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Letter to the Editor

## Autoimmune diseases are independently associated with COVID-19 severity: Evidence based on adjusted effect estimates

There have been several published articles reporting the association between autoimmune diseases and the risk of severity among patients with coronavirus disease 2019 (COVID-19). But the conclusions across studies are inconsistent.[1–6] Recently, Liu et al. performed a meta-analysis based on six studies with 2091 cases published in Journal of Infection to investigate the association between autoimmune diseases and severe or dead COVID-19.[7] Their results demonstrated that autoimmune diseases were not significantly associated with severe or dead COVID-19 (odds ratio (OR) = 1.21, 95% confidence interval (CI): 0.58–2.50 for severity and OR = 1.31, 95% CI: 0.33–5.20 for mortality).[7] This is an extremely interesting paper. However, the number of included studies and sample sizes are limited. Up to now, several papers with large sample sizes on this topic are emerging. Therefore, it is required to clarify the association between autoimmune diseases and COVID-19 severity based on updated data.

To our knowledge, several factors such as age, gender and underlying disorders (hypertension, diabetes, chronic obstructive pulmonary disease, cerebrovascular disease, cardiovascular disease, chronic kidney disease and obesity, etc.) significantly affected the clinical outcomes of COVID-19. This suggests that these risk factors might modulate the association of autoimmune diseases with COVID-19 severity. To obtain a precise conclusion, this meta-analysis was carried out based on published studies reporting adjusted effect estimates, rather than those reporting un-adjusted effect estimates.

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement. International databases of PubMed, Web of Science and EMBASE were searched to identify potential studies up to December 12, 2020. The following keywords were used: “coronavirus disease 2019″, “COVID-19″, “SARS-CoV-2″, “autoimmune diseases”, “rheumatic diseases”, “inflammatory bowel disease”, “psoriasis” and “systemic lupus erythematosus”. Only peer-reviewed articles published in English reporting adjusted effect estimates on the association between autoimmune diseases and COVID-19 severity (severe, critical and mortal outcomes) were eligibly included. Repeated articles, case reports, reviews, comments, protocols, errata, and articles without sufficient information were excluded.

Data were extracted by two independent authors (Jie Xu and Haiyan Yang) from each included study. Questions or disagreements were resolved by discussion or consultation with a third author (Yadong Wang). Baseline information extracted from the included literature includes author name, location, sample sizes, number of autoimmune diseases, types of autoimmune diseases, age, gender distribution, study design, adjusted effect estimates, adjusted risk factors and disease outcomes. All statistical analyses were conducted using Stata 12.1 software. Heterogeneity was tested using $I^2$ statistic. The pooled effects with 95% CI were estimated. Publication bias was examined by Begg’s test and Egger’s test. Sensitivity analysis was performed to assess the stability of results. The level of significance was set at $P < 0.05$.

A total of thirteen studies[1–6,8–14] reporting 58,183 laboratory-confirmed COVID-19 patients were included. The main characteristics of the selected studies are demonstrated in Table 1. Our meta-analysis based on adjusted effect estimates revealed that COVID-19 patients with autoimmune diseases had a significantly increased risk of severity compared to those without autoimmune diseases (pooled effect = 1.19, 95% CI: 1.05–1.35) (Fig. 1A). Sensitivity analysis exhibited that our results were stable and robust (Fig. 1B). Publication bias was observed in Egger’s test ($P = 0.017$), but not in Begg’s test ($P = 0.127$, Fig. 1C). Subgroup analysis by location revealed that co-existing autoimmune diseases were significantly associated with an elevated risk of COVID-19 severity among USA population (pooled effect = 1.36, 95% CI: 1.02–1.81). This significant association was also observed in studies with mean age < 65 years old (pooled effect = 1.29, 95% CI: 1.04–1.60), studies with proportion of male ≥ 50% (pooled effect = 1.31, 95% CI: 1.06–1.62) and OR-reported studies (pooled effect = 1.21, 95% CI: 1.04–1.41).

Limitations should be acknowledged in this study. First, the included studies were mainly from Europe and USA, thus the conclusion should be cautiously extrapolated to other regions (such as Asia and Africa). Second, Begg’s test showed no publication bias, but Egger’s test revealed obvious publication bias. Thus, our findings should be confirmed in the future when more published studies are available. Third, subgroup analysis by the types of autoimmune diseases was not performed since most of the included studies did not report specific type of autoimmune diseases. Fourth, data on medications of autoimmune diseases were only available in four eligible studies, moreover the medications varied greatly across these studies, we did not further investigate the effect of medications on the association between autoimmune diseases and COVID-19 severity currently.

In conclusion, our study based on adjusted effect estimates demonstrates that autoimmune diseases are independently associated with an increased risk of COVID-19 severity, which provides new insight on the association between autoimmune diseases and COVID-19 severity. Therefore, special preventive measures should be taken to protect individuals with co-existing autoimmune diseases from exposure to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and more clinical attention should be allocated to COVID-19 patients with autoimmune diseases to prevent disease progression.

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**Table 1**
Main characteristics of the included studies.

| Author | Location | No. of cases | No. of AD | Male (%) | Age[#] | Study design | Adjusted-effect (95% CI) | Adjusted factors |
|---|---|---|---|---|---|---|---|---|
| D'Silva et al. (PMID: 32,457,048) | USA | 156 | 52 | 30.8 | 62.9 ± 14.97 | Comparative cohort study | OR = 3.26 (1.17–9.09) | Age, body mass index |
| Pablos et al. (PMID: 32,796,045) | Spain | 456 | 228 | 39.9 | 65±18.90 | Comparative cohort study | OR = 1.82 (1.00–3.30) | Age, sex, obesity, diabetes, heart failure, glucocorticoids, antivirals |
| SisoAlmirall et al. (PMID: 32,822,413) | Spain | 322 | 21 | 50.0 | 56.7 ± 17.8 | Retrospective study | OR = 2.82 (1.00–7.84) | Hypertension, diabetes, obesity, dyslipidemia, cancer, chronic kidney disease, heart disease, chronic obstructive pulmonary disease, depression, cardiac arrhythmia, thyroid alterations, asthma, liver disease, cerebrovascular disease, alzheimer disease |
| Reilev et al. (PMID: 32,887,982) | Denmark | 11,122 | 348 | 42.2 | 47.67±21.64 | Population-based study | OR = 1.1 (0.8–1.6) | Age, sex |
| Morgenthau et al. (PMID: 32,915,271) | USA | 7337 | 37 | 55.5 | 61.31±20.02 | Retrospective study | OR = 1.8 (0.9–3.8) | Age, sex, cardiovascular disease, diabetes, chronic kidney disease, chronic obstructive pulmonary disease, cancer, obesity, smoking |
| Lauriola et al. (PMID: 32,926,573) | Italy | 377 | 28 | 65.8 | 71.8 ± 13.4 | Retrospective study | HR = 0.851 (0.410–1.765) | Sex, age, mechanical ventilation + continuous positive airway pressure, hypertension, diabetes, cancer, cardiovascular disease, chronic obstructive pulmonary disease, cerebrovascular disease, obesity, white blood cell above the median, C-reactive protein above the median, hydroxychloroquine, hydroxychloroquine + azithromycin |
| Balbi et al. (PMID: 33,033,861) | Italy | 340 | 18 | 74 | 67±14.15 | Retrospective study | OR = 3.22 (1.05–9.89) | Age, oxygen saturation, ratio of partial pressure of oxygen to fraction of inspired oxygen,% of lung involvement |
| Rodriguez-Molinero et al. (PMID: 33,057,443) | Spain | 418 | 21 | 56.9 | 65.4 ± 16.6 | Observational study | OR = 2.28 (0.73–7.08) | Age, sex, diabetes mellitus, dyslipidemia, obesity, chronic kidney disease, hypertension, heart failure, atrial fibrillation, dementia, obstructive sleep apnea syndrome |
| Clift et al. (PMID: 33,082,154) | UK | 10,776 | 309 | 55.3 | 69.63±17.90 | Cohort study | HR = 1.02 (0.75–1.38)[1] HR = 1.32 (1.06–1.65)[2] | Age, body mass index, townsend material deprivation score, ethnic group, domicile (residential care, homeless, neither), and a range of |
| Gu et al. (PMID: 33,084,902) | USA | 1139 | Unknown | 46.6 | 53.0 ± 17.9 | Retrospective study | OR = 1.45 (0.92–2.29) | Age, sex, and neighborhood socioeconomic disadvantage index |
| Izzy et al. (PMID: 33,088,846) | USA | 5190 | 158 | 45.8 | 51.33±22.25 | Unknown | OR = 0.82 (0.38–1.79)[3] OR = 1.37 (0.41–4.63)[4] OR = 1.92 (0.32–11.68)[5] | Age, gender, smoking status, body mass index, diabetes mellitus, hyperlipidemia, hypertension, obstructive lung disease, interstitial lung disease, coronary artery disease, chronic heart failure, cerebrovascular |
| Faye et al. (PMID: 33,132,221) | USA | 186 | 62 | 38.7 | 63.56±14.6 | Retrospective study | OR = 0.79 (0.37–1.67) | chronic kidney disease, |
| Murtas et al. (PMID: 33,023,649) | Italy | 20,364 | 665 | 47.5 | 65.5 ± 19.4 | Case-control study | OR = 0.95 (0.74–1.22) | comorbidities |

Note: AD, autoimmune diseases; USA, the United States of America; UK, the United Kingdom; CI, confidence interval; OR, odds ratio; HR, hazard ratio.
[#] The values are presented as mean ± SD (standard deviation);.
[1] : Men;.
[2] : Women;.
[3] : White;.
[4] : Latinx;.
[5] : African American.

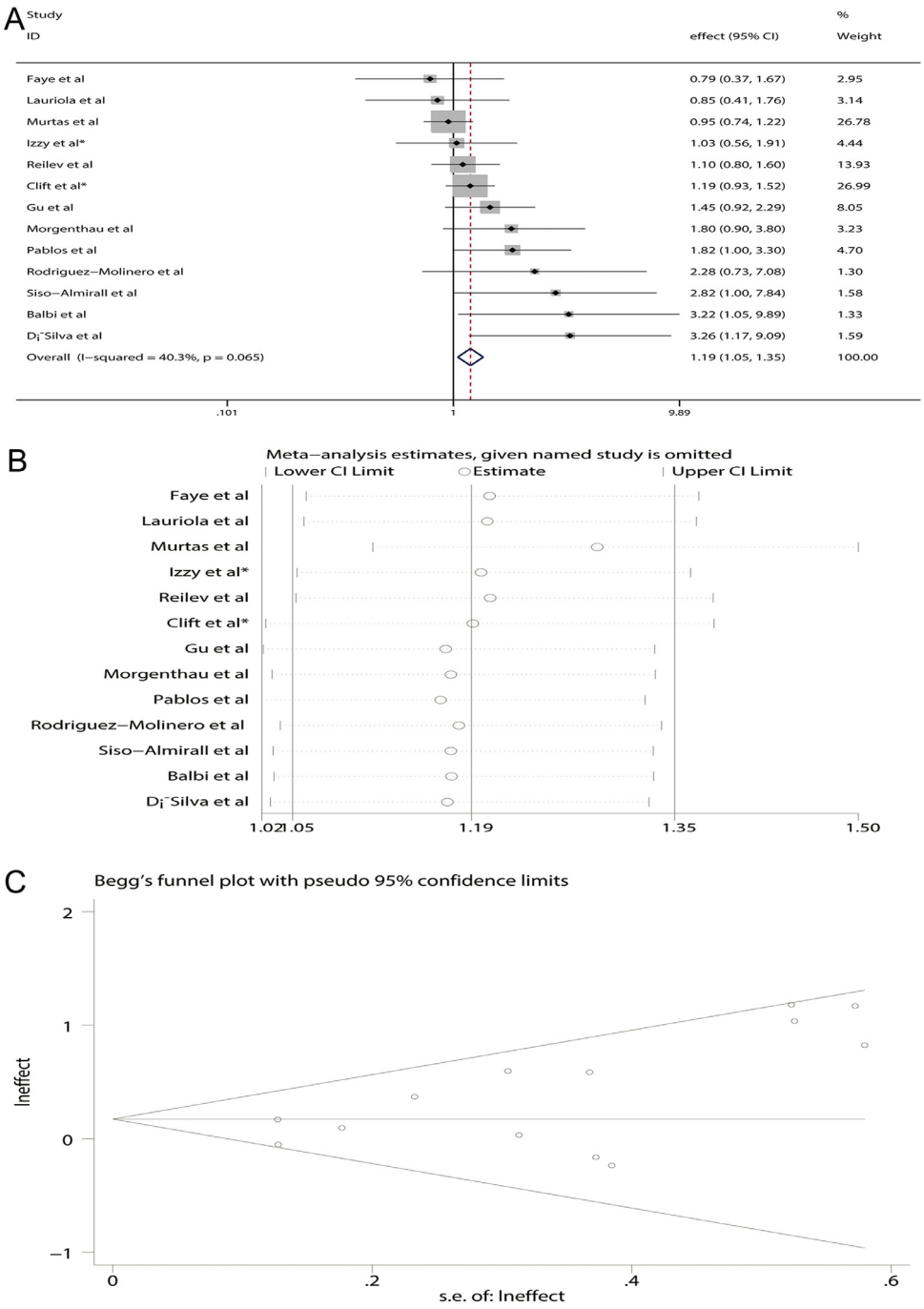


**Fig. 1.** (A) Forest plot on the association between autoimmune diseases and the risk of coronavirus disease 2019 (COVID-19) severity; (B) Leave-one-out sensitivity analysis was performed to evaluate the stability of results; (C) Publication bias was assessed by Begg's test. * indicates combined value from subgroups.

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