Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Estimating the effectiveness of remdesivir on risk of COVID-19 mortality: The role of observational data

Dear Editor,

A significant effect of remdesivir in reducing COVID-19 mortality is still claimed in several observational studies [1,2]. To provide a rational to conduct these studies, the authors usually do not take into consideration the evidence of meta-analysis of RCTs, presume *a priori* unreliable estimates of remdesivir treatment effect on COVID-19 mortality and do not apply a solid methodological approach which is mandatory when we look at comparing the effect estimates from randomized trials and observational studies [3].

In a recent study by Marrone et al. [2] the authors assumed an *a priori* 3% probability of death in COVID-19 hospitalized patients treated with dexamethasone *plus* remdesivir and 17% in dexamethasone alone. Nevertheless, at the time of study conduction, the only universally accepted treatment for COVID-19 hospitalized patients (dexamethasone) showed a far below estimate of treatment effect on mortality (rate ratio, 0.82; 95%CI, 0.72–0.94) [4]. It is worth mentioning that in the same study up to 65.9% of patients in the remdesivir *plus* dexamethasone group received high flow oxygen supplementary therapy at remdesivir start. In fact, if on the one hand in case of non-severe illness the World Health Organization recently released a conditional recommendation suggesting the treatment with remdesivir, on the other in case of severe or critical illness it is still not known whether remdesivir provides any protective effect against death [5].

In another large observational study estimating the effect of remdesivir on COVID-19 intra-hospital mortality, in which the authors compared the outcome of 28,855 remdesivir exposed patients with 16,687 remdesivir unexposed patients, the authors found that remdesivir exposure was associated with a significant reduction in mortality at 28 days [Hazard Ration 0.89 (0.82–0.96)] [1]. In this study, the main approach used to control for measured confounding by using propensity score matching followed by a standard Cox regression model which further controls for other factors at the analysis stage is unusual. Only a marginal Cox regression analysis can replicate the counterfactual of a randomised comparison in which everybody received remdesivir *vs.*, counter to the fact, everybody received standard of care. In addition, the authors could have evaluated also the impact of one or more potential unmeasured confounders hypothesised to have similar association with the intervention and the risk of outcome to one of the main predictors in the analysis (e.g. the use of corticosteroids or convalescent plasma) by calculating an e-value [6]. In the same manuscript the authors concluded that their data "complement ACTT-1 [7] and support remdesivir as a foundational treatment for hospitalized COVID-19 patients" suggesting a conceptual replication of the ACTT-1, a sentence that is not actually supported by the applied methodology [3].

In conclusion, the contribution of observational studies to assess the effectiveness of treatment for COVID-19 could be significant only if a rigorous methodology to emulate a hypothetical RCT, which represent nowadays the standard for this type of analyses, is applied.

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A.G and A.C.L. conceived the manuscript. G.C., A.L.R., L.O. and S.A. critically revised the initial draft and contributed to preparation of the article.

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