



(RESEARCH ARTICLE)



The prognosis role of ferritin in COVID-19: Experience of the Mohammed VI university hospital Oujda (Morocco)

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GSC Biological and Pharmaceutical Sciences, 2024, 28(03), 133–139

Publication history: Received on 28 July 2024; revised on 09 September 2024; accepted on 12 September 2024

Article DOI: <https://doi.org/10.30574/gscbps.2024.28.3.0322>

Abstract

Background: COVID-19 is an infectious disease caused by the virus SARS COV 2 that has rapidly spread worldwide since December 2019, resulting in millions of severe cases and deaths. Elevated serum ferritin levels have been noted in patients with COVID 19. The objective of our study is to verify the prognostic role of serum ferritin in predicting the severity of COVID 19.

Methods: This is a retrospective study of 319 patients with COVID-19 hospitalized at the CHU MOHAMMED VI OUIJDA during the period from August 1, 2021 to November 10, 2021. Our patients are divided into 2 groups: patients hospitalized in the intensive care unit and patients hospitalized in the other COVID units.

Results: 207 of our patients (64.9%) were hospitalized in the intensive care unit, compared with 35.1% hospitalized in other COVID units. Patients hospitalized in the ICU had higher serum ferritin levels with a mean of 3257.08 ng/ml compared to a mean maximum ferritin of 1311 ng/ml in other COVID units. The mean ferritin in the deceased patients was much higher 2135.33ng/ml than for the surviving patients 1361.17 ng/ml with a $p=0.009$. Follow-up of ferritin level during hospitalization also showed that the serum ferritin level before the pre-terminal event (death or survival) was much higher in the deceased patients with a level of 2557.80 ng/ml versus a level of 1194.90 for the survivors ($p<0,001$).

Conclusion: Our results confirmed that higher serum ferritin level is associated with more severe COVID 19 disease, and that ferritin can predict worsening and poor prognosis in COVID 19 patients.

Keywords: Ferritin; COVID19; Prognosis; Severity; Evolution

1. Introduction

Coronavirus 2019 (COVID-19) is a global pandemic caused by the SARS COV 2 virus that initially emerged in early December 2019 in the city of Wuhan, China. Because of its rapid spread worldwide and fatal cases, the World Health Organization (WHO) has deemed it a public health emergency of international concern [1].

Although most cases have a good clinical course and do not require hospitalization, others develop severe pneumonia with significant symptoms and a high mortality rate requiring ICU admission [2].

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The severity of COVID-19 lies primarily in the development of large amounts of pro-inflammatory cytokines that can eventually contribute to acute respiratory distress syndrome (ARDS) and multivisceral failure (MOF) [3].

Therefore, it becomes imperative that predictive biomarkers of severity be identified in order to treat critically ill patients quickly.

Ferritin is an eggshell-like protein capable of storing iron within it (up to 4500 iron atoms per ferritin molecule), making it the iron storage protein, particularly in hepatocytes and the macrophage (hepatosplenic) system [4]. However, in recent years, the literature has identified ferritin as a protein of the acute phase of inflammation, its production increasing in a situation of macrophagic activation; it regulates in particular the synthesis and release of cytokines that are responsible for the cytokine storm [5].

Thus, recent studies suggest that elevated ferritin levels may be associated with a poorer prognosis in patients with COVID 19. [6].

The aim of our study was to evaluate the prognostic value of ferritin in patients with COVID-19 hospitalized in the CHU MOHAMMED VI OUJDA - Hospital of reference of the Eastern region of Morocco- and to identify the roles of this biomarker in predicting the severity and clinical outcome of the disease, in order to stratify the risk of patients and to improve the overall clinical management of patients with COVID-19.

2. Materials and methods

2.1. Study population

Our study focused on 319 patients with COVID-19 hospitalized at the CHU MOHAMMED VI OUJDA during the period from August 1st, 2021 to November 10, 2021.

The diagnosis of COVID-19 was confirmed by real-time PCR detection of SARS COV 2 RNA from nasopharyngeal or oropharyngeal swab samples. All RT PCR testing of our patients was performed in our laboratory according to the manufacturer's protocol and following WHO guidelines in the diagnosis of COVID 19.

We included in our work all patients with a positive RT-PCR test for SARS COV 2 who were hospitalized in our hospital during the study period and who had at least one serum ferritin test. Patients who did not have a serum ferritin test were excluded from the study.

Our patients are divided into 2 groups; the first group corresponds to patients requiring hospitalization in the intensive care unit, while the second group includes patients hospitalized in the other COVID departments.

Patients were followed throughout the hospitalization period to determine the course of the disease leading either to death of the patients due to COVID-19-related complications or to survival and discharge from the hospital after stabilization of the clinical condition.

2.2. Data collection and sample processing

Venous blood samples were taken at different times during the hospitalization of each of our patients for biochemistry laboratory investigations.

Samples taken from red (dry tube) or green (heparinized tube) tubes were centrifuged for 10 minutes at 4000 rpm to obtain the serum or plasma to be measured.

For the determination of serum ferritin, the ferritin determination of our samples was performed on the ARCHITECT ci8200. The ARCHITECT Ferritin assay is a chemiluminescent microparticle immunoassay (CMIA) for the quantitative determination of ferritin in human serum and plasma. The performance of this method of dosage is verified by the scope A according to the standard ISO 15189 that ensures the reliability of the results obtained. This method verification is part of the quality process in which the Biochemistry laboratory of the CHU Mohammed VI of Oujda is committed.

2.3. Statistical analysis

Statistical analysis was conducted to assess ferritin levels and compare them between the 2 groups (ICU, other COVID departments), and to determine the prognostic significance of ferritin on the final outcome (survival or death) using IBM Statistical Package for the Social Sciences (SPSS), version 24. A p value less than 0.05 was considered statistically significant.

3. Results

The current study included blood samples from 319 patients infected with SARS COV 2. Patients ranged in age from one to 101 years, with a mean age of 65 years. Among the 319 patients included in our study, 152 were female and 167 were male.

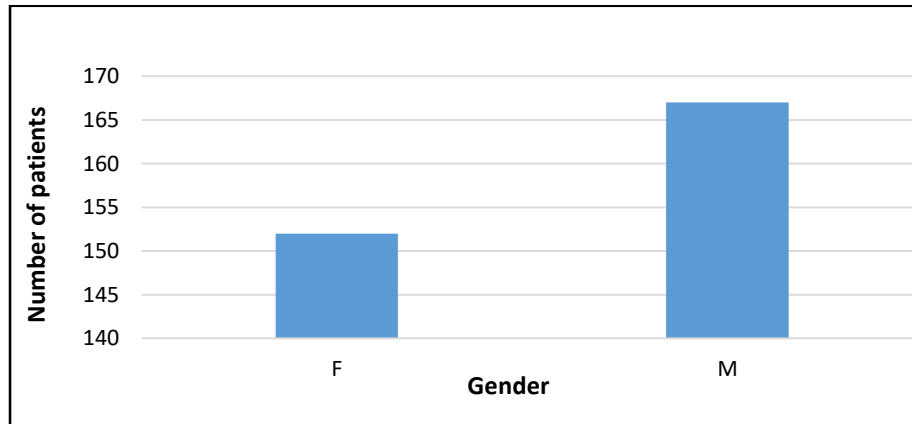


Figure 1 Distribution of patients by gender

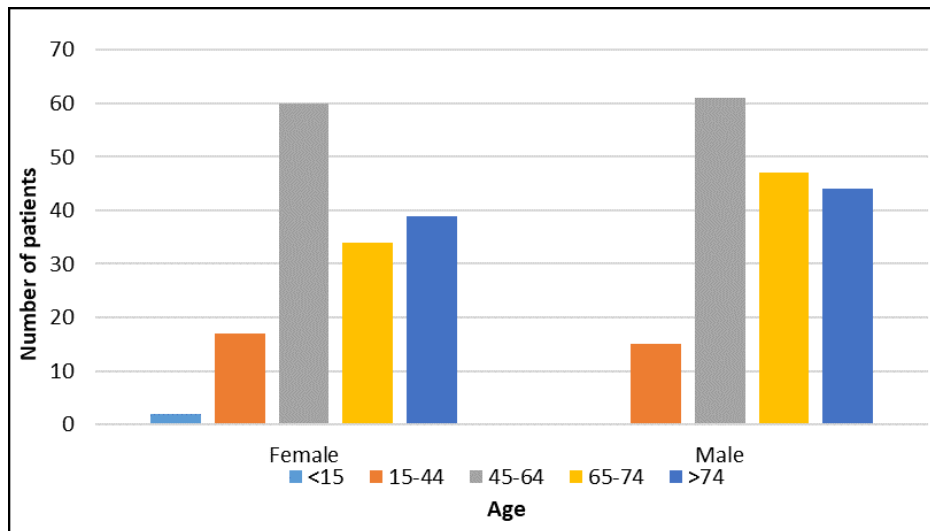


Figure 2 Distribution of patients by age

207 of our patients or 64.9% were hospitalized in the intensive care unit, compared with 112 patients or 35.1% hospitalized in other COVID departments. (Table 1).

The average length of hospital stay was 10.35 +/- 7.88 days in the intensive care unit, compared with 12.72 +/- 7.98 days in the other COVID departments, while 19 patients were transferred to the intensive care unit. 103 patients of the 207 patients hospitalized in the intensive care unit (49.75%) died compared with 3.5% in the other units. (Table 2)

Table 1 Distribution of patients in the different departments

		DEPARTMENT		Total
		Non ICU	ICU	
Gender	Female	61	91	152
	Male	51	116	167
Total		112	207	319

Table 2 Final evolution of the disease COVID 19

		Outcome		Total
		Survival	Death	
Department	Non ICU	108	4	112
	ICU	104	103	207
Total		212	107	319

The mean admission ferritin was 1718.13 ng/ml in the ICU compared to a mean ferritin of 1042.46 ng/ml in the other departments. Statistical analysis revealed a significant association between admission ferritin level and ICU hospitalization ($p=0.003$). However, patients hospitalized in the ICU achieved higher serum ferritin levels (Figure 3) with a mean of 3257.08 ng/ml versus a maximum mean ferritin of 1311 ng/ml in the other COVID services. ($p<0.001$) (Table 3).

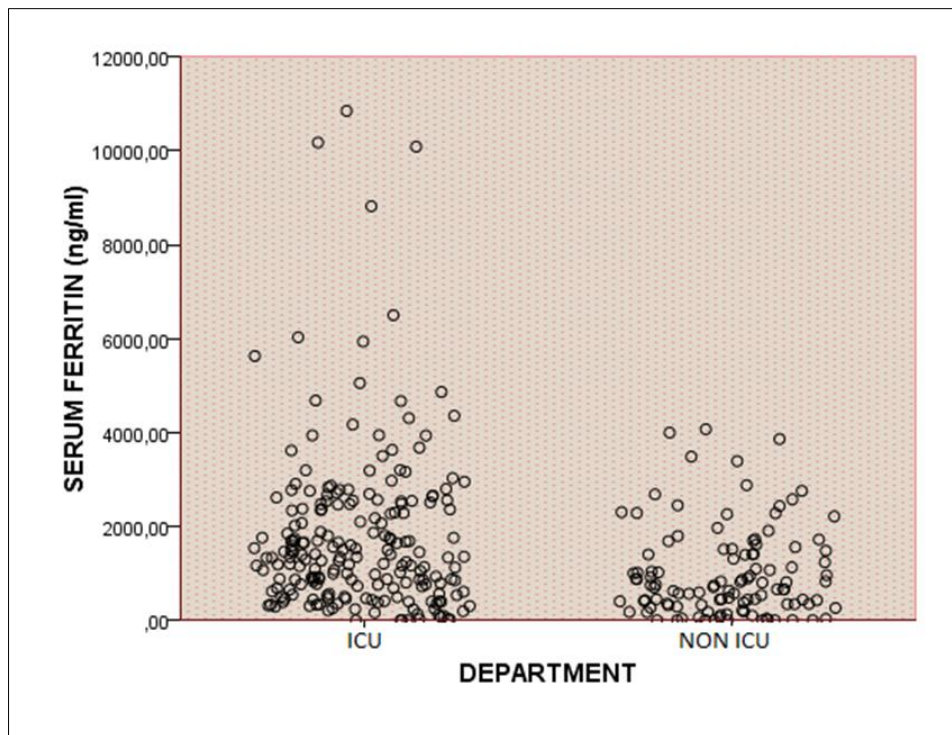


Figure 3 Serum ferritin in patients admitted to the intensive care unit and other units

Table 3 Serum ferritin levels in patients admitted to the intensive care unit and other units

		Department		p
		ICU	Non ICU	
Serum ferritin	Admission	1718,1324	1042,4687	0,003
	Average	1982,1568	950,8209	<0,001
	Maximum	3257,0769	1311,0062	<0,001

However, the mean ferritin for the patients who died was much higher 2135.33ng/ml than for the surviving patients 1361.17 ng/ml with a $p=0.009$. Follow-up of ferritin level during hospitalization also showed that the serum ferritin level before the preterminal event (death or survival) was much higher in the deceased patients with a level of 2557.80 ng/ml versus a level of 1194.90 for the survivors. ($p<0.001$) (Table 4)

Table 4 Serum ferritin levels in deceased and surviving patients

		OUTCOME		P
		Survival	Death	
Serum ferritin	Average	1361,1769	2135,3308	0,009
	Pre-terminal	1194,9051	2557,8093	<0,001

4. Discussion

Hyperferritinemia is the main characteristic of "hyperferritinemic syndromes" and the remarkably high levels of ferritin observed in these conditions appear to be not only the product of inflammation, but may also actively contribute to the development of the cytokine storm [7]. In addition, serum ferritin may be a direct marker of cellular damage, particularly when levels exceed 600 ng/mL [8, 9, 10], indicating a link between organ damage and ferritin production. When this process becomes too vigorous, it results in cell death, known as ferroptosis. However, COVID 19 seems to share some characteristics with hyperferritinemic syndromes. These results suggest that the typical inflammatory process begins with SIRS-SEPSIS and then affects iron metabolism. Iron deficiency, on the other hand, is the first sign in COVID patients, followed by SIRS and possibly severe sepsis.

Our study revealed that higher serum ferritin levels were found in patients with more severe COVID-19 involvement requiring hospitalization in an intensive care unit. Serum ferritin was also found to be extremely high in deceased patients with COVID-19.

Our results were in agreement with a retrospective study by Ruan et al [11] in which COVID-19 hospitalized patients with high ferritin levels had a significantly higher risk of death. Furthermore, in a recent systematic review and meta-analysis of the literature [12], COVID-19 patients with a poor outcome had higher serum ferritin levels than patients with a good outcome.

In fact, a 3- to 4-fold increase in serum ferritin has been reported in non-survivors of COVID-19 [13, 14, 15]. Hyperferritinemia correlates well with the severity of COVID-19, and serum ferritin levels increase with aggravation of infection. Therefore, high serum ferritin levels indicate a very severe infection and a poor prognosis, predicting the development of life-threatening complications, such as respiratory failure, organ dysfunction, need for ICU hospitalization, and death [15, 16, 17, 18, 19]. However, serum ferritin levels begin to decrease as COVID-19 patients begin to improve [20].

Our study also showed that elevated serum ferritin values before the terminal event (either survival or death) were more significantly associated with death as the final outcome. However, some reports have indicated that hyperferritinemia is associated with a more severe disease course [21]. The results of our study contrast with these previous reports, as elevated serum ferritin values, especially before the terminal event, were significantly associated with an unfavourable final outcome.

The results of our study may have important implications for clinical practice. They obviously indicate that hyperferritinemia may reflect the severity of the disease and that assessment of ferritin levels may help in the early identification of patients at high risk of poor outcomes who need to be treated in a more protective unit. In addition, assessment of ferritin can assist in making treatment-related decisions to prevent complications and/or death.

Nevertheless, our study presents some limits on the fact that the majority of COVID-19 patients in our hospital are severe or critical cases rather than mild or moderate cases, and despite the high frequency of demand and the high cost of a ferritin measurement, our laboratory was able to tackle the challenge.

5. Conclusion

In conclusion, this study confirmed the prognostic role of ferritin in COVID-19 hospitalized patients. Increased ferritin levels are associated with mortality, and ferritin is an independent predictor of mortality in COVID-19 patients in intensive care.

Patients with elevated ferritin levels should be considered critically ill and treated in an appropriate unit. In addition, COVID-19 appears to share some characteristics with hyperferritinemic syndromes with potential therapeutic implications.

Compliance with ethical standards

Acknowledgments

We would like to thank all the staff of the biochemistry laboratory of University Hospital Mohammed VI of Oujda and all the laboratory technicians. Similarly, we would like to express our gratitude to the director of establishment for authorizing us to carry out this study.

Disclosure of conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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