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Letter to the Editor

Harm of early dexamethasone for COVID-19 and bias in randomized trials

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Dear Editor,

Numerous unproven therapies for coronavirus disease 2019 (COVID-19) were adopted early on based on inadequate evidence [1]. The Randomized Evaluation of COVID-19 Therapy (RECOVERY) is a large simple trial designed to quickly evaluate treatments for hospitalised patients [2]. RECOVERY reported increased survival with dexamethasone, particularly among patients that required supplemental oxygen [2]. Patients with invasive mechanical ventilation (IMV) at randomization who received dexamethasone had a 28-day rate ratio (RR) for mortality of 0.64 (95%CI, 0.51–0.81), while those receiving supplementary oxygen with a non-invasive device had a RR of 0.82 (95%CI, 0.72–0.94). Conversely, patients without hypoxemia had a slightly higher risk of death, with a RR of 1.19 (95%CI, 0.92–1.55). Dexamethasone became standard care for every hospitalized patient who required supplementary oxygen [2,3]. This mortality benefit was uncertain for people who had been symptomatic for seven days or less, with a RR of 1.01 (95%CI, 0.87−1.17). Also, a marginal increase in RR for IMV (1.09, 95%CI 0.97−1.23) was reported in this subgroup. Several articles have argued early dexamethasone could prolong the viral replication phase and cause harm [3–7]. While unopposed viral replication makes biological sense, the possibility of finding this hazard due to confounding has not been evaluated. Let us use directed acyclic graphs (DAGs) to elucidate this [8].

Directed acyclic graph (DAG) of the recovery trial

Fig. 1 shows two versions of the causal model evaluated in the RECOVERY trial. Fig. 1A displays that 'Time with symptoms' is a cause of 'Viral load', which in this case will act as a modifier of the effect 'Dexamethasone' has on 'IMV'. Given the analysis referred to is stratified by 'Time with symptoms' (less than or equal or more than 7 days), we are effectively conditioning on 'Time with symptoms', which closes one backdoor path (or confounding path) that goes from 'IMV' through 'Viral load', 'Time with symptoms', 'Factors affecting disease severity', and ends in 'Disease severity (hypoxemia) at baseline'. However, no data on the distribution of important prognostic variables (like that included in Table 1 of the main analysis) is provided for this subgroup. That is, we do not know if random confounding due to uneven distribution of prognostic variables (and viral load at baseline) occurs. Additionally, by considering the outcome of 'IMV', one is effectively excluding every patient that had that degree of ventilatory support at randomization, which was the group with the most benefit in survival. The main analysis showed a longer time with symptoms at randomization among those receiving supplementary oxygen (median of 6 days for those with no oxygen requirement, 9 days for those with non-invasive supply, and 13 days for those with IMV). Consequently, this apparent harm likely reflects the lack of benefit among those with no hypoxemia.

Fig. 1B shows a DAG according to the subgroup analysis stratified by degree of supplementary oxygen requirement (or hypoxemia) and the outcome of 'IMV'. In their supplementary appendix, time with symptoms in the dexamethasone group and placebo groups while stratifying by degree of supplementary oxygen required are very similar (median of 6 vs 7 days in those with no supplementary oxygen requirement, 8 vs 9 days in those with non-invasive oxygen requirement, and 13 vs 13 days in those with IMV). Thus, this balance effectively controls for 'Time with symptoms'. Additionally, 'Factors affecting disease severity', such as age and comorbidities, are well balanced. Thus, there is likely no random confounding in the analysis stratified by degree of supplementary oxygen requirement, which allows for an adequate estimation of the effect dexamethasone has on IMV.

Importantly, the trial does not include information on viral load [2]. Thus, the hypothesis of dexamethasone increasing viral load is not testable in this study. This is elegantly acknowledged by the RECOVERY investigators. However, articles arguing against use of early dexamethasone also do not have data on viral load nor appropriate designs to address this question, yet most cite the RECOVERY trial in favor of their argument [4–7]. Accounting only for time with symptoms and dexamethasone, as proposed in the causal diagram shown in Fig. 1A, is inadequate. Proposing a biological explanation of a study finding is only adequate when a causal model has been built and confounding has been accounted for. For example, a study that specifically evaluated viral kinetics in patients that received corticosteroids found no change in viral clearance among those that received them [9]. Moreover, a meta-analysis of randomized trials of steroids (which included RECOVERY) for critically ill patients with COVID-19 showed benefit of the

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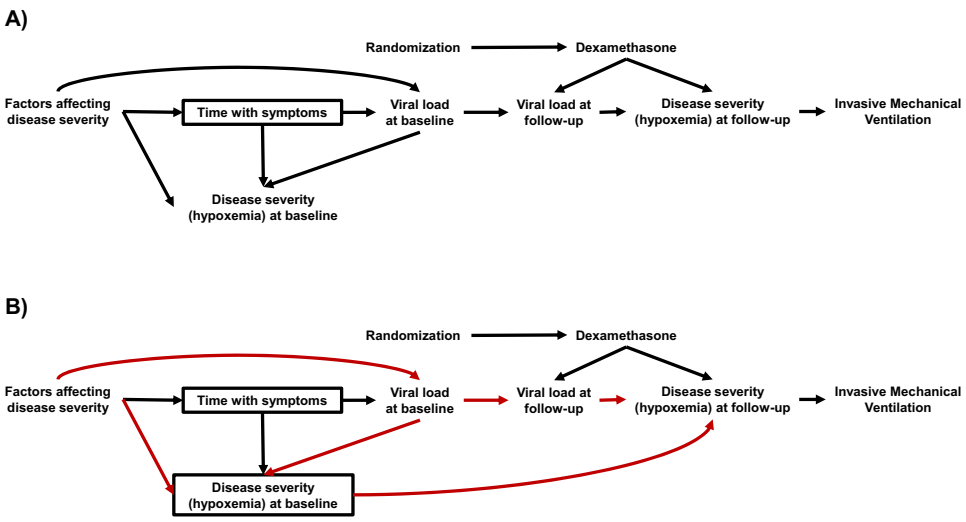

Fig. 1. A) Causal diagram when stratifying the analysis by 'Time with symptoms'. B) Causal diagram when stratifying the analysis by 'Disease severity (hypoxemia)'. Biasing paths are shown in red.

treatment regardless of time with symptoms [10]. These studies disagree with the hypothesis of dexamethasone promoting viral replication in those treated during their first week of symptoms, as one would expect patients to do worse when treated early.

In conclusion, dexamethasone should not be delayed in patients that are hypoxemic during their first week of symptoms, which is akin to waiting for respiratory failure and IMV, as the biggest benefit was seen in this population. Arbitrary subgroup selection in randomized trials may lead to biased estimates such as in this example.

Declaration of Competing Interest

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Access to data

Not applicable.

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