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Comment on: Effectiveness of remdesivir in patients with COVID-19 under mechanical ventilation in an Italian ICU

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Sir,

We read with great interest the paper by Pasquini *et al.*[1] supporting the effectiveness of remdesivir in improving the survival of critically ill patients with COVID-19. However, we think that the results obtained by the authors need to be interpreted cautiously because of their possible serious biases.

The study included 51 patients of whom 25 received remdesivir a median of 7 days (IQR = 4–8 days) after ICU admission (the treatment group) and 26 who did not receive the drug (the control group). We wonder how many of the critically ill patients in the treatment group died before starting remdesivir and how they were considered in the analysis.

The possibility that a critical patient assigned to an experimental treatment may die pending the availability of the drug is not to be overlooked. In our clinical centre, which (to the best of our knowledge) was the first Italian centre to have access to the compassionate use of remdesivir,[2] 69 ICU patients were considered eligible for the treatment between 23 February and 20 March 2020, but 9 (13%) did not actually start the drug because a rapid and severe deterioration in their general condition led to their deaths.

If the patients who died within the 4–8 days before remdesivir became available in the study by Pasquini *et al.*[1] were included in the control group, an immortal time bias may have affected the final results and given a spurious survival advantage to the treated group.

Immortal time bias can arise when the period between cohort entry and the date of first exposure to a drug is not accounted for in the analysis.[3,4] In this specific case, the selection of the treated and untreated groups was based on an event (treatment with remdesivir) that followed the participants' study entry (time zero: ICU admission). This time lag is called 'immortal' because the subjects who end up in the treatment group have to be alive until the start of treatment, otherwise they would fall into the untreated group, and this could distort the observed effects and generate an illusion of treatment effectiveness.

Immortal time bias can be prevented by aligning assignment to the treatment or non-treatment groups with time zero. If this cannot be done, time-dependent analyses can be used to reduce the impact of the bias.[5]

Furthermore, we think it is questionable to exclude the SOFA score from variables included in the multivariate analysis of factors associated with mortality because there was a significant between-group difference in the score at the time of admission and it is well known that this clinical parameter provides valuable prognostic information in the case of patients admitted to an ICU.

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Transparency declarations

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