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Treating COVID-19 with NRICM101 and NRICM102 – Author's reply 2

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In their Correspondence to the editor, Chang, Sun and Hung raise several concerns, including clustering effects, statistical approach, effects of co-medication, and drug safety. In this response we focus on the most notable one regarding the use of frailty model, while the rest of the issues are addressed in other replies.

Regarding the clustering effects, it is worthwhile to explain to Chang and colleagues and a wider audience who may not have a clear picture about the epidemic response in Taiwan. COVID-19 treatment in Taiwan is provided in healthcare facilities designated by Taiwan Centers for Disease Control (CDC), strictly following the protocol stipulated in the “Interim Clinical Guidance for Management of Patients with Confirmed 2019 Novel Coronavirus (2019-nCoV) Infection” and administration of TCM solely depends on the “Traditional Chinese Medicine Clinical Guideline for COVID-19” [1] issued by the Ministry of Health and Welfare. Difference in care between hospitals seems unlikely in this context. So in our opinion, the clustering effect may be negligible.

Nevertheless, we agree that theoretically, there might be a potential for correlation of outcomes among patients admitted to the same hospital. However, Cox model with frailty does not fit our data because frailty models are random effects models for time-dependent variables. In our study, independent variables such as demographic characteristics, comorbidity, disease severity, medication, etc. have been matched, and time course of disease progression is rather short. So to deal with both measured and unmeasured confounders, we followed the advice of one of the reviewers to adopt marginal Cox regression analysis after propensity score matching, which is an established practice to keep bias to a minimum [2].

Minor issues in the Correspondence such as exclusion criteria/rationale, dose/duration of TCM treatment and drug safety are discussed or disclosed in the Article and supplementary files [1]. Thus we encourage interested readers to revisit the article and at the same time welcome further dialogues.

Declarations of interest

None.

Data availability

No data was used for the research described in the article.

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