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

We sincerely appreciate the interest of Guangting Zeng and Jing Liu in our manuscript exploring the impact of dexa-methasone on coronavirus disease 2019 (COVID-19) outcomes in patients with hematologic malignancies. 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 of corticosteroids in patients with severe COVID-19,[2] based on the results of the RECOVERY randomized controlled trial (dexamethasone) and REMAC-CAP trial (hydrocortisone).[3,4] Nevertheless, it should be strongly considered that in both trials patients with hematologic malignancies were underrepresented (no information about prevalence of hematologic malignancies in the study population provided in RECOVERY trial, 11.8% *vs.* 6.0% of patients with immunosuppressive disease in the hydrocortisone and no-hydrocortisone groups, respectively, in the REMAC-CAP trial). Consequently, the European recommendations for the management of COVID-19 in patients with hematologic malignancies from the European Conference on Infections in Leukaemia (ECIL), propose limiting the use of dexamethasone to patients with severe and critical disease, while avoiding this treatment in patients with mild-moderate disease.[5] Second, in our study both univariable and multivariable analyses showed that the exclusive use of dexamethasone in COVID-19 therapy affected the risk of clinical failure. As we were conscious of these limitations related to the absence of randomization and its retrospective design, we implemented a propensity score for receiving dexamethasone into the model. Hence, we estimated the effect of dexamethasone accounting for the covariates predicting the treatments received, notably COVID-19 severity, observing the same results. Regarding the differences among treatment groups, most of them were statistically significant when comparing the group treated with dexamethasone only and group treated with antiviral strategies, due to the predominance of patients not requiring hospital admission in the latter group (8.2% *vs.* 40.8%). Nevertheless, when comparing the dexamethasone only and dexamethasone plus antivirals groups, the differences were less significant. To address these differences, we performed various subset analyses. The deleterious role of dexamethasone as monotherapy was 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 was present even during the predominance of the omicron variant of the severe acute respiratory coronavirus 2 (SARS-CoV-2), when most patients had received vaccines, and in the same measure for patients needing to be hospitalized in normal wards or in intensive care units. 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 overuse 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 our Letter, the process of immune-mediated viral clearance is often impaired in high-risk hematologic patients, leading to prolonged viral shedding in up to 25% of patients with hematologic 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 in early stages of infection, antiviral strategies protect hospitalized COVID-19 patients requiring oxygen therapy from progression to severe disease or death.[8,9]

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Disclosures

No conflicts of interest to disclose

Contributions

Both authors wrote, reviewed and approved the replay to the comment.

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