Letter to the Editor

Use of rapid ferritin test to predict clinical deterioration in at home COVID-19 patients

COVID-19 placed increased burdens on National Health Service hospitals and necessitated significant adjustments to their structures and processes. There was a large increase in emergency room admission and an overload of intensive care units (ICU) from the beginning of the pandemic. COVID-19 has a variable clinical presentation on a spectrum from asymptomatic carriage to life-threatening organ dysfunction with severe pneumonia, acute respiratory distress syndrome (ARDS) and death.[1] It may be useful for predicting the risk of clinical deterioration and the need of hospitalization to identify parameters that in association with symptoms such as dyspnea and fever and signs such as oxygen desaturation can allow general practitioners to identify patients at risk.[2] Hyperferritinemia caused by the excessive inflammation due to the infection is a feature of hemophagocytic lympho-histiocytosis (HLH) and is associated with cytokine storm, admission to the ICU and high mortality, and represents an indication to recognize high-risk patients to guide the therapeutic intervention,[3,4] as corticosteroid treatment. Early administration of corticosteroids is the mainstay of first-line treatment for HLH.[5] We, like many other authors, recently published that serum Ferritin is an independent risk factor for ARDS in COVID-19 patients.[6–8] Our study demonstrates that serum Ferritin is a good discriminator of the combined outcome of either death or ICU admission and that hyperferritinemia was observed in all patients with severe disease on admission. ROC curve analysis confirmed the excellent prognostic accuracies of serum Ferritin in discriminating patients with severe clinical conditions for concentrations above $>644\,\mu g/L$ with a sensitivity 88,33% and a specificity 93,83%; (AUC 0.939, CI: 0,894 to 0,985 $p < 0.001$) (Fig. 1A) but if we should set the sensitivity to 100% to enclose all the patients with severe disease then we should choose the serum Ferritin cut-off $> 244\,\mu g/L$.(sensitivity 100,00 specificity 44,44) (Fig. 1B).

Recently it has been affirmed the validity of plasma collection cards for ferritin assessment. Routinely, ferritin is assessed from venous blood sampling. An alternative method involves the collection of capillary blood and has been used for the assessment of iron status in various vulnerable populations.[9] It is therefore conceivable in the field of COVID-19 management to use a rapid semi-quantitative screening assay able to detect ferritin levels above $244\,\mu g/L$, as available on the market. In Italy, the timely identification of COVID-19 positive patients with risk of adverse outcome is performed by the Special Continuity Care Units (USCA).[10] The US-CAs are aimed at implementing the management of the suspected or confirmed COVID-19 patients in the area of territorial assistance and perform home visits to verify the need of hospitalization, in order to reduce the pressure on emergency rooms. The clinical instability related to the alteration of physiological parameters (blood pressure, heart rate, respiratory rate, body temperature, level of consciousness, oxygen saturation) – Modified Early Warning Score (MEWS) -, is evaluated and allows identification of people at risk of rapid clinical deterioration or death.[11] Considering the above, we suggest the use of rapid ferritin test in addition to clinical evaluation by MEWS in at home management of suspected or confirmed SARS-CoV-2 patients to correctly evaluate the possibility of early corticosteroid treatment and the need of hospitalization to avoid the crowding of emergency rooms.
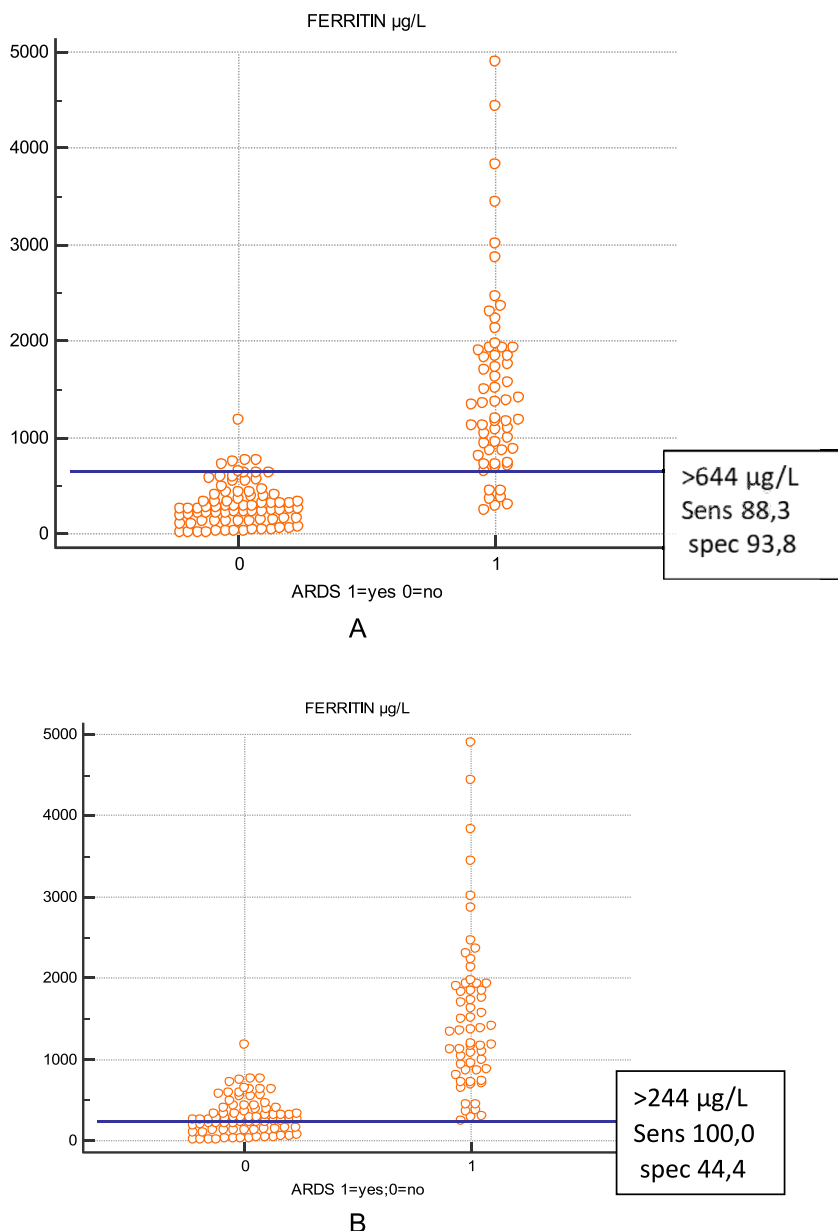
Fig. 1. (A) interactive Dot Diagram of ROC curve analysis for ferritin levels >644 µg/L. (B) interactive Dot Diagram of ROC curve analysis for ferritin levels >244 µg/L.

References

1. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19). A review. *JAMA* 2020;**324**:782–93. doi:10.1001/jama.2020.12839.
2. Henry BM, de Oliveira M, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. *Clin Chem Lab Med* 2020.
3. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020;**395**:1054–62. doi:10.1016/S0140-6736(20)30566-3.
4. Cheng L, Li H, Li L, Liu C, Yan S, Chen H, Li Y. Ferritin in the coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis. *J Clin Lab Anal.* 2020;**34**(10):e23618 Epub 2020 Oct 19. PMID:33078400PMCID: PMC7595919. doi:10.1002/jcla.23618.
5. Kolilekas L, Loverdos K, Giannakaki S, Vlassi L, Levounets A, Zervas E, Gaga M. Can steroids reverse the severe COVID-19 induced "cytokine storm"? *J Med Virol.*

2020;**92**(11):2866–9 Epub 2020 Jun 29. PMID:32530507PMCID: PMC7307112. doi:10.1002/jmv.26165.
6. Gandini O, Criniti A, Ballesio L, Giglio S, Galardo G, Gianni W, Santoro L, Angeloni A, Lubrano C. Serum Ferritin is an independent risk factor for Acute Respiratory Distress Syndrome in COVID-19. *J Infect.* 2020 S0163-4453(20)30617-4Epub ahead of print. PMID:32946917PMCID: PMC7490639. doi:10.1016/j.jinf.2020.09.006.
7. Lin Z, Long F, Yang Y. Serum ferritin as an independent risk factor for severity in COVID-19 patients. *J Infect* 2020 Epub ahead of print. doi:10.1016/j.jinf.2020.06.053.
8. Gandini O, Criniti A, Gagliardi MC, Ballesio L, Giglio S, Balena A, Caputi A, Angeloni A, Lubrano C. Sex-disaggregated data confirm serum ferritin as an independent predictor of disease severity both in male and female COVID-19 patients. *J Infect.* 2020 S0163-4453(20)30654-XEpub ahead of print. PMID:33131700PMCID: PMC7578700. doi:10.1016/j.jinf.2020.10.012.
9. Koehler K, Marks-Nelson E, Braga CP, Beckford S, Adamec J. Validity of plasma collection cards for ferritin assessment-A proof-of-concept study. *Eur J*

Haematol. 2020;**104**(6):554–61 Epub 2020 Mar 3. PMID:32058611. doi:10.1111/ejh.13397.

10. Circolare del Ministero della salute del 30 novembre 2020. "Gestione domiciliare dei pazienti con infezione da SARS-CoV-2" https://www.trovanorme.salute.gov.it/norme/renderNormsanPdf?anno=2020&codLeg=77456&parte=1%20&serie=null

11. Barnett WR, Radhakrishnan M, Macko J, Hinch BT, Altorok N, Assaly R. Initial MEWS score to predict ICU admission or transfer of hospitalized patients with COVID-19: a retrospective study. *J Infect.* 2020 S0163-4453(20)30583-1Epub ahead of print. PMID:32888979PMCID: PMC7462753. doi:10.1016/j.jinf.2020.08.047.

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