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Research Article

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Assessment of Ferritin Level In Covid-19 Patients: Does It Predict Severity?

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Abstract: Corona-virus disease-2019 (COVID-19) increased burdens on health systems. A hyper inflammatory response including high ferritin has been a hallmark of COVID-19 infection and is thought to be a key mediator of morbidity and mortality. We aimed to measure ferritin level and investigate its correlation with disease severity and outcome of Sudanese COVID-19 patients. A prospective study enrolled 100 COVID-19 patients in Khartoum state during the period from July to October 2020. We collected participants' data regarding demographics, clinical presentations, comorbidities, disease severity, and clinical courses during hospitalization, and outcomes. Serum ferritin level was measured for all patients and ferritin level more than 250 µg/L was considered elevated. Among 100 patients, 68(68%) were males, the most common age group was 51-70 years 58(58%). The major comorbidities were Hypertension 48 (48%) and DM 47 (47%). Just under half of the patients presented with mild pneumonia (n=45; 45%) and about one-third (n=37; 37%) received mechanical ventilation. Hyperferritinemia (ferritin>250 µg/L) was observed in 74(74%) patients. Additionally, 40(40%) had ferritin levels above 1000 µg/L. High ferritin levels were significantly common among patients with shortness of breath (P. value= 0.002), hypertension (P. value= 0.01), diabetes (P. value= 0.025), chronic renal diseases (P. value= 0.007), cardiovascular disease (P. value= 0.036), smoking (P. value= 0.03), need for mechanical ventilation (P. value= 0.000), and longer hospital stay duration above 7 days (P. value= 0.000). On the other hand, high ferritin level was correlated with severe pneumonia (P. value= 0.000), ARDS (P. value= 0.000) and sepsis (P. value= 0.009). As well, high ferritin level was associated with high mortality (P. value= 0.000). we concluded that the ferritin level was very high among COVID-19 patients and associated with increased severity of the disease and poor outcome.

Keywords: Acute Respiratory Distress Syndrome, COVID-19; Diabetes Mellitus; Ferritin Level; Isolation Centers; Severity.

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1. INTRODUCTION

Coronavirus Disease 2019 (COVID-19) caused severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), it caused a global outbreak transmitted by a human-to-human contact at December 2019 [1]. World Health Organization (WHO) had considered COVID-19 as pandemic on March 11, 2020, More severe course of the disease, poorer outcome, and worse prognosis was associated with comorbidities such as diabetes mellitus, heart diseases, lung diseases, and malignancy than previously healthy individuals [1]. The aim of the study is to assess the correlation between Ferritin as an inflammatory marker and severity of COVID-19; our objective is to measure ferritin level and investigate its correlation with disease severity. There are more than 234 million confirmed cases of coronavirus disease (COVID-19)worldwide, resulting in around a 4.8million deaths as of October 2021. This disease has had a catastrophic impact on both health and the economy. Disease presentation widely varies from asymptomatic infection to severe disease leading to death with variable incubation period and viral clearance duration [4]. The first COVID-19 case in Sudan was documented in March 2020; also, there are more than 38,345 confirmed cases of coronavirus disease (COVID-19) and over 2,906 deaths as of October 2021. The cytokine storm is a dysregulated immune response thought to have a significant role in the immunopathogenesis of COVID-19 similar to severe influenza; Cytokines including TNF-α, IL-6, IL-12, and IL-8 are massively expressed during the progression of COVID-19 and may potentially cause acute respiratory distress syndrome (ARDS) and systemic organ failure [6,7,8]. Serum ferritin, d-dimer, lactate dehydrogenase, and IL-6 were linked to worsening disease and a clue of higher risk of mortality [8]. Ferritin is an intracellular iron storage protein, which is well known as a part of acute phase reactants, which is elevated in inflammatory conditions, including acute infections [9]. Ferritin had both immune-suppressive and pre-inflammatory effects, contributing to the cytokine storm state. Cytokine storm syndrome had accompanied fatal outcomes by COVID-19, so the Severity of COVID-19 was suggested to depend on the cytokine storm syndrome. Diabetic patients usually have elevated serum ferritin levels, which could explain their higher probability of experiencing severe complications from COVID-19 [10]. Hyperferritinemia was associated with higher intensive care unit admissions mortalities and represented a precious indicator to recognize high-risk patients to guide the management. Thus, as a pro-inflammatory factor in the uncontrolled cytokine storm, the predictive role of the ferritin level in the risk of poor outcome in COVID-19 patients requires further verification [1]. This study is the first in Sudan and among a few similar studies in Africa and developing counties. The study aimed to evaluate the association of serum ferritin level with severity and outcome of COVOD-19 in a cross-sectional perspective multicentre's hospital-based study of hospitalized cases with COVID-19 in Isolation Centers (Khartoum isolation center and Albaraha medical city isolation center) in Khartoum State, Sudan.

2. MATERIAL AND METHODS

This is a cross-sectional multicentric hospital-based study conducted in isolation centers (Khartoum isolation center and Albaraha medical city isolation center) in Khartoum State, Sudan during the period from July to October 2020. We targeted all admitted COVID-19 adult patients. We included all hospitalized adult COVID-19 patients who accepted to participate in the study during the study period. We excluded any patients less than 16 years old, or patients who refused to participate in the study. We used the total coverage sampling technique to include all admitted COVID-19 patients during the study period. We reached the sample size of 100 hospitalized for Covid-19 patients in isolation centers during study period, who accepted in the study from patients with Covid-19 admitted to isolation centers.

Patients Data Collection Tools

Data collection was carried out by the principal investigator. Data was collected through structured questionnaires composed of demographics, clinical presentations, comorbidities, disease severity, clinical courses during hospitalization, and outcomes. Severity stratification and management were conducted according to guidelines of case management of COVID-19formulated by the general directorate of health emergencies and epidemic control, Federal Ministry of Health in Sudan. Serum ferritin level was measured for all patients and high ferritin level was defined if above 250 µg/L.

3. STATISTICAL ANALYSIS

Data were analyzed by using a computer program Statistical Package for Social Sciences (SPSS V. 21.0). The analyzed data is presented in tables and figures designed by Microsoft Excel 2010. The Chi-square test was used as a significance test and P. values were considered as significant at a level of ≤ 0.05.

3.1 Ethical Consideration

This study was conducted in inconsistency with Helinsky's declaration of the international conference on harmonization, regulations, and laws of Sudan, Ethical approval was obtained from the Ministry of Health in Khartoum State (SMOH3510). Written and verbal consent were obtained from all patients. Data is used anonymously by using identity numbers instead of names is order to protect the patient's identity and kept securely and in a separate file. No reference to any individual participant made in study reports. Only the study staff knew the subject identities.

4. RESULTS

In this study, we gathered data from 100 COVID-19 patients. Males constituted 68(68%) and the most commonage group was 51-70 years 58(58%). Most of the patients 83(83%) had a cough, 80(80%) shortness of breath, 80(80%) fever and 14(14%) patients had other symptoms. Hypertension (48; 48%) and DM (47; 47%) were the major comorbidities, less than half of patients 45(45%) had mild pneumonia, 27(27%) had severe pneumonia,29(29%) had ARDS, 14(14%) had sepsis and 2(2%) patients had septic shock. In the clinical course during hospital admission, 37(37%) patients received mechanical ventilation and 17(17%) patients received non-invasive ventilation (table 1). Hyperferritinemia (ferritin>250 µg/L) was observed in 74(74%) patients (Table 2). High ferritin level was significantly common among patients with shortness of breath (87.8% vs 57.7%; P. value= 0.002).The association between comorbidities and ferritin levels showed that patients with hyperferritinemia were more tended to have hypertension (; P. value= 0.01), diabetes (P. value= 0.025), chronic renal diseases (P. value= 0.007), cardiovascular disease (P. value= 0.036), and smoking (P.

value= 0.03) Considering disease severity and ferritin levels, hyperferritinemia was significantly correlated with severe pneumonia (P. value= 0.000), ARDS (P. value= 0.000) and sepsis (P. value= 0.009), most of the patients with severe pneumonia (84.6%) had ferritin levels from 501-1000 µg/L, ARDS (82.4%) from 1001-2000 µg/L, and sepsis (30.4%) above 2000 µg/L. High ferritin levels were significantly associated with the need for mechanical ventilation (P. value= 0.000). Patients with high ferritin levels were more tended to have longer hospital stay duration above 7 days compared to those with normal ferritin levels (P. value= 0.000), high ferritin levels were predominant in non-survived patients compared to normally discharged patients (P. value= 0.000) (table 3).

Table 1Sociodemographic factors and clinical picture of study participants

Factor	N	%
Gender		
Male	68	68
Female	32	32
Age groups (years)		
31-50	10	10
51-70	58	58
>70	32	32
Presenting complain		
Cough	83	83
Dyspnea	80	80
Fever	80	80
Others	14	14
Comorbidities		
HTN	48	48
DM	47	47
CVD	16	16
CKD	15	15
Asthma	7	7
COPD	1	1
Others	11	11
Severity		
Mild	45	45
Severe	27	27
Sepsis	14	14
Septic Shock	2	2
ARDS	29	29
Assisted Ventilation		
None	46	46
NIV	17	17
MV	37	37
Length of Hospitalization		
≤ 7 days	74	74
>7 days	26	26

	Outcome	
Discharge	59	59
Death	41	41

ARDS: Acute Respiratory Distress Syndrome, CKD: Chronic Kidney Disease, COPD: Chronic Pulmonary Obstructive Disease, CVD: Cardiovascular Disease, DM: Diabetes Mellitus, HTN: Hypertension, MV: Mechanical Ventilation, NIV: Non-Invasive Ventilation.

Table1 shows that more than two-thirds of patients were male, 90% percent were above the age of 50, almost half of them either present with diabetes, hypertension of both of them. and 80% percent were presented with the triple signs of cough, fever, and dyspnea, more than 25% were either severely ill or presented with acute respiratory syndrome. Almost have of patients either received none invasive ventilation or mechanical ventilation. The death occurred in 41% of patients.

Table 2 Demonstrate Ferritin Level Among Study Populations		
Ferritin (µg/L)	**N**	**%**
< 250	26	26
250-500	21	21
201-1000	13	13
1001-2000	17	17
>2000	23	23

Table 2 shows that only one-quarter of patients were having normal ferritin levels less than 250 µg/L and almost one-quarter of patients were having a severely high level of ferritin more than 2000 µg/L.

Table 3 Association Between Ferritin Level And Sociodemographic Factors And Clinical Picture Of Study Participants			
Factor	**Ferritin level N (%)**		**P. value**
	High (≥250 ug/L)	**Low (<250 ug/L)**	
Gender			
Male	48(70.6)	20(29.4)	0.188
Female	26(81.3)	6(18.8)	
Age groups (years)			
31-50	6(60)	4(40)	0.251
51-70	43(74.1)	15(25.9)	
>70	25(78.1)	7(29.1)	
Presenting complain			
Cough	60(81.1)	23(88.5)	0.297
Dyspnea	65(87.8)	15(57.7)	0.002
Fever	59(79.7)	21(80.8)	0.578
Others	8 (10.8)	6 (23.1)	0.113
Comorbidities			
HTN	41(55.4)	7(26.9)	0.010
DM	39(52.7)	8(30.8)	0.025
CVD	15(20.3)	1(3.8)	0.036
CKD	15 (20.3)	0(0.0)	0.007
Asthma	3(4.1)	4(15.4)	0.073
COPD	1(1.4)	0(0.0)	0.740
Others	9(12.2)	2(7.7)	0.514
Smoking	11(14.9)	0(0.0)	0.030
Severity			
Mild	19(25.7)	26(100)	0.000
Severe	27(36.5)	0(0.0)	0.000
Sepsis	14(18.9)	0(0.0)	0.009
Septic Shock	2(2.7)	0(0.0)	0.546
ARDS	29 (39.2)	0(0.0)	0.000
Assisted Ventilation			
None	20(27.1)	26(100)	0.000
NIV	17 (22.9)	0(0.0)	0.152
MV	37 (50.0)	0(0.0)	0.000
Length of Hospitalization			
≤ 7 days	46(66.2)	25(33.8)	0.000
>7 days	25(96.2)	1(3.8)	
Outcome			
Discharge	35(59.3)	24(40.7)	0.000
Deth	39(95.1)	2(4.9)	

ARDS: Acute Respiratory Distress Syndrome, CKD: Chronic Kidney Disease, COPD: Chronic Pulmonary Obstructive Disease, CVD: Cardiovascular Disease, DM: Diabetes Mellitus, HTN: Hypertension, MV: Mechanical Ventilation, NIV: Non-Invasive Ventilation.Table3 shows that Ferritin level was found to be significantly related to a great deal of the patient characteristics, that it was found to have significant statistical relations with, HTN (p-value 0.010), DM (p-value 0.025), CVD (p-value 0.036), CKD(p-value 0.007), Smoking (p-value 0.030). also, it was found to be highly related Severity to the severity of the disease Mild (p-value 0.000), Severe (p-value 0.000) or presented with ARDS (p-value 0.000) the ferritin level showed positive statistical significance among those who undergo mechanical ventilation or not (p-value 0.000). also, it was found to be highly significant with a good prognosis among hospitalization of 7 days or less (p-value 0.000) and among patients who were able to make it and recover (p-value 0.000)

5. DISCUSSION

To the best of our knowledge, this was the first study conducted in Sudan to evaluate the ferritin level and to investigate its correlation with disease severity and outcomes. In this study, males were predominantly affected by COVID-19 more than females with males to female ratio (2.1:1), consistent with several previous studies about the incidence of SARS-CoV-2 infection [11,12,13]. On another side, many studies conducted by Li et al. published in the New England Journal of Medicine (NEJM) [14] and Jian-Min J et al [15] observed similar susceptibility to SARS-CoV-2 between males and females. There is no clear explanation as to why men and women would be at different risks of infection; however, some have proposed genetic mechanisms or sex-specific effects [16]. Whether there are differences in the risk of infection between men and women requires further research. More than half of our patients aged from 51-70 years. These results were comparable to Marta C et al in Italy (median=67.5 years) [17] and Jian-Min J et al in China (median=62 years) [15]. However, lower age groups were reported by Chinese studies of Huang C et al (Median= 47 years) [12], Li et al. (Median= 49 years; 15-89 years) [14], and Chung M et al (Median= 51 years) [18]. The most common symptoms were cough, fever, and dyspnea. These symptoms could be explained by the fact that in normal lung tissue, ACE2 (receptor of SARS-CoV-2) is mainly expressed by type I and type II alveolar epithelial cells. It was reported that 83% of II-type alveolar cells expressed ACE2. Therefore, SARS-CoV-2 infection causes damages to most II-type alveolar cells [19]. Correspondingly, a meta-analysis of Leiwen F et al that included 43 studies involving 3600 patients reported Among COVID-19 patients, fever (83.3%), cough, and fatigue were the most common clinical symptoms [20]. In another meta-analysis conducted by Pengfei S et al (included a total number of 50466 patients with SARS-CoV-2 infection) showed that fever, cough, and muscle soreness or fatigue were the major symptoms [21]. Remarkably, Hypertension and DM were the major comorbidities among the participants. This could be due to the effect of DM as it decreases immunity [22]. The preponderance of hypertension among our study patients as the major comorbid endorsed to ACEI and ARBs which is generally used in hypertension management, as in one experimental study with animal models, both angiotensins converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) have been shown to up-regulate ACE2 (receptor of SARS-CoV-2) expression in the lung and heart [23]. Our findings were consistent with a systemic review conducted by Azin T et al who analyzed 8 articles that included 417 patients in which hypertension, diabetes, cardiovascular disease, and pulmonary disease were the most common co-morbidities among COVID-19 patients [24]. Also, Subodh S et al reported among 1786 COVID-19 patients, hypertension (15.8%) is the most common comorbidity [25]. Noticeably, this study demonstrated that hyperferritinemia (ferritin>250 µg/L) was observed in 74(74%) of patients. Hyperferritinemia caused by excessive inflammation due to the infection is a feature of hemophagocyticlympho-histiocytosis (HLH) and is associated with cytokine storms. The possible mechanisms include increased ferritin synthesis by proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin 6 (IL-6), and IL-lβ. This leads to increased inflammation that causes cell damage and the release of ferritin [26,27]. This was similar to the studies of Jonathan F et al who reported the rate of 72.5% [9] and Chen et al who analyzed the clinical characteristics of 99 patients, and found 63 (63.6%) of them had serum ferritin way above the normal range [of 11], although our rate was higher than the study of Hemanth R et al who studied 50 COVID-19 patients and found 58% of patients had ferritin levels above the normal range [28]. Additionally, (40%) of our patients had ferritin levels above 1000 µg/L. This result is comparable to Jonathan F et al who reported 53.4% of CIVID-19 patients had ferritin levels above 1000 µg/L (9). Our study showed that high ferritin levels were significantly common among patients with shortness of breath (87.8%). This study demonstrated that hypertension, diabetes, chronic renal diseases, cardiovascular disease, and smoking were significant independent risk factors of high ferritin levels among our study groups. These observations were strongly in agreement with the systemic review of Linlin C et al who analyzed a total of 52 records involving 10 614 COVID-19 patients and found that patients with one or more comorbidities including diabetes, thromboembolic events, and cancer had significantly higher levels of ferritin than those without [1]. Also, the mini-review of Manuel V et al reported DM was significantly associated with elevated serum ferritin levels [10]. In the same line, Huang et al reported COVID-19 patients with hypertension had higher levels of ferritin than those patients that were without [29]. In this study, we found that there was a strong association between disease severity and ferritin levels in which, hyperferritinemia was significantly correlated with severe pneumonia, ARDS, and sepsis, while normal ferritin levels were common among patients with mild pneumonia. Moreover, ferritin levels from 501-1000 µg/L associated with severe pneumonia, from 1001-2000 µg/L with ARDS, and ferritin levels >2000 µg/L associated with sepsis. These findings explained by high ferritin levels are associated with massive cytokine storm syndrome in COVID-19 infection along with other pro-inflammatory markers, including CRP and IL-6. In the systemic review of Linlin C et al, the ferritin level was significantly higher in more severely ill patients than that in less severe patients [1]. Also, Qin et al reported that COVID-19 patients with high levels of ferritin have greater proportions of severe cases [30]. Similarly, Sun et al revealed that high disease severity has greater proportions of an increased level of ferritin than low disease severity and suggested that serum ferritin is a potential risk factor of poor prognosis in COVID-19 patients [31]. In the study by Hou et al, ferritin was selected as a predictive marker of severe COVID-19 [32]. The current study considerably showed that a high ferritin level was associated

with the need for mechanical ventilation. Our findings were following Herold et al who noticed ferritin level was found related to ICU transfer and treatment with mechanical ventilation [33]. One of the most interesting findings of the present study was that patients handling ferritin levels were more tended to have longer hospital stay duration above 7 days compared to those with normal ferritin levels. In this study high ferritin levels were predominant in non-survived patients compared to normally discharged patients; this may reflect that high ferritin levels increase the mortality among the participants. Noticeably we found that as the ferritin level increased the mortality increased. These observations were strongly in agreement with the systemic review of Linlin C et al who stated the non-survivors with COVID-19 had a significantly higher level of ferritin compared with the COVID-19 survivors [1]. Zhou et al reported on 191 COVID-19 patients the level of serum ferritin was elevated in non-survivors compared with survivorpatients[8]. Cecconi et al also revealed that ferritin can aid the early identification and management of patients at risk of death in hospitalized COVID-19 patients 34. Ayanian et al also indicated that high levels of ferritin (≥450 ng/mL) were associated with death 35.

6. LIMITATIONS

One of the limitations of this is that the sample size was small in comparison to the prevalence of the disease. The study may also not be truly representative of all patients of COVID-19 because it is hospital-based and the involvement of patients was not from all COVID-19 centers in Sudan. Despite these limitations, this study is novel and reflects the value of ferritin level in stratification of severity and predicting prognosis of COVID-19. To the best of our knowledge, this is the first study in Sudan to assess ferritin levels among COVID-19 patients.

7. CONCLUSION

This study concluded that Sudanese COVID-19 patients commonly presented with high ferritin levels above the normal range. High ferritin level was significantly associated with shortness of breath at presentation, hypertension, diabetes, chronic renal diseases, cardiovascular disease, smoking as comorbidities, and the need for mechanical ventilation and longer hospital stay. Moreover, High ferritin levels were significantly correlated with COVID-19 severity and mortality.

8. AUTHORS' CONTRIBUTIONS STATEMENT

All authors contributed to equally the study conception and design. All authors read and approved the final manuscript.

9. DECLARATIONS

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article.

10. CONFLICT OF INTEREST

Conflict of interest declared of none.

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