]. Pasini *et al*., (2021) found elevated ferritin concentration among individuals through long-COVID syndrome [25]. Similarly, this study result confirms the association between raised ferritin concentration and mortality, in line with other findings [22, 26, 27].

Results from our study highlight that mortality rates were slightly higher in males than in females, particularly in the 46-90 age group ($p = 0.0001$). Elevated ferritin levels were in turn associated with a higher mortality rate.

In our single-center cohort study, a notable increase in the death rate among the COVID-19-infected upper ferritin tertile group compared to the middle and lower tertile was observed. In contrast, the survival rate was better among people having serum ferritin level in the lower and middle tertiles upon admission.

Inflammation markers, like ferritin, play crucial roles in the progression of the disease from viral invasion to inflammatory reactions [28, 29]. Ferritin cellular dynamics and its role as a pro- or anti-inflammatory marker during infection remain unclear [30]. Studies have shown that ferritin expression is regulated via raised serum iron, hypoxia, and inflammation. Amid inflammation, it can be released from macrophages or injured cells and controlled by different cytokines [30]. Cytosolic H-ferritin aids in the host's ability to endure infections, sepsis, and oxidative stress [31, 32], influencing outcomes in diseases such as malaria and sepsis [33]. Although higher ferritin levels are linked to poorer outcomes in COVID-19, there is limited data on non-linear relationships with outcomes or their interactions with immunomodulatory treatments.

We determined a ferritin threshold for predicting mortality at 506 ng/mL, with a sensitivity of 72.5% and specificity of 72.7% (AUC 0.78). Ferritin levels above 506 ng/mL indicate a higher risk of developing severe COVID-19 cases. Bozkurt *et al.*, (2021) documented a ferritin cut-off ≥264.5 ng/mL amid 73.9% sensitivity and 94.2% specificity [34], while Cao *et al*., recognized a cut-off at 272.5 ng/mL by 96% sensitivity and 70% specificity [35]. Hyperferritinemia is a risk factor for heightened COVID-19 severity, indicating the potential use of

iron chelators and adjustments in dietary iron intake for COVID-19 patients.

Reports on COVID-19 have identified elevated serum ferritin levels in severely infected patients, indicating it as a biomarker of disease severity among hospitalized individuals. Serum ferritin concentration could serve as a promising indicator of mortality in COVID-19 cases.

The limitation of the current study is its retrospective nature and the estimation of only baseline ferritin levels, without assessing subsequent or pre-COVID-19 ferritin levels. Furthermore, in this study, ferritin levels were accessible for 80% of potentially eligible patients during the cohort's inception period, which might have introduced bias. Despite a high event rate in this high-risk COVID-19 population, the relatively small sample size and number of events could have resulted in unstable estimates within subgroups, thereby limiting the generalizability of our findings to patients currently being admitted with COVID-19.

Conclusion

Early estimation of ferritin can indicate COVID-19 infection severity and other outcomes linked to it. Being readily available and relatively inexpensive, ferritin a commonly tested biomarker, can enhance treatment outcomes. Assessment of ferritin concentration on disease staging could help understand disease intensity and predict clinical outcomes. Therefore, serum ferritin levels can be regarded as a dependable and economical method for directing further treatment.

Acknowledgements

We are thankful to staff at Department of Pathology, Benazir Bhutto Hospital Rawalpindi for providing data.

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