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

We appreciate the work published by Aiello *et al.* in *Haematologica* in which they describe that dexamethasone treatment of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection is associated with increased mortality in patients with hematologic malignancies.[1] Due to the clear association between inflammatory dysregulation and adverse clinical outcomes,[2] international guidelines unanimously recommend the use of corticosteroids in hospitalized patients with acute respiratory failure from coronavirus disease 2019 (COVID-19) to reduce mortality in such patients.[3] Glucocorticoid therapy reduces neutrophil influx, blocks T-cell responses, and reduces the cytokine storm. However, excessive doses can trigger immunosuppression, which can be fatal, especially in an immunosuppressed population.[4] The study by Aiello *et al.* seems to raise an alarm about whether glucocorticoid therapy should be used in patients with hematologic malignancies. Is it true that hematologic malignancy patients do not benefit from glucocorticoid therapy? Here, we highlight some points of the study that deserve attention.

First, although the study by Aiello *et al.* included a large number of patients in multiple centers, due to the retrospective nature of the study and the relatively loose inclusion and exclusion criteria, bias may be unavoidable. Significant differences were observed between the subgroups, including differences in age, comorbidities, status of hematologic malignancy control, vaccination rates, duration of infection, severity of symptoms of the infection, and proportions of admissions to hospital and to Intensive Care Units (ICU). The baseline characteristics of the population given dexamethasone were significantly worse, with lower rates of vaccination, more severe symptoms of infection, and higher rates of hospital admission and ICU admission, which were associated with the risk of death and poor prognosis. In addition, the study was non-randomized and non-interventional, treatment was decided by the attending physician, and based on experience and consensus, glucocorticoid therapy is often used in critically ill patients or those with severe COVID-19, especially in the case of an inflammatory storm.[4] This means that people treated with dexamethasone are already critically ill and have a higher risk of death. Therefore, the causal relationship between dexamethasone and the risk of death in patients needs to be examined carefully.

Second, corticosteroids are commonly used to control inflammation in COVID-19 patients. However, there is debate about the optimal timing, dosage, and duration of corticosteroid therapy. While corticosteroids have anti-inflammatory effects, they also suppress the immune response, potentially hindering pathogen clearance and promoting viral replication. Immunocompromised patients are at risk of persistent COVID-19, which is a persistent symptomatic disease with active viral replication.[5] Studies have shown that nearly 14% of patients with hematologic malignancies and SARS-CoV-2 infection still have detectable SARS-CoV-2 viral RNA for 30 days or more.[6] There is persistent viral replication in the lungs, which is associated with secondary infection and accelerated death.[7] The dosage and duration of dexamethasone use were not described in detail in the study by Aiello *et al.* High doses and long courses of glucocorticoid therapy may be associated with an increased risk of death.[4] High doses and long courses of glucocorticoid therapy inhibit viral clearance, and may lead to high blood sugar, increasing the risk of secondary infections, such as invasive aspergillus.[8] It is, therefore, necessary to identify whether there is persistent SARS-CoV-2 replication in a specific type of immune dysfunction, while carefully considering the dose and timing of corticosteroid use to control inflammation while reducing adverse reactions.

The study by Aiello *et al.* revealed that patients with hematologic malignancies infected with SARS-CoV-2 have a high risk of death, with a 90-day mortality rate of about 20%. Encouragingly, death was significantly reduced with antiviral therapy, whether combined with dexamethasone or not. Treatment options include convalescent plasma, monoclonal antibodies and antiviral drugs, both as monotherapy and in combination therapy. We sincerely hope that the authors will conduct further studies to evaluate the efficacy of several treatments and combinations to provide quality options for these immunocompromised patients. Especially with the emergence of new mutant strains, most monoclonal antibodies may face the possibility of being evaded and ineffective.

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Disclosures

No conflicts of interest to disclose.

Contributions

GZ initiated and conceptualized the idea and wrote the comment.
JL revised the comment.

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