The misleading "pooled effect estimate" of crude data from observational studies at critical risk of bias: The case of Tocilizumab in COVID-19

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Dear Editor,

I read with interest the study by Malgie et al. [1]. Although multiple well-designed observational studies and early press-release data from randomized trials (EMPACTA and CORIMUNO-TOCI) suggest that tocilizumab use is associated with better outcomes in COVID-19 patients, the meta-analysis conducted by Malgie et al. [1] has major flaws that threaten its data validity and conclusions. It is incumbent on scientists and journals to make readers aware of these flaws, particularly during this pandemic where there has been a massive output of observational studies and a paucity of randomized trials [2].

First, Malgie et al. [1] inappropriately pooled crude unadjusted data to estimate an overall effect estimate of Tocilizumab association with different outcomes of COVD-19 and used this pooled estimate to calculate what is, very likely, an inflated number needed to treat. Observational studies are prone to multiple biases, including treatment selection bias and confounding. Including crude data in a meta-analysis has been strongly discouraged by the Cochrane group [3] (Table).

Second, Malgie et al. [1] inappropriately included in their meta-analysis studies at critical risk of bias [4] (Table). Moreover, the authors mistakenly over-score the quality of included studies on, at least, 2 important items of the MINORS scale. They scored 2 items as (reported and adequate) for all 10 studies: 1) baseline equivalence of groups: 2 for all 10 studies, and 2) adequate statistical analysis: 2 for all 10 studies. However, only three [5-7] out of ten studies should score 4/4 while the other seven studies should score 0/4. These same three studies are the only studies at (moderate risk of bias) as per the Cochrane ROBINS-I scale, while the other seven studies are at (critical risk of bias) and therefore should not have been included in the meta-analysis.

Third, Malgie et al. [1] did not address the potential impact of “immortal time bias” or “survivor bias”, which occurs because patients who live longer are more likely to receive treatment than those who die early [8]. Immortal time, in observational studies, refers to the period between the time point when patients enter the study cohort and the point when they receive the examined treatment (tocilizumab). During this period between admission and treatment initiation, death cannot occur in the treatment group because those patients must, by design, survive long enough to receive treatment. In other words, the patients who survive to receive treatment are considered “immortal” between admission and treatment. Not accounting for this immortal time in the design or analysis of observational studies leads to inflated treatments’ effect estimates. Based on data from at

least 1 study in COVID-19 [9] and multiple influenza studies [10], relative risk for mortality increased by up to 60% when treatment (such as steroids) was considered as a time-dependent variable in Cox regression analysis [9]. Among the 10 included studies by Malgie et al., only one [5] has adjusted for this immortal bias.

In conclusion, although systematic reviews are needed to critically appraise and summarize the cumulative evidence, they can misinform readers if they do not follow rigorous standards of conduct and reporting.

Conflict of Interest: None

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Table. Selected Recommendations from Cochrane Handbook for Systematic Reviews of Interventions *

Recommendation	Rationale/explanation
Unlike for randomized trials, it will usually be appropriate to analyze adjusted, rather than unadjusted, effect estimates (i.e. analyses should be selected that attempt to control for confounding).	To minimize the important effect confounding that affect the validity of observational studies
Review authors may have to choose between alternative adjusted estimates reported for one study and should choose the one that minimizes the risk of bias due to confounding.	Adjusted effect estimates obtained from conventional regressions analyses (logistic regression, Cox regression) or those obtained for example from propensity score (PS) matched cohorts or PS score adjusted models.
Review authors should exclude from analysis any non-randomized study of intervention (NRSI) judged to be at critical risk of bias and may choose to include only studies that are at moderate or low risk of bias, specifying this choice a priori in the review protocol.	Using ROBINS-I quality assessment, authors should describe a 'target trial', which is a hypothetical pragmatic randomized trial of the interventions compared in the study, conducted on the same participant group and without features putting it at risk of bias. Assessment of risk of bias in a non-randomized study should address pre-intervention, at-intervention, and post-intervention features of the study. Studies are then classified for overall risk of bias, as 'Low', 'Moderate', 'Serious' or 'Critical' risk of bias.

* *Cochrane Handbook for Systematic Reviews of Interventions* version 6.1 (updated September 2020). Cochrane, 2020. Available from www.training.cochrane.org/handbook.