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Original Research Article

Association between Ferritin and COVID-19 Mortality in 1310 Moroccan Patients

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Abstract: The clinical picture of SARS-CoV-2 infection is variable, ranging from moderate to severe and critical forms. Various studies have shown that disturbances in certain biochemical parameters are correlated with the severity of the disease. They can be used to predict the risk of complications, allowing early and appropriate care of these patients. The aim of our study is to evaluate the correlation between admission ferritin levels and mortality in COVID-19 patients. We used data from the records of patients with positive RT-PCR admitted to the Mohamed V Military Training Hospital in Rabat between april 2020 and december 2021. Demographic and biologic data were exctracted from DxLab LIS of Dedalus. 1.310 patients are included; the average age is 56 years and 72% of patients are male. The all-cause mortality of seriously ill hospitalized patients in the intensive care units are 23%. 73% of patients who died were over 60 years. The mean ferritinemia at admission was 2040 ng/ml for patients who died versus 521 ng/ml for the survivors ($p < 0.01$). The AUC of the ROC curve for ferritin levels predicting all-cause mortality is 0.745. The threshold of 800 ng/ml allows a sensitivity of 72% and a specificity of 30%. Logistic regression analysis showed that ferritin levels above 800 ng/ml and age above 60 years are risk factors for mortality ($p<0.01$) independently of each other. At hospitalisation of COVID-19 patients, high ferritin levels would be correlated with a bad prognosis justifying an early and adapted care of these patients.

Keywords: SARS-CoV-2 (COVID-19), diagnosis, hyperferritinemia, severity, mortality, comorbidity.

INTRODUCTION

First details of COVID 19 disease were reported in December 2019. The virus responsible, Severe Acute Respiratory Coronavirus 2 (SARS-COV-2), causes a constellation of symptoms affecting various organs. One of the most severe clinical pictures is characterized by an acute inflammatory syndrome "cytokine storm" suggestive of secondary hemophagocytic lymphistiocytosis. Ferritin, a positive acute phase protein, reaches very high concentrations in the serum group of severe patients and has been proposed by different authors as a bad prognostic factor in COVID-19.

The aim of our retrospective descriptive study is to analyse the correlation between admission ferritin levels of patients hospitalized with COVID-19 and all-cause mortality.

MATERIAL AND METHODS

We included adult patients hospitalized at the Mohamed V Military Instruction Hospital in Rabat for COVID-19 between April 2020 and December 2021. Only patients with a positive PCR result from a nasal or pharyngeal swab and at least one ferritin test on admission are included. Serum ferritin determination is performed by immunochimiluminescence (CMIA) on Abbott Architect. All demographic and biological data are extracted from the DxLab LIS of Dedalus. The prognosis of seriously ill patients admitted to the Intensive Care Unit is determined by the physician.

The descriptive statistical study analyzed the demographic characteristics of the patients and their ferritinemia results. Thereafter, we studied the correlation between admission ferritin levels and all-cause mortality. The $\chi 2$ test is performed at the 1% significance level. We calculated specificities and sensitivities to generate a "receiver-operator" (ROC)

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curve. Then we calculated the area under the curve (AUC) and used the J Youden statistic to evaluate the ferritinemia threshold that provides the best performance for predicting all-cause mortality. Descriptive statistics, data analysis and graphing were performed using Excel and SPSS software.

RESULTS AND DISCUSSION

We included 1.310 patients, 72% are mal. Age ranged from 18 to 98 years with a mean of 56 years and a standard deviation of ± 3 years. 47% of patients are over than 60 years of age, 29% between 40 and 60 years, 17% between 25 and 40 years and 8% are under 25 years. According to gender, the average age of men is 56.4 years while 56 years for women. The all-cause mortality for seriously ill patients hospitalized in the ICU is 23%. It is 34% for men and 28% for women. 73% of patients who died were over 60 years of age. The mean ferritin level at admission in patients is 1,106 ng/ml, ranging from 2 ng/ml to 40,000 ng/ml. A level higher than 300 ng/ml is found in 70% of patients. Mean ferritin at admission was 2,040 ng/ml for the group of dead patients versus 521 ng/ml for the survivors (p <0.01). The following table summarizes the evolution of the kinetics of ferritinemia according to the days of hospitalization for surviving and non-surviving patients.

Table 1: Evolution of ferritin according to the days of hospitalization

	Mean ferritin for survivors (ng/ml)	Mean ferritin for non-survivors (ng/ml)
Day 1-3	522	2,109
Day 4-6	690	2,634
Day 7-10	783	1,843
Day 11-14	846	1,054

The AUC of the ROC curve for ferritin levels allowing to predict all-cause mortality is 0.745. A threshold of 800 ng/ml provides a sensitivity of 72% and a specificity of 30% (Figure 1).

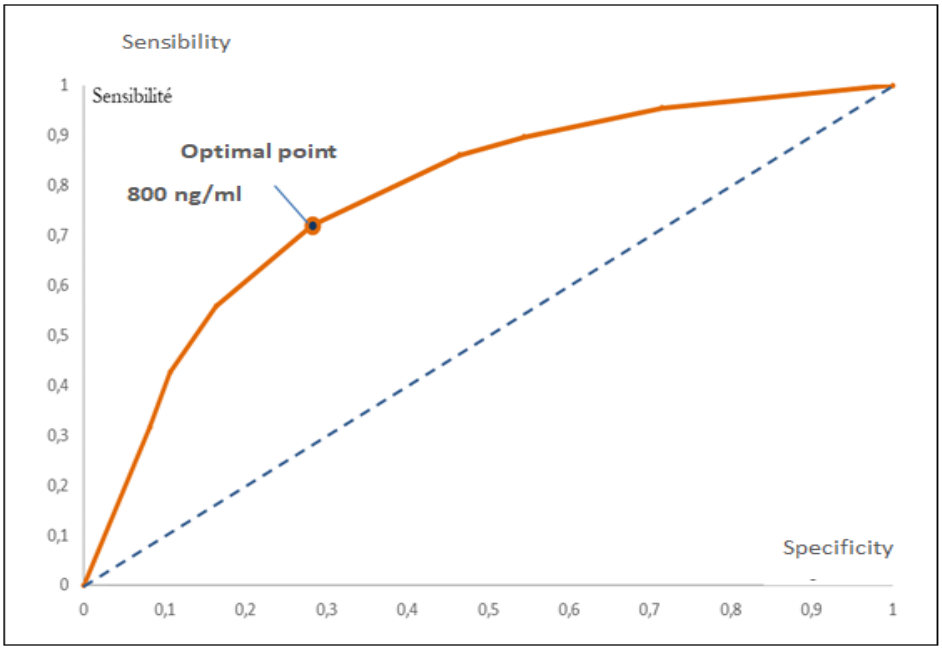

Figure 1: ROC curve for ferritin at admission and mortality

Moreover, analysis using a logistic regression model shows that a ferritin level above 800 ng/ml, regardless of age, reduces very significantly the survival probability for an individual with Covid-19 (p<0.01). Similarly, an age over 60 years, regardless of ferritin level, significantly increases the probability of death (p<0.01).

There is no consensus on the criteria for hospitalization of infected patients, so there is heterogeneity in the demographics data of the patient populations. In our study, the majority of patients are male with an average age of 55 years. This male predominance is found in other Moroccan studies [1, 2] but also in most international meta-analysis [3, 4]. The mechanism is not yet fully elucidated. According to some authors, if the angiotensin-converting enzyme 2 (ACE2) receptor, the main cellular receptor of SARS-CoV-2, favors the penetration of the virus into the cell, its soluble form may constitute a protective factor against COVID-19. The positive correlation between circulating ACE2 activity and estrogen expression

would explain the relative protection of women compared to men in COVID-19 [5, 6]. For various studies, the age category of hospitalized COVID-19 patients is between 49 and 69 years [3, 4, 7], with severe forms occurring in adults older than 60 years of age and in those with certain comorbidities, such as cardiovascular disease and diabetes [8, 9]. Furthermore, mortality related to COVID-19 is variable depending on the inclusion criteria and confounding factors. The majority of international publications report high in-hospital mortality exceeding 20% [10-12]. In our series, the rate is 23% for patients admitted to the ICU, close to the 21% found in our first study (1) but much lower than the rates exceeding 45% reported by other authors [2, 13, 14]. Old age and the presence of comorbidity have been identified as risk factors for mortality by various authors [10, 14-16]. In our study, the mortality rate is higher in patients over 60 years of age; therefore, the age is an independent risk factor. Zhou *et al*., [10] report similar data with a male mortality of 70% for an average age of 69 years with the presence of comorbidity in 67% of cases. In France, 89% of the patients who died were over 65 years of age and 90% had a comorbidity, the main ones being diabetes, cardiac pathology, hypertension, pulmonary pathology or morbid obesity [15]. In our study, the association of comorbidity and mortality could not be performed because of data's collection mode.

The clinical manifestations of COVID-19 range from asymptomatic, mild, moderate to severe and critical forms. Symptomatic infections cases are often associated with several biochemical disturbances including hyperferritinemia. Wu *et al*., [10] report an increase in 78.5% of patients and for Zhou *et al*., [8], 80% of patients had a ferritin level above 300 ng/ml, close to the rate found in our series. Furthermore, ferritin levels are statistically higher in group of patients with severe forms versus non-severe (1,17,18). Taneri *et al*., [19] in a meta-analysis including 57,563 COVID-19 patients confirmed this statistically significant difference with $p < 0.001$.

In our study population, we found a significant difference in ferritin between the group including dead patients and the survivor group, the levels in both groups remain high during the 14 days of hospitalization. Zhou *et al*., [10] reported a mean ferritin level of 1,435 ng/ml in the non-survival group versus 503 ng/ml in the survival group ($p<0.001$) with high levels after 16 days of hospitalization. For lino et al (14), the non-survivor group had a mean ferritin level of 4,207.7 ng/ml versus 1,717.1ng/ml for survivors ($p <0.05$). For Meng Jin *et al*., [20] the mean ferritin in deceased patients is 1,407 ng/ml versus 566.90 ng/ml for survivors ($p < 0.001$). Similar results were found by Chen *et al*., [21] with a significant difference in median ferritin levels between the non-survival and survival groups with 1,414 ng/ml versus 481.2 ng/ml respectively. Meta-analysis [4, 18, 22] have confirmed this strong correlation with $p<0.001$. Some authors have determined the threshold of ferritinemia allowing the best performances in terms of sensitivity and specificity to predict mortality. Qeadan *et al*., [23] found for a threshold of 714.3 ng/ml, close to the one used in our study, an AUC of 0.997 with an Odds ratio (OR) of 3.7. These authors also reported a variability of the threshold according to sex: 733.3 ng/ml for women with an AUC of 0.996 and an OR of 5.1 while for men, it is 740 ng/ml, an AUC of 0.998 and an OR of 3.4. For Zhou *et al*., [10], in univariate analysis, a ferritin level above 300 ng/ml has an OR of 9.10. In a Brazilian study, Lino *et al*., [14] reported an AUC of 0.79 with a higher threshold of 1,873 ng/ml allowing a sensitivity of 68.4% and specificity of 79.3%. Analysis using a logistic regression model confirmed that ferritin level higher than 1,873 ng/ml and age over 60 years were risk factors for mortality independently of each other, with an OR of 6.04 (p: 0.016) and an OR of 10.490 (p: 0.008) respectively.

The pathophysiology of the elevated ferritin levels found in patients with serious condition and in non-survivors is not fully elucidated. For different authors, these levels do not only reflect a response of the acute phase of the inflammation but probably play a critical role in contributing to the development of the cytokine storm [24]. Therefore, the H chain of ferritin could play an important role in the activation of macrophages to increase the secretion of inflammatory cytokines [25].

Another explanation for these increased ferritin levels could be the stimulation by IL6 of the JAK/STAT3 signaling pathway leading to the transcription of the gene for Hepcidin, the main homeostasis hormone of iron metabolism [24]. The increase in hepcidin blocks ferroportin, a protein that transports iron out of cells, causing cellular sequestration of iron mainly in hepatocytes, enterocytes and macrophages. This intracellular sequestration of iron leads to an up-regulation of cytosolic ferritin, which sequesters and stores iron to prevent free radical's damage induced by iron [24, 26]. The dramatic increase in ferritin levels in severe COVID-19 associated with lymphopenia, reduced NK cell activity, liver function disturbances and coagulation abnormalities have made it associated with hyperferritinemic syndromes [25, 27]. These syndromes, which include still disease, septic shock, macrophage activation syndrome and catastrophic antiphospholipid syndrome, are characterized by life-threatening hyperinflammation that eventually leads to multivisceral failure [25-27]. On the basis of such results, some authors have even suggested the use of rapid capillary blood ferritin tests at home for COVID-19 patients, in addition to clinical evaluation. This approach would allow the possibility of early treatment with corticosteroids and the need for hospitalization to be properly assessed in order to avoid saturation of the

emergency services [28]. Future studies would also explore the impact of new drugs targeting iron metabolism in severe forms of COVID-19 [26, 27].

However, our study has several limitations, mainly related to the retrospective nature of the study and the collection of data from the LIS and not from the patient record (absence of clinical data and notions of comorbidities). On the other hand, our work cannot claim to reflect the true mortality of patients since the prognosis could only be determined for patients transferred to the ICU. Furthermore, the interpretation of ferritin was done in the absence of any pre-diagnostic COVID-19 knowledge of the patients' iron metabolism (iron deficiency or inflammatory anemia, hemoglobinopathies).

CONCLUSION

To our knowledge, our work is the most extensive Moroccan study dealing with the place of ferritin as a marker of clinical deterioration and bad prognosis in hospitalized COVID- 19 patients. However, the interpretation of ferritin must be done taking into account clinical, radiological data and other biological parameters of inflammation, coagulation and organ damage.

REFERENCES

1. El Ouadani, M. (2022). Protein C reactive, Ferritin and Procalcitoninin 300 Morrocan Patients with COVID-19. Clinical laboratory, 10/2022.
2. Bay Bay, Y. (2021). Caractéristiques des patients Covid-19 admis en services de réanimation à l'hôpital Ibn Sina de Rabat : Etude descriptive à propos de 230 cas. Thèse 83/2021, Faculté de Médecine et de Pharmacie de Rabat, Maroc.
3. Zeng, F., Huang, Y., Guo, Y., Yin, M., Chen, X., Xiao, L., & Deng, G. (2020). Association of inflammatory markers with the severity of COVID-19: a meta-analysis. *International Journal of Infectious Diseases*, *96*, 467-474.
4. Elshazli, R. M., Toraih, E. A., Elgaml, A., El-Mowafy, M., El-Mesery, M., Amin, M. N., ... & Kandil, E. (2020). Diagnostic and prognostic value of hematological and immunological markers in COVID-19 infection: A meta-analysis of 6320 patients. *PloS one*, *15*(8), e0238160.
5. Bonny, V., Maillard, A., Mousseaux, C., Plaçais, L., & Richier, Q. (2020). COVID-19: Pathogenesis of a multi-faceted disease. *La Revue de medecine interne*, *41*(6), 375-389.
6. Ciaglia, E., Vecchione, C., & Puca, A. A. (2020). COVID-19 infection and circulating ACE2 levels: protective role in women and children. *Frontiers in pediatrics*, *8*, 206.
7. Plaçais, L., & Richier, Q. (2020). COVID-19: caractéristiques cliniques, biologiques et radiologiques chez l'adulte, la femme enceinte et l'enfant. Une mise au point au cœur de la pandémie. *La Revue de médecine interne*, *41*(5), 308-318.
8. Wu, C., Chen, X., Cai, Y., Zhou, X., Xu, S., Huang, H., ... & Song, Y. (2020). Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA internal medicine*, *180*(7), 934-943.
9. Wang, D., Hu, B., Hu, C., Zhu, F., Liu, X., Zhang, J., ... & Peng, Z. (2020). Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. *Jama*, *323*(11), 1061-1069.
10. Zhou, F., Yu, T., Du, R., Fan, G., Liu, Y., Liu, Z., ... & Cao, B. (2020). Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *The lancet*, *395*(10229), 1054-1062.
11. Feld, J., Tremblay, D., Thibaud, S., Kessler, A., & Naymagon, L. (2020). Ferritin levels in patients with COVID-19: a poor predictor of mortality and hemophagocytic lymphohistiocytosis. *International journal of laboratory hematology*, *42*(6), 773-779.
12. Paranjpe, I., Russak, A. J., De Freitas, J. K., Lala, A., Miotto, R., Vaid, A., ... & Nadkarni, G. N. (2020). Retrospective cohort study of clinical characteristics of 2199 hospitalised patients with COVID-19 in New York City. *BMJ open*, *10*(11), e040736.
13. Ruan, Q., Yang, K., Wang, W., Jiang, L., & Song, J. (2020). Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive care medicine*, *46*(5), 846-848.
14. Lino, K., Guimarães, G. M. C., Alves, L. S., Oliveira, A. C., Faustino, R., Fernandes, C. S., ... & Almeida, J. R. (2021). Serum ferritin at admission in hospitalized COVID-19 patients as a predictor of mortality. *Brazilian Journal of Infectious Diseases*, *25*(2), 101569.
15. Réseau sentinelles, France. https://websenti.u707. Jussieu.fr/sentiweb 1é Avril 2020.
16. Zhou, S., Mi, S., Luo, S., Wang, Y., Ren, B., Cai, L., & Wu, M. (2021). Risk factors for mortality in 220 patients with COVID-19 in Wuhan, China: a single-center, retrospective study. *Ear, Nose & Throat Journal*, *100*(2_suppl), 140S-147S.
17. Dahan, S., Segal, G., Katz, I., Hellou, T., Tietel, M., Bryk, G., ... & Dagan, A. (2020). Ferritin as a marker of severity in COVID-19 patients: A fatal correlation. *The Israel Medical Association journal: IMAJ*, *8*(22), 429-434.
18. Cheng, L., Li, H., Li, L., Liu, C., Yan, S., Chen, H., & Li, Y. (2020). Ferritin in the coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis. *Journal of clinical laboratory analysis*, *34*(10), e23618.
19. Taneri, P. E., Gómez-Ochoa, S. A., Llanaj, E., Raguindin, P. F., Rojas, L. Z., Roa-Díaz, Z. M., ... & Muka, T. (2020). Anemia and iron metabolism

in COVID-19: a systematic review and meta-analysis. *European journal of epidemiology*, *35*(8), 763-773.

20. Jin, M., Lu, Z., Zhang, X., Wang, Y., Wang, J., Cai, Y., ... & Wang, Z. (2021). Clinical characteristics and risk factors of fatal patients with COVID-19: a retrospective cohort study in Wuhan, China. *BMC infectious diseases*, *21*(1), 1-13.
21. Chen, T., Wu, D. I., Chen, H., Yan, W., Yang, D., Chen, G., ... & Ning, Q. (2020). Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *bmj*, *368*.
22. Huang, I., Pranata, R., Lim, M. A., Oehadian, A., & Alisjahbana, B. (2020). C-reactive protein, procalcitonin, D-dimer, and ferritin in severe coronavirus disease-2019: a meta-analysis. *Therapeutic advances in respiratory disease*, *14*, 1753466620937175.
23. Qeadan, F., Tingey, B., Gu, L. Y., Packard, A. H., Erdei, E., & Saeed, A. I. (2021). Prognostic values of serum ferritin and D-dimer trajectory in patients with COVID-19. *Viruses*, *13*(3), 419.
24. Gómez-Pastora, J., Weigand, M., Kim, J., Wu, X., Strayer, J., Palmer, A. F., ... & Chalmers, J. J. (2020). Hyperferritinemia in critically ill COVID-19 patients–is ferritin the product of inflammation or a pathogenic mediator?. *Clinica Chimica Acta; International Journal of Clinical Chemistry*, *509*, 249-251.
25. Colafrancesco, S., Alessandri, C., Conti, F., & Priori, R. (2020). COVID-19 gone bad: A new character in the spectrum of the hyperferritinemic syndrome?. *Autoimmunity reviews*, *19*(7), 102573.
26. Ruscitti, P., & Giacomelli, R. (2020). Ferritin and Severe COVID-19, from Clinical Observations to Pathogenic Implications and Therapeutic Perspectives. *The Israel Medical Association journal: IMAJ*, *22*(8), 516-518.
27. Mahroum, N., Alghory, A., Kiyak, Z., Alwani, A., Seida, R., Alrais, M., & Shoenfeld, Y. (2022). Ferritin–from iron, through inflammation and autoimmunity, to COVID-19. *Journal of Autoimmunity*, *126*, 102778.
28. Gandini, O., & Lubrano, C. (2021). Use of rapid ferritin test to predict clinical deterioration in at home COVID-19 patients. *Journal of Infection*, *82*(3), e11-e13.