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Letter to the Editor

The association between severe or dead COVID-19 and autoimmune diseases: A systematic review and meta-analysis [☆]



Dear Editor,

Recently, Chen Tao (Doctor) and colleagues published a retrospective study, and delineated the clinical characteristics of patients with coronavirus disease 2019 (COVID-19) who died¹. They found that chronic hypertension and other cardiovascular comorbidities were more frequent among deceased patients than recovered patients¹. And there was no difference in the prevalence of the autoimmune disease between the two group patients¹. We appreciate this discovery, however, the conclusion of their study drew from a retrospective study, and the number of patients is only 113. Higher levels of evidence are needed to evaluate the association between severe or death COVID-19 and autoimmune disease. Therefore, we conducted the present systematic review and meta-analysis.

Studies published up to 8 May 2020 were searched through PubMed, Embase.com, Web of Science and Cochrane Library. The published language was not restricted. Keywords included “COVID-19”, “coronavirus disease-19”, “new coronavirus”, “2019-nCoV”, “novel corona virus”, “novel coronavirus”, “nCoV-2019”, “2019 novel coronavirus”, “coronavirus disease 2019”, “SARS-CoV-2”, “severe acute respiratory syndrome coronavirus 2”, “autoimmune disease”, “clinical characteristic”, “clinical feature”, “risk factor”, and “comorbidities”. In addition, we searched the reference lists of eligible studies and relevant reviews to find potentially eligible studies (See search strategy of PubMed in Appendix Table 1).

Study inclusion criteria: (1) patient was diagnosed as COVID-19 by the laboratory test; (2) provided data of autoimmune disease with severe or non-severe patients or between death and survivors. Study exclusion criteria: (1) studies did not provide the prevalence of autoimmune disease; (2) studies without comparisons (severe versus non-severe patients, death versus survival); (3) studies sample size is less than 10 patients; (4) abstracts, news, comments, editorials and review articles. According to the published studies², the severity of disease was defined mainly on the basis of the symptoms present at diagnosis (e.g. patients with pulse oxygen saturation (SpO₂) less than 90%, or need of intensive care unit (ICU) care, or with acute respiratory distress syndrome).

Study selection and data extraction were independently conducted by two reviewers. Disagreements were resolved by consensus or by a third investigator. We extracted the following data: first author, year of publication, country of the corresponding author, publication language, recruitment time frame, age and sex of

patients, sample size, number of participants in severe (or death) and non-severe (or survival) disease groups, and outcomes of interest. The primary outcome was the association between autoimmune disease and risk of severe disease in patients with COVID-19. The secondary outcome was the association between autoimmune disease and risk of mortality in COVID-19 patients.

Review Manager 5.3 (Nordic Cochrane Centre, Copenhagen, Denmark) was used to estimate pooled odds risk (OR) and its 95% confidence interval (CI) for dichotomous outcomes using the Mantel-Haenszel statistical method with the random-effects model. We used the I² statistic to assess the heterogeneity, value of <25%, 26–50%, and >50% considered as low, moderate, and high degrees of heterogeneity, respectively. Subgroup analysis was conducted for the secondary outcome between different countries. In addition, we also conducted sensitivity analysis by excluding studies published in Chinese to assess the stability of the results.

A total of 2472 records were obtained through systematic electronic searches and other ways. After screening titles, abstracts, and full texts, 6 studies^{1,3–7} were included for analysis (See flowchart in Appendix Fig. 1). All studies were published in 2020, incorporated a total of 2091 patients (1192 males, 57.01%). The sample size of patients per study ranged from 109 to 1000. Only one study from USA⁷, five studies from China^{1,3–6}. One study published in Chinese⁴, and five studies published in English^{1,3,5–7}. See detail in Table 1. The range of quality scores was 5 to 8, with a median of 7 (7.17±1.17) (Appendix Table 2).

The meta analysis showed that autoimmune disease was associated with a 1.21-fold increased risk of severe COVID-19 disease (3 studies^{3,5,7}, 1276 patients; OR=1.21, 95%CI: 0.58 to 2.50, *P*=0.79; I²=0%) (Fig. 1A). We found that autoimmune disease was associated with a 1.31-fold increased risk of mortality in patients with COVID-19 (3 studies^{1,4,6}, 835 patients; OR=1.31, 95%CI: 0.33 to 5.20, *P*=0.95; I²=0%) (Fig. 1B). Although these two analysis results are not statistically significant (*P*>0.05). The subgroup analysis based on countries indicated no significant association between autoimmune disease and risk of mortality in patients with COVID-19 from China (2 studies^{1,6}, 651 patients; OR=1.11, 95%CI: 0.20 to 6.27, *P*=0.94; I²=0%).

COVID-19 is an acute inflammatory infectious disease. It is now generally accepted that the occurrence of autoimmune diseases is related to autoinflammatory⁸. Over the course of the COVID-19 pandemic, Zachary SW and colleagues proposed three key reasons that COVID-19 may affect patients with autoimmune diseases⁹. Understanding how COVID-19 is associated with rheumatic diseases is imperative for rheumatology health professionals and people living with rheumatic diseases. Our study showed that autoimmune disease was slightly associated with increased risk of severity and mortality of COVID-19 through meta-analysis, but the statistical difference was not significant. In terms of treatment and prognosis, COVID-19 patients combined with autoimmune diseases may

[☆] **Key message:** Autoimmune disease was slightly associated with increased risk of severity and mortality of COVID-19 disease.

Table 1
Characteristics of included studies.

Study	Country	Language	Age.year ^a	Sex		Severe		Non-severe		Death		Survival	
				Male	Female	Events	Total	Events	Total	Events	Total	Events	Total
Wei YY ³	China	English	42.3±15.3	95	72	0	30	2	137				
Wang L(1) ⁴	China	Chinese	63.0(51.0–70.0)	88	114					1	33	3	169
Du RH ⁵	China	English	70.7±10.9	74	35	1	51	0	58				
Wang L(2) ⁶	China	English	69.0 (65.0–76.0)	168	171					1	65	4	274
Chen T ¹	China	English	62.0 (44.0–70.0)	171	103					1	113	1	161
Argenziano MG ⁷	USA	English	63.0(50.0–75.0)	596	404	9	231	26	769				

^a Age data presented as median (IQR) or mean ±SD.

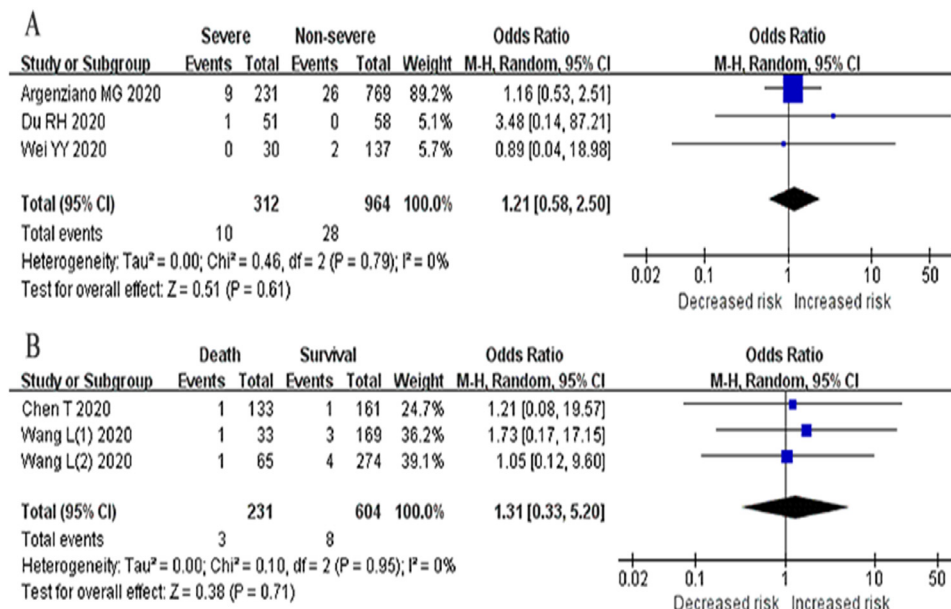


Fig. 1. Association between autoimmune disease and COVID-19 disease (A: Severe versus Non-severe patients; B: Death versus Survival).

not need special attention. Nevertheless, we cannot let our guard down. Because our study was limited by small sample size, and five included studies are from China, the results should be interpreted with caution. In addition, researchers should also pay more attention to the impact of the types of autoimmune diseases and drugs on treatment and prognosis.

In conclusion, we should not relax our focus on the COVID-19 patients with autoimmune diseases. More high-quality studies from different regions are needed to better understand the association between COVID-19 disease and autoimmune diseases.

Declaration of Competing interest

The authors declare that they have no competing interests.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi: [10.1016/j.jinf.2020.05.065](https://doi.org/10.1016/j.jinf.2020.05.065).

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