Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

American Journal of Emergency Medicine 47 (2021) 315

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

Can on-admission anemia predict severe COVID-19 cases? A discussion about statistical and clinical significance

Dear Sir,

I read the article titled "On-admission anemia predicts mortality in COVID-19 patients: A single center, retrospective cohort study" published in the American Journal of Emergency Medicine by Oh et al. [1]. According to the authors; anemia on admission was independently associated with increased odds of all-cause mortality in patients hospitalized with COVID-19. The study was conducted with an adequate sample size in COVID-19 patients and it has several limitations regarding to its retrospective design. However, I think it has also serious methodological limitations. Given the rapid increase in emergency department (ED)-based prognostic studies on COVID-19, readers need to be aware of these limitations.

It is known that iron metabolism is impaired during the course of COVID-19 infection. Anemia could be developed due to iron-restricted erythropoiesis arising from alterations in iron metabolism. Iron availability is also impaired due to ferritin acting as an acute phase reactant in the disease course [2,3]. A recent meta-analysis indicated that, a significant difference in mean ferritin levels of 606.37 ng/mL was found between survivors and non-survivors, but not in hemoglobin levels. Despite this finding, hemoglobin levels were found to be lower in severe cases [2]. The results of the study of Oh et al. are compatible with the current literature from this viewpoint. However, the authors cited two previous studies on the topic that anemia could be an indicator for COVID-19 severity. Like the current study, the studies of Bellmann-Weiler et al. and Tao et al. also show that the limits of the confidence interval forming the odds ratio are very wide and about to cut the value of 1. [4,5].

The first problem that stands out in the study of Oh et al. is the sample selection method: The authors stated that they randomly selected 750 of 4356 COVID-19 confirmed patients admitted to the emergency department. It is unclear how this choice was made, it is not understandable why random sampling method was used for a retrospective cohort study. The principles of this sampling are also not detailed, this may cause a selection bias for a retrospective study.

The second important problem is how the hemoglobin values are handled in the study. In the manuscript, the only place where we can see the exact hemoglobin values of the patients is the demographic and clinical characteristics table. Accordingly, the mean hemoglobin values of patients with good outcome were found to be 11.22 ± 2.99, and the mean hemoglobin values of patients with severe outcomes were found to be 11.10 ± 2.91 ($p = 0.658$). As a result, the hemoglobin difference between patients with good and severe outcomes is on average 0.1 g/dL. This difference is both statistically and clinically insignificant. In this comparison, in which hemoglobin is considered as a continuous variable, it is not understood why it was converted into a categorical (binary) variable in the multivariate model. It is quite clear that there is no difference between the mean hemoglobin values across different outcomes.

Due to these two problems, it is difficult to use anemia as a severity marker in COVID-19 patients according to this results. Although ferritin can be treated as an acute phase reactant in these patients, many confounding factors for anemia may accompany the clinical picture on admission to the ED. When creating a regression model for the severity of COVID-19, all variables that describe the current clinical situation should be included in the model, and a multicollinearity analysis should be applied for potentially correlated variables before proceeding further. In the regression analysis, dichotomization of data can result in exaggerated or incorrect results.

Conflict of interest and source of funding

None declared.

References

[1] Oh SM, Skendelas JP, Macdonald E, et al. On-admission anemia predicts mortality in COVID-19 patients: a single center, retrospective cohort study. Am J Emerg Med. 2021 Mar;29 [In Press].
[2] Taneri PE, Gómez-Ochoa SA, Llanaj E, et al. Anemia and iron metabolism in COVID-19: a systematic review and meta-analysis. Eur J Epidemiol. 2020;35(8):763–73.
[3] Henry BM, de Oliveira MHS, Benoit S, et al. 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;58(7):1021–8.
[4] Bellmann-Weiler R, Lanser L, Barket R, et al. Prevalence and predictive value of anemia and dysregulated Iron homeostasis in patients with COVID-19 infection. J Clin Med. 2020;9(8):2429.
[5] Tao Z, Xu J, Chen W, et al. Anemia is associated with severe illness in COVID-19: a retrospective cohort study. J Med Virol. 2021;93(3):1478–88.

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11 April 2021

https://doi.org/10.1016/j.ajem.2021.05.016