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LETTER TO THE EDITOR

Higher ferritin levels in COVID-19 patients are associated with hyperinflammation, worse prognosis, and more bacterial infections without pronounced features of hemophagocytosis

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Dear Editor,

We have read with great interest the recently published paper by Dong et al. [1] reporting associations of hyperferritinemia with adverse clinical outcomes in COVID-19 patients. Due to different clinical associations present in our cohort of mostly severe and critical COVID-19 patients treated in our institution (University Hospital Dubrava, Zagreb, Croatia) and wider overview of clinical outcomes available from the hospital registry project, we aimed to update the current report with our experience. A total of 3245 consecutive COVID-19 patients hospitalized in period 3/2020–6/2021 who had available data on ferritin at the time of hospital admission were retrospectively analyzed. Details on data collection and presentation have been published previously [2].

Median age was 72 years, median Charlson comorbidity index (CCI) was 4 points, and most patients were males (1876, 57.8%) and had severe or critical COVID-19 on admission (2925, 90.1%) as defined by WHO guidelines [3]. Median ferritin levels were 769 µg/L, interquartile range (IQR, 409–1436). A total of 2200 (67.8%) of patients had ferritin levels > 500 µg/L, whereas other potential features of hemophagocytosis like body temperature > 38.5 °C (24.7%), hemoglobin levels < 90 g/L (4.7%), platelets $< 100 \times 10^9$/L (5.2%), absolute neutrophil count $< 1.0 \times 10^9$/L (0.5%), triglycerides ≥ 3 mmol/L (8.4%), and fibrinogen ≤ 1.5 g/L (0.6%) were less frequent.

Associations of ferritin stratified at quartiles with clinical characteristics are provided in Supplementary Table 1. Patients belonging to higher ferritin quartiles more frequently had severe/critical COVID-19 on admission, longer duration, and higher intensity of symptoms prior to hospitalization. Patients with higher ferritin were more likely to be younger, of male sex and to have active malignancy, less likely to have diabetes mellitus, arterial hypertension or chronic kidney disease, and had lower CCI. Higher ferritin levels were significantly associated with higher absolute neutrophil and lower lymphocyte count, higher hemoglobin, MCV and MCHC, lower RDW, and subtly lower platelets. Higher ferritin was also associated with higher CRP, LDH, D-dimers, fibrinogen, and triglycerides, as well as with an increase in liver blood tests and higher transferrin saturation ($P < 0.05$ for all analyses).

Associations of ferritin stratified at quartiles with clinical outcomes are shown in Fig. 1. Higher ferritin was associated with higher in-hospital mortality, higher need for mechanical ventilation, and propensity for bacterial sepsis ($P < 0.05$ for

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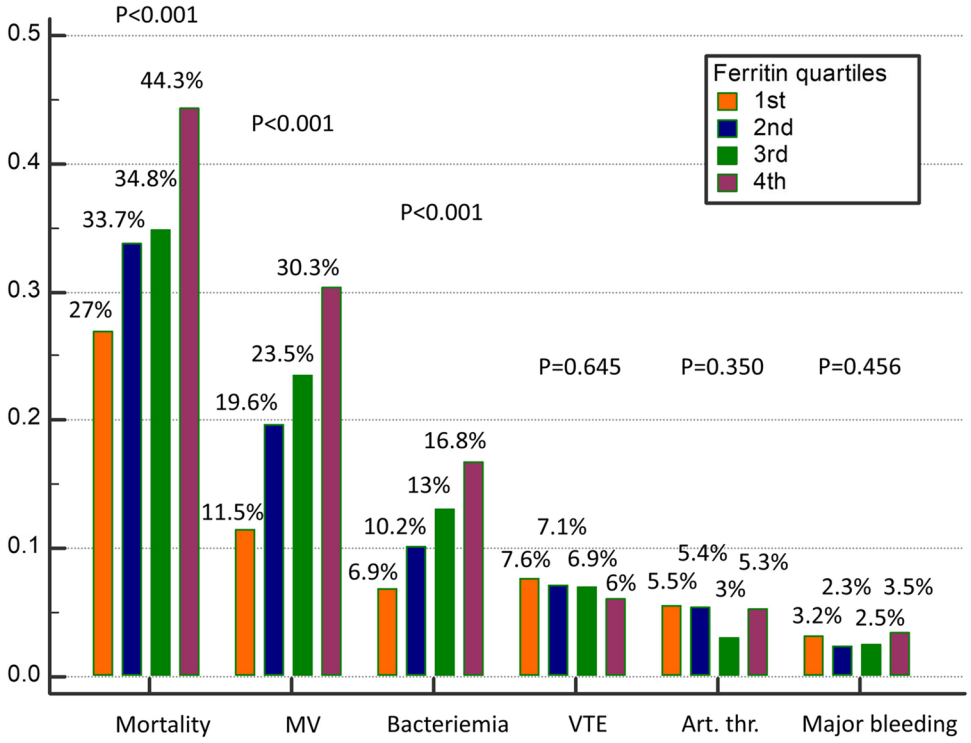

Fig. 1 Associations of ferritin levels at the time of hospital admission stratified at quartiles with clinical outcomes (in-hospital mortality, mechanical ventilation (MV), bacterial sepsis, venous thromboembolism (VTE), arterial thrombosis, and major bleeding)

all analyses), whereas there was no significant relationship with arterial or venous thromboses and major bleeding. In the multivariate analysis adjusted for particular comorbidities presented in Supplementary Table 2, higher ferritin was associated with increased mortality independently of age, active malignancy, diabetes mellitus, chronic kidney disease, and chronic liver disease.

Our data from a high-volume dedicated COVID-19 center show that extremely increased ferritin levels are common at the time of hospital admission, whereas features of hemophagocytosis are not. Increased ferritin levels seem to be driven by more severe COVID-19 inflammatory response and longer duration of the disease, and not by age, overall comorbidity burden and metabolic comorbidities. Higher ferritin is associated with features of hyperinflammation but there is no consistent association with markers of hemophagocytosis (instead higher ferritin was associated with increasing fibrinogen levels, higher white blood cells, and higher hemoglobin). Patients belonging to higher ferritin quartiles were prone to respiratory deterioration and death but also to the occurrence of bacterial superinfections. Iron overload is considered to contribute to impaired immune response and higher microbial virulence as shown prior to the COVID-19 era [4], and similar phenomena might be present in COVID-19 patients as well.

Our analyses are limited by retrospective nature, single-center experience, inability to longitudinally assess ferritin measures for all patients and possible confounding of ferritin levels with particular comorbidities that are highly prevalent in real-life elderly patients. We focused on ferritin levels at the time of hospital admission as the time of the start of follow-up for clinical outcomes. The current study adds to understanding of biology of commonly encountered high ferritin levels in severe and critical COVID-19 patients and supports the view that severe COVID-19 can be considered as a separate entity among hyperferritinemic syndromes. Ferritin levels are independently associated with impaired survival.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00277-022-04813-y.

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Declarations

Ethical approval The study was approved by the Institutional Review Board. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Informed consent Not applicable due to the retrospective nature of the study.

Conflict of interest The authors declare no competing interests.

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