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Commenting on baricitinib versus tocilizumab in mechanically ventilated patients with COVID-19: a nationwide cohort study

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To the editor

We read with great interest the article by You et al., which provides valuable insights into the comparative efficacy of baricitinib and tocilizumab in mechanically ventilated COVID-19 patients [1]. While the study's findings are important, especially regarding the lower 30-day mortality in the baricitinib group, we believe that the issue of confounding by indication was not sufficiently addressed and may have significantly influenced the results.

Confounding by indication occurs when treatment assignment is influenced by disease severity, leading to a bias in outcome comparison between treatment groups. In this study, patients in the tocilizumab group appeared to be more severely ill at baseline compared to those in the baricitinib group. Although the authors employed propensity score matching (PSM) to balance baseline characteristics, the data suggest that the tocilizumab group had a higher severity of illness, which could explain some of the observed differences in mortality. Notably, patients in the tocilizumab group had longer durations of mechanical ventilation prior to drug administration, higher use of extracorporeal membrane oxygenation (ECMO), and more severe comorbidities, as detailed in the supplementary tables. These factors strongly suggest that tocilizumab was more likely administered to patients in critical condition, potentially skewing the mortality comparison in favor of baricitinib.

Furthermore, while PSM is effective at balancing observable variables, it may not fully account for unmeasured or residual confounders, such as the timing of drug administration relative to disease progression or the specific clinical criteria that influenced treatment choices. Baricitinib was administered for a median of 8 days, while tocilizumab was often given as a single dose. This difference in treatment duration and pharmacodynamics could have further impacted the results. Baricitinib, with its broader anti-inflammatory effects and prolonged administration, may have provided a more sustained reduction in inflammation, whereas the single-dose nature of tocilizumab could have limited its efficacy in severely ill patients.

Additionally, the study does not provide sufficient detail regarding the criteria used to determine whether

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a patient received baricitinib or tocilizumab beyond the similar indications in general consideration [2]. Without understanding the clinical decision-making process, it is difficult to evaluate the extent to which confounding by indication may have influenced the results. If tocilizumab was preferentially administered to patients with more rapidly progressing or refractory disease, the higher mortality rate in this group might reflect underlying disease severity rather than a difference in drug efficacy [3].

It may be beneficial to consider a subgroup analysis excluding patients requiring total parenteral nutrition (TPN), as those unable to tolerate enteral nutrition typically represent a more critically ill population with poorer prognostic indicators, such as higher Sequential Organ Failure Assessment (SOFA) scores [4]. These patients are more likely to receive intravenous therapies, including tocilizumab, which is administered as an injection. This could introduce a potential confounder, as the preference for tocilizumab in this critically ill subgroup might reflect the inability to administer oral medications like baricitinib, rather than a direct reflection of the drug's relative efficacy. Consequently, these factors could disproportionately affect mortality rates in the tocilizumab group, further complicating direct efficacy comparisons.

In light of these concerns, we suggest that future studies consider using SOFA or APACHE II scores in PSM to better control for baseline severity differences. If SOFA or APACHE II data are unavailable, matching based on laboratory data associated with SOFA or APACHE II scores at the time of ICU admission or intubation could serve as a proxy for disease severity [5–7]. Incorporating these variables may help mitigate confounding and strengthen the conclusions. Additionally, more detailed time-dependent analyses, such as the duration of mechanical ventilation or timing of drug administration, would clarify the true effects of these therapies in critically ill patients.

Ultimately, randomized controlled trials remain the gold standard to address these concerns, but in the interim, the use of more nuanced statistical matching techniques may help refine comparisons between baricitinib and tocilizumab in this population.

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Declarations

Conflict of interest
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