haematologica
Journal of the Ferrata Storti Foundation

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Received: May 15, 2024.
Accepted: May 28, 2024.

Citation: Tommaso Francesco Aiello and Carolina Garcia-Vidal. Reply to the Comment on Dexamethasone treatment for COVID-19 is related to increased mortality in hematologic malignancy patients: results from the EPICOVIDEHA Registry. Haematologica. 2024 June 6. doi: 10.3324/haematol.2024.285875 [Epub ahead of print]

Reply to the Comment on Dexamethasone treatment for COVID-19 is related to increased mortality in hematologic malignancy patients: results from the EPICOVIDEHA Registry

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We sincerely appreciate the interest of Guangting Zeng and Jing Liu in our manuscript exploring the impact of Dexamethasone treatment outcomes of COVID-19 in hematologic malignancy patients. In this regard, we find it pertinent to clarify certain aspects highlighted by these authors in their comment[1]. First, international guidelines cited by Guangting Zeng support the benefit from corticosteroids in patients with severe COVID-19[2], based on the results of the RECOVERY RCT study (dexamethasone) and REMAC-CAP study (Hydrocortisone) [3,4]. Nevertheless, it should be strongly considered that in both trials patients with hematological malignancy were underrepresented (no information about prevalence of hematological malignancies in the study population provided in RECOVERY RCT trial, 11.8% Vs 6.0% of patients with immunosuppressive disease in hydrocortisone and no-hydrocortisone groups, respectively). Consequently, the european recommendations for the management of COVID-19 in patients with hematological malignancies from de European Conference on Infections in Leukemia (ECIL), propose to limit the use of dexamethasone to patients with severe and critical disease, avoiding this treatment in patients with mild-moderate disease[5]. Second, both univariable and multivariable analysis showed that the exclusive use of dexamethasone in COVID-19 therapy affected the risk of clinical failure. As we were conscious of the limitations of our study related to the absence of randomization and its retrospective design, we implemented a propensity score for receiving dexamethasone into the model. Hence, we estimate the effect of dexamethasone accounting for the covariates predicting the receiving treatments, notably COVID-19 severity, observing the same results. Regarding the differences among treatment groups, most of them are statistically significant when comparing dexamethasone only group to antiviral strategies, due to the predominance of patients not requiring

hospital admission in the only antiviral strategies group (40.8% Vs 8.2%). Nevertheless, when comparing dexamethasone only and dexamethasone plus antivirals groups, those differences are less significant. To address these differences, we have performed various subset analyses. The deleterious role of dexamethasone in monotherapy has been observed in all of them. For instance, survival curves for the three groups according to different treatment strategies showed that the detrimental effect of dexamethasone monotherapy is observed even during the predominance of SARS-CoV-2 omicron variant, when most patients had received vaccines, and in the same measure for patients needing to be hospitalized in normal ward or in intensive care unit (ICU). Third, our study provides real-life evidence against the indiscriminate use of dexamethasone in patients with hematologic malignancies, especially when this treatment is administered without concomitant antiviral therapeutics. Several guidelines alert that the over-use of corticoids, especially in early phases of the disease, may lead to detrimental effects, as supported by the evidence of our study[2,5]. Fourth, as we stated in the manuscript, the process of immune-mediated viral clearance is often impaired in high-risk hematological patients, leading to prolonged viral shedding in up to 25% of patients with hematological malignancies[6]. Interestingly, glucocorticosteroids have been described as potential enhancers of respiratory virus replication, dampening type I and III interferon production, especially in primary airway cells[7]. Different published studies, in accordance with our data, support the hypothesis that at early stages of the infections, antivirals strategies protect hospitalized COVID-19 patients requiring oxygen therapy from progression to severe disease or dead[8,9].

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