Response to: 'Concerns about 'Long-term cardiovascular outcomes in COVID-19 survivors among non-vaccinated population: A retrospective cohort study from the TriNetX US collaborative networks' by Renin Chang *et al*

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We would like to thank Renin Chang and his collegues for the interest they have expressed in our recently published article 'Long-term cardiovascular outcomes in COVID-19 survivors among non-vaccinated population: A retrospective cohort study from the TriNetX US collaborative networks'[1] and the eClinicalMedicine editorial team to give us the opportunity to address their comments.

First, Renin Chang et al. concerned about the Neyman bias on the exclusion of patients who died within 30 days of the index date. In the present study, we conducted a 12-month follow-up study of the cohort who survived the first 30 day on the risk of cardiovascular events as well as the survival analyses. 30 days were used as the stratification and at least two visits to healthcare organizations could reduce the bias of loss of follow up and avoid reverse causality. In addition, as suggested by Renin Chang et al., we have performed a sensitivity analysis from the first day after the first occurrence of the index event. The results revealed that the risks of the cardiovascular outcomes and two composite endpoints, major adverse cardiovascular event (HR [95% CI] = 1.702 [1.667–1.738]) and any cardiovascular outcome (HR [95% CI] = 1.514 [1.496–1.533]) were similar with the risks beyond the first 30 d of infection. However, the mortality risks (HR [95% CI] = 2.691 [2.601–2.784]) were inevitably higher than former one (Figure 1, Table 1).

Renin Chang et al. also suggested a self-matched study design. In our cohort, propensity score matching 1:1 by age at index, race, gender, socioeconomic status (SES), comorbidities, blood type, alcohol-related disorders, nicotine dependence, and body mass index (BMI) was used. Furthermore, it was well matched (Std diff <0.1). Propensity score matching has been used increasingly in retrospective analyses of clinical trial data sets, registries, observational studies, electronic medical record analyses, and more. Although the method has some limits, it attempts to adjust post hoc for recognized unbalanced factors at baseline.[2]

Renin Chang et al. also refer to inaccuracies of ICD-10 on the diagnosis of the cardiovascular outcomes. We can only agree with this remark as we have noted in our article. There were a lot of population-based studies on the consequences of COVID-19 including cardiovascular outcomes by using ICD-10 as the diagnosis.[3-5] Moreover,most of the cardiovascular diseases were diagnosed according to a comprehensive judgment of clinical manifestations, electrocardiogram and laboratory examinations. In addition, myocarditis that represents a category of diseases need cardiac MRI and endomyocardial biopsy to identify.[6] Thus, ICD10 maybe the proper one at present.

Contributors

W.J.-W. wrote the draft of the manuscript; S.I.-W. have performed data analysis; James Cheng-Chung Wei revised the manuscript critically. All authors

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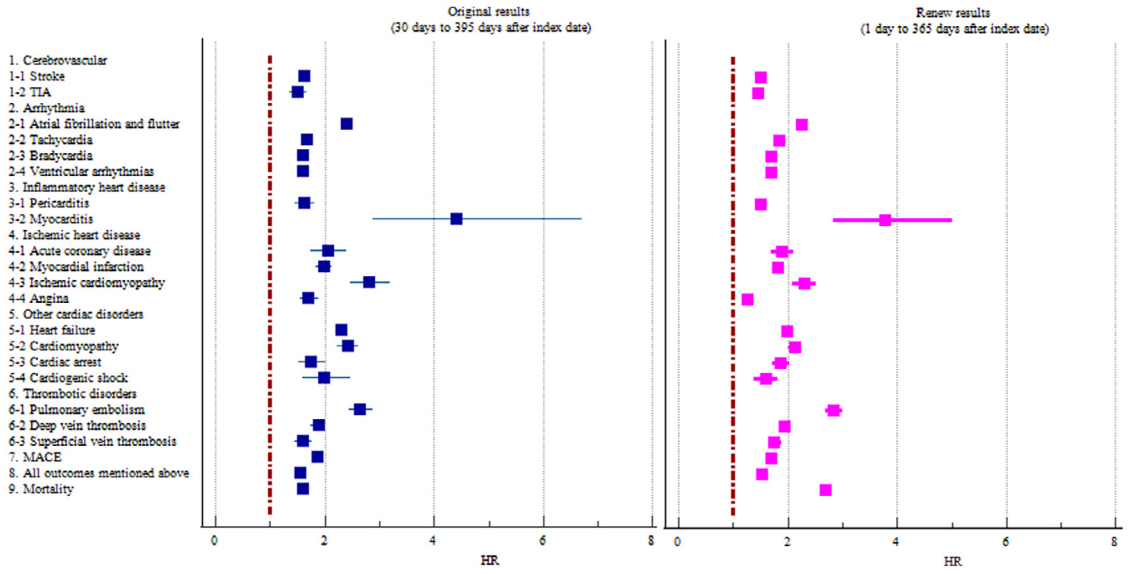

Figure 1. Incidence of outcomes among COVID-19 group compared to control subjects (after prosperity score matching).

Outcome	Hazard ratio (95%CI)	
	Original results[a]	Renew results[b]
Cerebrovascular		
Stroke	**1.618 (1.545−1.694)**	**1.496 (1.446−1.548)***
TIA	**1.503 (1.353−1.670)**	**1.451 (1.344−1.567)**
Arrhythmia		
Atrial fibrillation and flutter	**2.407 (2.296−2.523)**	**2.245 (2.171−2.321)***
Tachycardia	**1.682 (1.626−1.740)**	**1.840 (1.797−1.885)***
Bradycardia	**1.599 (1.521−1.681)**	**1.685 (1.628−1.745)***
Ventricular arrhythmias	**1.600 (1.535−1.668)**	**1.698 (1.649−1.748)***
Inflammatory heart disease		
Pericarditis	**1.621 (1.452−1.810)**	**1.512 (1.401−1.632)**
Myocarditis	**4.406 (2.890−6.716)**	**3.767 (2.835−5.007)**
Ischemic heart disease		
Acute coronary disease	**2.048 (1.752−2.393)**	**1.890 (1.702−2.098)**
Myocardial infarction	**1.979 (1.831−2.138)**	**1.825 (1.735−1.921)***
Ischemic cardiomyopathy	**2.811 (2.477−3.190)**	**2.289 (2.087−2.509)**
Angina	**1.707 (1.545−1.885)**	**1.268 (1.180−1.363)***
Other cardiac disorders		
Heart failure	**2.296 (2.200−2.396)**	**1.993 (1.934−2.054)***
Cardiomyopathy	**2.413 (2.235−2.606)**	**2.119 (2.005−2.241)***
Cardiac arrest	**1.751 (1.526−2.008)**	**1.864 (1.714−2.026)***
Cardiogenic shock	**1.988 (1.599−2.473)**	**1.594 (1.391−1.826)**
Thrombotic disorders		
Pulmonary embolism	**2.648 (2.443−2.870)**	**2.842 (2.683−3.010)***
Deep vein thrombosis	**1.879 (1.751−2.017)**	**1.949 (1.855−2.047)***
Superficial vein thrombosis	**1.592 (1.442−1.756)**	**1.753 (1.635−1.880)***
MACE	**1.871 (1.816−1.927)**	**1.702 (1.667−1.738)***
Any cardiac outcome mentioned above	**1.552 (1.526−1.578)**	**1.514 (1.496−1.533)***
Mortality	**1.604 (1.510−1.703)**	**2.691 (2.601−2.784)***

***Table 1*: Incidence of outcomes among COVID-19 group compared to control subjects (after prosperity score matching).**

Note. TIA: Transient Ischemic Attack; MACE: Major Adverse Cardiac Event.

*Proportionality ($P < 0.001$).

[a] Time window was started 30 days after the first occurrence of the index event and ended 395 days after the first occurrence of the index event.

[b] Time window was started 1 days after the first occurrence of the index event and ended 365 days after the first occurrence of the index event.

contributed to manuscript revision, read and approved the submitted version.

Declaration of interests

The authors declare no competing interests.

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