Making sense of non-randomized comparative treatment studies in times of Covid-19:A case study of tocilizumab

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1 OBJECTIVES

Tocilizumab (TCZ) is an interleukin-6 inhibitor and the second established effective drug for the treatment of hospitalized patients with Covid-19. In this study, we sought to validate the recent positive findings from the randomised clinical trial RECOVERY and to evaluate the challenges in the analysis and interpretation of non-randomized comparative effectiveness studies in Covid-19.

2 METHODS

- We performed a retrospective cohort study using an openly available database of hospitalized Covid-19 patients in Spain
- The primary outcome was all-cause in-hospital mortality at 28 days
- We used multivariable Fine and Gray competing risk models to account for negligible risk of death after discharge, and adjusted for both fixed and time-variant confounders to investigate the effect of TCZ on the primary outcome
- TCZ was modelled as a time-updated covariate to account for immortal time bias from hospital admission to TCZ administration

3 RESULTS

Of 2547 patients admitted to hospital with a diagnosis of COVID-19, 440 received at least one dose of TCZ. Compared to the control group, patients receiving TCZ were younger (mean age 66.5 vs 68.2 years) and had more severe Covid-19 in terms of markers of disease severity such as AST, CRP, D-dimer and LDH.
Patients were followed up for a median time of 7 days (IQR 4-11) and the median time to TCZ administration from hospital admission was 3 days (IQR 1-4).
The proportion of deaths at 28 days follow-up was higher in the TCZ group, 91 patients of whom died (20.7%) compared to the control group, of which 267 patients died (12.7%).
In the unadjusted analysis, TCZ was associated with a higher risk of mortality (sHR 2.35, 95% CI 1.86 to 2.98, P<0.001). After adjustment for fixed confounders this effect decreased (sHR 1.92, 95% CI (1.42, 2.60), p<0.001) and after adjustment for time-variant and -invariant confounding the effect of TCZ was no longer statistically significant (sHR 1.20, 95% CI 0.86 to 1.64, P=0.26).

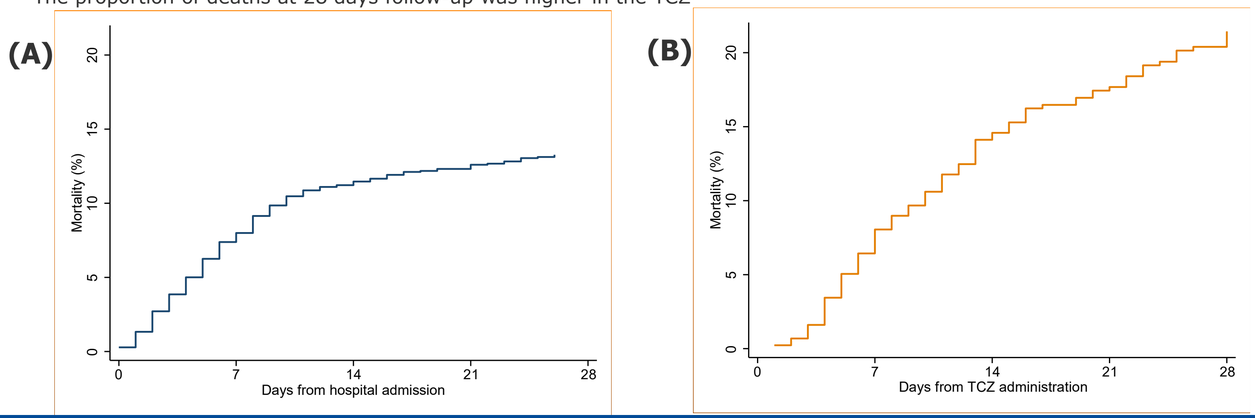

Figure 1. Cumulative incidence of mortality (A) from time of hospital admission in patients not treated with tocilizumab or up to the point of treatment and (B) from time of tocilizumab administration in 440 patients treated with tocilizumab

- Predictors of 28-day mortality in hospitalized Covid-19 patients included older age, being male, chronic heart failure, ischemic heart disease, pulmonary disorder, cancer, peripheral vascular disease, low saturated oxygen, ALT, platelet count and lymphocytes and high AST, CRP, LDH, urea, glucose, WBC and sodium levels and steroid use at admission (**Figure 2**).
- All were adjusted for in the multivariable analysis. Time-variant confounders were saturated oxygen, heart rate, ALT, AST, platelet count, CRP LDH, urea, glucose WBC lymphocytes, monocytes, sodium and steroid use. All other confounders were at admission only.
- **Figure 3** shows the impact of different types of adjustments on the estimate of the effect of TCZ on 28-day mortality. The unadjusted analysis suggested a detrimental effect, as did adjusting for time-invariant confounders but with a smaller effect.
- None of the estimates reflected the conclusions of treatment efficacy in RECOVERY or of the positive findings in other studies as reported in the most recent meta-analysis of TCZ. However, the 95% CI of our main analysis overlapped with that from RECOVERY.

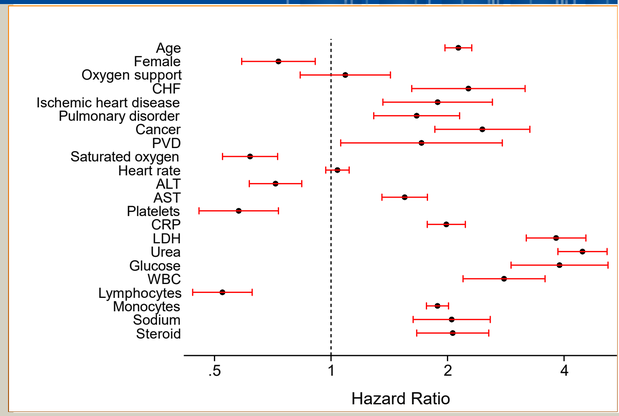

Figure 2. Univariable associations between patient characteristics at admission and 28-day mortality

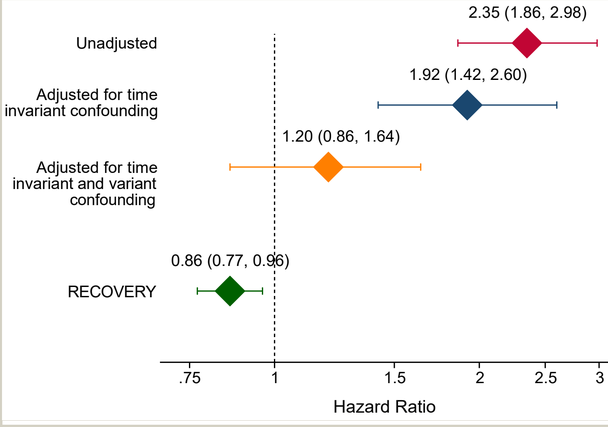

Figure 3. Hazard ratios comparing 28-day mortality in patients taking TCZ vs no TCZ estimated using different methods

4 CONCLUSIONS

Our observational study failed to find a benefit of tocilizumab on all-cause in-hospital mortality in Covid-19 patients compared with randomized trials, highlighting the impact that unmeasured confounding and other sources of bias can have in a retrospective observational setting. For future observational studies, we recommend prospective data collection to ensure all variables have the necessary quality, completeness and timing for reliable treatment evaluation.