

Hyperferritinemia as a Potential Predictor of – COVID - 19 Severity and Mortality among a Sample of Quarantine Hospital's Patients in Ajdabiya /Libya

<http://www.doi.org/10.62341/arsh1727>

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Abstract

The COVID-19 pandemic, caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has resulted in unprecedented global social and economic impacts. The disease is accompanied by a cytokine storm syndrome, which is an uncontrolled immune response characterized by the release of large quantities of inflammatory cytokines, including TNF- α , IL-6, IL-12, and IL-8, during the progression of the illness. This response leads to acute respiratory distress syndrome and systemic organ failure. Evidence suggests that serum levels of ferritin, D-dimer, and lactate dehydrogenase also increase during disease exacerbation, indicating a heightened risk of mortality. Serum ferritin serves as a marker of lymphocytic proliferation by phagocytosis, known as a complication of viral infections. Hyperferritinemia resulting from excessive inflammation due to viral infection is associated with an increased risk of admission to the intensive care unit and shows a close correlation with poor patient recovery and higher mortality rates.

This study aimed to examine the association between serum ferritin levels and the severity of viral infection and mortality rate. The results indicated that older patients (>65 years) had elevated

ferritin levels (876.857 ± 377.08) compared to younger patients (<65 years) (634.243 ± 282.140) ($p < 0.05$). Additionally, the results showed no significant difference between males and females in ferritin levels ($p > 0.05$). Furthermore, diabetic patients and those with hypertension exhibited higher ferritin levels (710.458 ± 283.62 and 637.810 ± 256.329 , respectively) compared to patients without comorbidities (502.82 ± 160.72) ($p > 0.05$).

KEYWORD: COVID-19, hyperferritinemia, potential predictor, mortality, severity.

فرط فيريتين الدم كمتنبئ محتمل لشدة الإصابة بفيروس كورونا COVID-19 وارتفاع معدل الوفيات لدى عينة من مرضى مستشفى الحجر الصحي في مدينة أجدابيا / ليبيا

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الملخص

تسبب وباء فيروس كورونا (COVID-19) الناجم عن متلازمة الالتهاب التنفسي الحاد الوخيم 2 (SARS-CoV-2) في حدوث تأثيرات اجتماعية واقتصادية عالمية غير مسبوقة. تُرافق الإصابة بالمرض متلازمة عاصفة السيتوكين، وهي استجابة مناعية غير منضبطة، حيث يتم إطلاق كميات هائلة من السيتوكينات الالتهابية، بما في ذلك TNF- α و IL-6 و IL-12 و IL-8، خلال تطور المرض. تؤدي هذه الاستجابة إلى حدوث متلازمة الضائقة التنفسية الحادة وفشل أجهزة الجسم. تشير الدلائل إلى أن مستويات الفيريتين في المصل و D-dimer ودهيدروجيناز اللاكتات تزداد أيضًا أثناء تفاقم

المرض، مما يشير إلى خطر الوفاة. يُعتبر الفيريتين في المصل علامة على كثرة الكريات للمفاوية بالبلعمة، والتي تُعرف بمضاعفات العدوى الفيروسية. يرتبط فرط الفيريتين الناجم عن الالتهاب المفرط بسبب العدوى الفيروسية بزيادة خطر الدخول إلى وحدة العناية المركزة، كما يُظهر ارتباطًا وثيقًا بضعف تعافي المرضى وارتفاع معدل الوفيات.

هدفت هذه الدراسة إلى اختبار ارتباط مستويات الفيريتين في المصل بشدة الإصابة بالفيروس ومعدل الوفيات. أظهرت النتائج أن المرضى الأكبر سنًا (< 65 عامًا) لديهم مستويات مرتفعة من الفيريتين (876.857 ± 377.08) مقارنة بالمرضى الأصغر سنًا (> 65 عامًا) (634.243 ± 282.140) ($p < 0.05$). بالإضافة إلى ذلك، لم تُظهر النتائج فرقًا معنويًا بين الذكور والإناث في مستويات الفيريتين ($p > 0.05$). كما أظهرت النتائج أن مرضى السكري والمصابين بارتفاع ضغط الدم لديهم مستويات مرتفعة من الفيريتين (710.458 ± 283.62 و 637.810 ± 256.329 على التوالي) مقارنة بالمرضى غير المصابين بأمراض مصاحبة (502.82 ± 160.72) ($p > 0.05$).

الكلمات المفتاحية: فيروس كورونا، فيريتين، متنبئ محتمل، الموت، شدة

INTRODUCTION

Ferritin is among the most commonly ordered laboratory tests in both primary and secondary healthcare, with its levels often falling outside the reference ranges. It acts as an indirect indicator of the body's total iron reserves, and low levels of ferritin are highly indicative of iron deficiency. However, hyperferritinemia is a non-specific finding that is frequently disregarded in general medical practice. In everyday clinical settings, only about 10% of cases are associated with iron overload, while the majority are attributed to acute phase reactions and reactive increases in ferritin resulting from underlying health conditions. It is crucial to differentiate whether an iron overload is present or absent in cases of hyperferritinemia, although this distinction can often be quite complicated (Sandnes et al., 2021)

The World Health Organization (WHO) China Country Office reported pneumonia cases of unknown origin in Wuhan, China, on December 31, 2019. The causative agent was identified as a novel Coronavirus (2019-nCoV) on January 7, 2020, which has not previously been found in humans. Later, it spread fast on an epidemic scale, causing over three million confirmed cases and two hundred thousand deaths as of May 5th, 2020, and the WHO proclaimed a "International Public Health Emergency." 2020 (Xia .Xu 2020).

The level of ferritin in the blood increases during viral infections and can be used as a measure of viral replication.(Li Y,*et al* 2019)(Baraboutis IG *et al* 2020)and hyperferritinemia, which is produced by excessive inflammation caused by infection, are related with intensive care unit admission and high mortality, and constitute an indicator to identify high-risk patientsv (Kernan.*etal*2017) (Carcillo*et al* 2017) Serum ferritin, a characteristic of hemophagocytic lymphohistiocytosis, a known consequence of viral infection, is linked to poor recovery in COVID-19 patients. According to several research, the H chain of ferritin triggers macrophages to release more inflammatorycytokines providing an indication of the risk of mortality(Zhou, *et al* 2020).

(Lu *et al*2020) discovered that COVID-19 patients with high ferritin levels have a higher proportion of severe and fatal cases (P =.0016).

(Sun *et al*2019) discovered that severe patients and discharged patients have higher proportions of elevated ferritin levels than non-severe patients and hospitalized patients (100% vs. 50%, 92.3% vs. 37.9%, P.001), implying that serum ferritin is a potential risk factor for poor prognosis in COVID-19 patients. Studies that examined the relationship between ferritin levels and baseline circumstances (comorbidity, gender) and found that patients with one or more comorbidities such as diabetes, thromboembolic events, and cancer had considerably higher ferritin levels than those who did not.(Yan *et al*-2020) discovered that severe diabetes individuals had greater ferritin levels than nonsevere diabetic

patients. we aim to investigate the clinical features of COVID-19 patients depended on the ferritin levels as one of the essentially inflammatory mediator leadto disease severity and mortality.

We need for further data about serum ferritin and disease severity ,so our study aim to investigate the clinical features of COVID-19 patients depended on the ferritin levels as one of the essentially inflammatory mediator lead to disease severity and mortality .These findings may help us extend our understanding of the risk factors associated with disease severity.

2. MATERIALS AND METHODS

2.1. Patients

The Almedani military Hospital is the major nationally designated hospital only providing medical care for adult patients with COVID-19 in Ajdabiya.The current retrospective cohort study has been conducted on a series of 107 COVID-19 patients who wereadmitted during the period from April 2020 to August 2020. Diagnosiswas based on a positive result for the COVID-19 nucleicacid via real-time reverse transcript-ion-polymerase chain reaction (rRT-PCR) in samples from blood or respiratorytract swabs which were performed at CentralLaboratories,informed writtenconsent from theirmedical reports was obtained.Detailed medical history for the included patients was recorded in the form of age, gender, and comorbidity (diabetes mellitus and and hypertension) and ferritin levels.

2.2. Study characteristic

The study classified patients into two groups of survival and non - survival and comparisons the ferritin levels for them depended on age, gender and comorbidity (diabetes and hypertension)

2.3. Statistical Analysis

IBM SPSS Statistics v.22 was used for the analysis of the data. Mean \pm SD was used for the expression of quantitativedata, while, number and percentage were used forqualitative .A P-value < 0.05 was considered statistically significant.

RESULTS

The study population included 107 confirmed and hospitalized COVID-19 patients who were categorized according to disease severity into 66 survivor patient and 41 non-survivor patients. Female accounted (58 (54.2 %) survivor 38 (57.6 %) and non-survivor 20(48.8 %)). Male accounted (49 (45.8 %) survivor 28 (42.4 %) and non-survivor 21 (51.2 %). Table 1.

Out of these, 107 patients 72(67.3%) of them were (< 65 years) 54 (81.8%) were survivor and 18 (43.9 %) non- survivor; and 35 (32.7 %) of them were (\geq 65 years) 12 (18.2 %) were survivor and 23 (56.1 %) were non-survivor; with significant differences ($p < 0.05$) between the two survivors and the two non- survivors groups for the two ages groups. Table 1. The total average age was (57.28 ± 15.84) and here was a significant older age among dead patients (67.90 ± 10.93) than recovery ones (50.69 ± 13.60) ($p < 0.05$). Table 1 Among these patients 29 (27.1 %) with non-comorbidity, 24 (22.4 %) were had diabetes mellitus only, 29 (27%) had hypertension only and 25 (23.4 %) had both diabetes mellitus and hypertension Table 1.

Table 1: Demographic and Clinical Data of the Included COVID-19 Patients.

	All patients	Survivor	Non-Survivor	p.value
(%) N	107 (100%)	66 (61.7%)	41 (38.3%)	0.00
(Age Mean \pm SD)	15.84 \pm 57.289	\pm 50.697 13.50	\pm 67.902 10.930	0.00
N 65 > (%)	72 (67.3%)	54 (%81.8)	18 (%43.9).	
N 6 \leq (%)	35 (%32.7)	12 (%18.2)	23 (%56.1)	
Sex Female N (%)	58 (%54.2)	38 (%57.6)	20 (%48.8)	0.375

Male N (%)	49 (%45.8)	28 (%42.4)	21 (% 51.2)
comorbidity	29 (%27.1)	28 (%42.4)	1 (%2.4)
Non- comorbidity Diabetes Melluites N (%)	24 (%22.4)	13 (%19.7)	11 (%26.8)
Hypertension N(%)	29 (%27.1)	24 (%36.4)	5 (%12.2)
Diabetes + Hypertension N(%)	25 (%23.4)	1 (%1.5)	24 (%58.5)

Notes: p-value < 0.05 is considered significant. p-value > 0.05 is considered nonsignificant

Table 2 shows the laboratory findings for Minimum and maximum ferritin levels in patients there were significantly higher mean values (713.62 ± 334.67) among COVID-19 patients and more significantly higher mean values for non-survivor patients (910.51 ± 387.81) than survivor patients (521.280 ± 224.556) ($p < 0.05$).

Table 2. Minimum and Maximum Ferritin Levels in COVID-19 Patients.

All Covid-19 patients SD)± (MeanFerritin levels			
Allpatients	Survivor	Non-survivor	P. value
(334.675 ± 713.602)	± 591.280 (224.556)	± 910.512 (387.81)	0.000

Table 3. Mean± SD of Ferritin Levels in Survivor and Non-Survivor COVID-19 Patients.

Ferritin (ng /dl)	Normal range	Minimum	Maximum	Mean ±) (SD
	250	adjustment 233.0	2116.0	± 713.602) (334.675

Notes: p-value < 0.05 is considered significant. p-value > 0.05 is considered nonsignificant

For aged groups

The older age patients > 65 years were recorded more highly significant ferritin level (876.857 ± 377.08) then young patients < 65 (634.243 ± 282.140) ($p < 0.05$) (Table 4). Additionally the non - survivor patients for each aged group were recorded more elevated significantly mean ferritin levels then survivor patients of the same group ($p < 0.05$) (Table 5).

Table 4. Mean±SD of Ferritin Levels in COVID-19 Patients for two aged groups > 65 and ≥ 65 Years.

Age Group	< 65 years	≥ 65 years	P. value
Age (Mean (SD ±	(9.82 ± 48.7361)	(5.85 ± 74.88)	0.009
Ferritin level (Mean ± SD)	(634.243 ± 282.140)	(876.857 ± 377.089)	

Notes: p-value < 0.05 is considered significant. p-value > 0.05 is considered nonsignificant.

Table 5. Mean±SD of Ferritin Levels in Survivor and Non-Survivor COVID-19 Patients for two aged groups < 65 and ≥ 65 Years

Ferritin levels (Mean ± SD)				
Age groups				
Survivor	Non-survivor	Survivor	Non-survivor	P. value
(570.62 ± 207.83)	(825.11 ± 382.0)	(684.25 ± 279.86)	(977.34 ± 587.04)	0.002 0.009

Notes: p-value < 0.05 is considered significant. p-value > 0.05 is considered nonsignificant

Ferritin levels for both gender and groups

There were non-significant difference between male and female for ferritin levels and a non-significant difference between them for both survivor and non-survivor groups ($p > 0.05$) (Table 6).

Table 6. Mean \pm SD of Ferritin Levels in Survivor and Non-Survivor Male and Female COVID-19 Patients

Ferritin levels (Mean \pm SD)		P. value	
	Female	Male	
All patients	(52.4%) 58	(45.8) 49	
survivor	(248.4 \pm 592.89)	(191.74 \pm 589.089)	0.673
Non-survivor	(249.97 \pm 828.00)	(477.75 \pm 989.09)	0.215

Notes: p-value < 0.05 is considered significant. p-value > 0.05 is considered nonsignificant.

For comorbidity

Among the co-morbidities associated with COVID-19 in our study, diabetes mellitus and hypertension. The patients with diabetes and those with hypertension were showed significantly elevated mean levels for ferritin (710.458 ± 283.62) (637.810 ± 256.329) respectively then patients with non-comorbidity (502.82 ± 160.72) ($p > 0.05$) (Table 7-8).

For patients were had both diabetes and hypertension the ferritin mean level were recorded more highly significantly values (1007.208 ± 406.65)

Then patients with non-comorbidity (502.82 ± 160.72) ($p > 0.05$) (Table 9).

Table 7. Mean±SD of Ferritin Levels in Non-comorbidity and Diabetes COVID-19 Patients.

All Covid-19 patients			
	Non-comorbidity	Diabetes	P. value
Age (Mean ± SD)	(8.5 ± 41.89)	(12.5 ± 64.0)	0.00
Ferritinlevels((Mean ± SD	± 827 .502) (160.726	(283.0 ± 710.4)	0.008

Notes: p-value < 0.05 is considered significant. p-value > 0.05 is considered nonsignificant

Table 8. Mean±SD of Ferritin Levels in Non-comorbidity and Hypertension COVID-19 Patients.

All Covid-19 patients			P. value
	Non-comorbidity	Hypertension	
Age (Mean ± SD)	(8.5 ± 41.89)	(12.33 ± 57.7)	0.00
Ferritinlevels (Mean ± SD)	± 827 .502) (160.726	(256.32 ± 637.810)	0.005

Notes: p-value < 0.05 is considered significant. p-value > 0.05 is considered nonsignificant

Table 9. Mean±SD of Ferritin Levels in Non-comorbidity COVID-19 Patients and in patients effected with both Diabetes and hypertension

All Covid-19 patients			P. value
	Non-comorbidity	DiabetesandHypertension	
Age (Mean ± SD)	(8.5 ± 41.89)	(11.7 ± 68.16)	0.00
Ferritinlevels (Mean ± SD)	± 827 .502) (160.726	(406.0 ± 1007.20)	0.00

DISCUSSION

Our study was a descriptive research of 107 COVID-19 hospitalized patient in Ajdabyia Libya. The study was designed to demonstrate the clinical features of COVID-19 depended on the ferritin levels as one of the essentially inflammatory cytokines lead to disease severity and mortality. The current study evidenced significant deferens in average age among survivor vs. non-survivor patients and that non-survivor COVID-19 was more frequent in older age, while survivor was more frequent in younger patients. Theses In agreement with the findings of, (Liu *et al*, 2020) 10 were reported that elderly patients with COVID-19 are more likely to progress to severe COVID-19 disease in comparison with young and middle aged COVID-19 patients. Also, (Mahase *et al*, 2020) and (Yang *et al*, 2020) reported similar finding this could be explained by the age-dependent decline in cell-mediated immune function and reduced humoral immune function. (Kuo *et al*, 2020) reported that biological aging was an optimal predictor of disease severity after performing biological age evaluations comprised of chronological age and nine Pheno Age (Guner *et al*, 2020). The one and only independent risk factor for SARI/critical illness is still age. Patients over 65 had an 8-fold greater risk of developing SARI or a critical illness, according to research. Patients receiving critical care had a median age that was higher than patients who weren't admitted to the ICU (66 vs. 51 years) (Gao *et al*, 2020).

We have observed that higher mean values of ferritin level in COVID-19 patients than the normal range; and observed more higher significantly mean values of ferritin among the non-survivor then survivor patients. In accordance with this (Cheng *et al*, 2020) were suggested that the non-survivors with COVID-19 had a significantly higher level of ferritin compared with the COVID-19 survivors in addition (Qin *et al*, 2020) reported that COVID-19 patients with high levels of ferritin have greater proportions of severe and deceased cases, (Sun *et al*, 2020) revealed that severe patients and discharged patients have greater proportions of increased level of ferritin than non-severe.

Xiaoming (Li 2020) It has been reported that fatal COVID-19 outcomes are accompanied by cytokine storm syndrome, and that disease severity is dependent on it; many inflammatory cytokines including TNF-, IL-6, IL-12, and IL-8 are released in massive amounts during disease progression, causing potential acute respiratory distress. Evidence suggests that serum ferritin, d-dimer, lactate dehydrogenase, and IL-6 levels rise as the disease progresses, indicating a higher chance of death. Ferritin after full stop must be space levels with COVID-19 2020 (Linlin Cheng 2021) Ferritin is an iron-storing protein whose serum level reflects normal iron levels and aids in the diagnosis of anemia caused by iron deficiency. **Ferritin is a result of excessive inflammation.**

Our study showed no significant but also plays a pathogenic role in the inflammation process through its bind with the T-cell immunoglobulin and mucin domain 2 (TIM-2) by promoting the expression of multiple pro-inflammatory mediators (Cheng *et al*, 2020)

The increase in the serum ferritin levels following viral infection could be attributed to iron release into the reticuloendothelial system, and increased intracellular ferritin synthesis and release, with the decreased ability of ferritin transport into spleen and liver (Senjo *et al*, 2018).

(Zhou *et al*, 2020) revealed that the increase in ferritin level is associated with the worsening of the COVID-19. Our finding revealed higher significantly differences in ferritin levels among old patients (≥ 65 years) then those with young age (<65 years) furthermore, the old patients of both survivor and non-survivor were recorded more significant ferritin levels compared with same groups of young patients this evidence un agreement with meta-analysis study were revealed no significant effect of age, of the investigation on the pooled results; In line with our findings, (Xia Xu *et al*, 2020) the analysis showed the age was positively correlated with some indexes, such ferritin, which may further elucidate that the severe inflammatory response more possibly take place among the old population.

Current study showed no significant difference between male and female patients in terms of number or ferritin levels which indicate no differences in disease severity between them which was inconsistent with the results of a study performed by (Zhang *et al*, 2020) were showed that males were more likely to be infected than females. (Guang Chen *et al*, 2020) were showed that a male predominance in the incidence of COVID-19 and indicating males are more susceptible to SARSCoV- 2 infection than females. (Gao *et al*, 2020) were showed higher disease severity was found to be associated with male gender and in un agreement with (Qin *et al*, 2020) were showed significantly different for ferritin level in male COVID-19 patients versus the female.

Among the co-morbidities associated with COVID-19 in our study the ferritin levels were recorded highly significant values in diabetes and hypertension patients the present study revealed that the occurrence of diabetes mellitus could be a important predictor for the severity of COVID-19. In line with our findings, (Marhlet *a,l*2020) reported a higher risk for COVID-19 among diabetic patients because of the associated dysregulation of angiotensin-converting enzyme 2 (ACE2), liver dysfunction, and chronic inflammation. Also, (Singh *et al*, 2020) provided evidence of increased incidence and severity of COVID-19 in diabetic patients.

(Wang *et al*, 2020) revealed a positive correlation between levels of ferritin and glycosylated hemoglobin (HbA1c) while other studies observed that patients with diabetes had higher ferritin levels than those without (Guo *et al*, 2020; Yan *et al*, 2020; Zhang *et al*, 2019). In addition, Wang *et al* revealed a positive correlation between levels of ferritin a revealed that hyperglycemia was related with increased mortality in patients with COVID-19. The prevalence of hyperglycemia may be associated localization of ACE 2 expression in the pancreas in patients with SARS was reported to damage islets, resulting in hyperglycemia¹⁹; this finding proposed that hyperglycemia may also be a sign of severe COVID-19. (Xiaochen *et al*, 2020)

Inconsistent, with (Huang *et al*, 2020) COVID-19 patients with hypertension had slightly lower levels of ferritin than those patients that were without and in agreement with our finding (Xiaochen *et al*, 2020) where found.

CONCLUSION

The current study examined the clinical features of COVID-19 in a cohort of hospitalized patients, focusing on ferritin levels as a potential indicator of disease severity. Our findings revealed no significant differences in ferritin levels between male and female patients, suggesting that gender does not influence disease severity in this cohort. This contrasts with previous studies that indicated a male predominance in COVID-19 infections and severity. Furthermore, we observed significantly higher ferritin levels in patients with comorbidities such as diabetes and hypertension. Diabetes mellitus emerged as a significant predictor of COVID-19 severity, highlighting the increased risk associated with diabetes due to dysregulation of the angiotensin-converting enzyme 2 (ACE2) and chronic inflammation. A positive correlation was noted between ferritin levels and glycosylated hemoglobin (HbA1c), indicating that hyperglycemia may also be linked to higher mortality in COVID-19 patients. Interestingly, while some studies reported lower ferritin levels in hypertensive patients, our findings aligned with observations of elevated ferritin levels in this group. Overall, the results underscore the complex interplay between ferritin levels, comorbidities, and disease outcomes in COVID-19. The study suggests that ferritin levels can serve not only as a valuable biomarker for predicting disease severity in patients with COVID-19 but also as an indicator for mortality risk. This highlights the need for further investigation into these relationships.

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