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Letter to the Editor

Impacts of immunosuppression and immunodeficiency on COVID-19: A systematic review and meta-analysis

Minotti Chiara and colleagues recently published a systematic review that investigated the current knowledge on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) cases in children and adults with immunosuppression and concluded that immunosuppressed patients with Coronavirus disease 2019 (COVID-19) seem to be few in relation to the overall figures and to present a favorable outcome as compared to other comorbidities.[1] We congratulate and applaud Minotti et al' important work, but this study drew conclusions only based on the systematic review without a meta-analysis. Therefore, we conducted a systematic review and meta-analysis to quantitatively assess whether immunosuppression and immunodeficiency are associated with increased risk of severe disease and mortality in patients with COVID-19.

We searched the PubMed, EMBASE.com, Web of Science, the Cochrane Central Register of Controlled Trials (CENTRAL), China National Knowledge Infrastructure (CNKI), Chinese Biomedical Literature Database (CBM), and Wanfang Database up to April 25, 2020. The following terms were used for the search: "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", "immunosuppression", "immunosuppressive", "immunodeficiency", "HIV", "clinical characteristic", "clinical feature", "risk factor", and "comorbidities". Reference lists of eligible studies and relevant systematic reviews were manually searched for potentially eligible studies.

We included studies that met the following criteria: (1) patients have a laboratory-confirmed diagnosis of COVID-19; (2) provided data of immunosuppression, immunodeficiency, or human immunodeficiency virus (HIV) between patients with severe or non-severe disease or between non-survivors and survivors; (3) studies published in Chinese and English. We excluded following studies: (1) studies with a sample size of no more than 10 patients; (2) studies did not provide the prevalence of immunosuppression, immunodeficiency, or HIV; (3) studies without comparisons (e.g. severe versus non-severe patients); (4) review articles, abstracts, letters, and editorials. In the current analysis, we considered a severe disease as patients experiencing acute respiratory distress syndrome (ARDS), requiring vital life support, requiring mechanical ventilation, or requiring intensive care unit admission (ICU) support.[2]

The primary outcome was the association between immunosuppression or immunodeficiency and risk of severe disease in patients with COVID-19. The secondary outcome was the association between immunosuppression or immunodeficiency and risk of mortality in COVID-19 patients.

Two reviewers conducted study selection and data extraction. Disagreements were resolved by consensus or by a discussion with a third reviewer. The abstracted data included: first author, year of publication, country of the corresponding author, publication language, recruitment time frame, age and sex of patients, sample size, and outcomes of interest.

Stata 13.0 (Stata Corporation, College Station, Texas, USA Stata) 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. Statistical heterogeneity was evaluated using I^2 statistic, and values of $<25\%$, 26-50%, and $>50\%$ considered as low, moderate, and high degrees of heterogeneity, respectively. Subgroup analysis was conducted for the primary outcome between different countries. We also performed sensitivity analyses by excluding studies published in Chinese to assess the stability of results.

2176 records were obtained through systematic electronic searches. After screening titles, abstracts, and full texts, 8 studies[3–10] were included for analysis. All the included studies were published in 2020, incorporated a total of 4007 patients (2256 males) between December 11, 2019 and April 15, 2020. Two studies[3,9] published in Chinese, 6 studies[4–8,10] published in English, 7 studies[3–9] from China, and 1[10] study from the USA. The sample size per study ranged from 79 to 1,590 (Table 1).

The meta-analysis showed that immunosuppression was associated with a 3.29-fold increased risk of severe COVID-19 disease (3 studies,[3–5] 776 patients; OR = 3.29, 95%CI: 0.89 to 12.21, $P = 0.075$; $I^2 = 5.5\%$), although the statistical difference was not significant (Fig. 1). Sensitivity analysis indicated the result (OR = 4.32, 95%CI: 1.00 to 18.64) did not change substantially after excluding the Chinese study.[3] We found that immunodeficiency was associated with a 1.55-fold increased risk of severe COVID-19 disease (5 studies,[6–10] 3,231 patients; OR = 1.55, 95%CI: 0.70 to 3.45, $P = 0.285$; $I^2 = 0.0\%$), but the statistical difference was not significant (Fig. 2). Sensitivity analysis by excluding the Chinese study[9] showed a similar result (OR = 1.52, 95%CI: 0.67 to 3.47). The subgroup analysis based on countries indicated the association between immunodeficiency and severe COVID-19 disease in China (OR = 2.15, 95%CI: 0.50 to 9.22) was stronger than that in the USA (OR = 1.34, 95%CI: 0.51 to 3.50), Fig. 2. One study[6] involving 1,590 patients reported the data on immunodeficiency between dead and surviving COVID-19 patients. The result revealed that there was no correlation ($P = 1.000$) between immunodeficiency and the risk of death in patients with COVID-19.

Our study showed that immunosuppression and immunodeficiency were associated with the increased risk of severe COVID-19 disease, although the statistical differences were not significant. These findings suggest that healthcare professionals need to be alert to the increased risk of serious diseases associated with COVID-19 infection in patients with immunosuppression and immunodeficiency/HIV. In response to the COVID-19 pandemic, special preventive and protective measures should be provided for

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Table 1
Characteristics of included studies.

Study	Country	Language	Recruitment time frame	Sample	Age, years[a]	Sex		Immunosuppression	Immunodeficiency/HIV
						Male	Female		
Fang XW[3]	China	Chinese	2020.1.22-2020.2.18	79	45.1(16.6)	45	34	1(1.27%)	
Feng Y[4]	China	English	2020.1.1-2020.2.15	476	53(40-64)	271	205	7(1.47%)	
Zhang GQ[5]	China	English	2020.1.2-2020.2.10	221	55(39-66.5)	108	113	3(1.36%)	
Guan WJ[6]	China	English	2019.12.11-2020.1.31	1590	48.9(16.3)	904	686		3(0.19%)
Wang DW[7]	China	English	2020.1.1-2020.1.28	138	56 (42-68)	75	63		2(1.45%)
Wu J[8]	China	English	2020.1.20-2020.2.19	280	43.1(19.0)	151	129		1(0.36%)
Yuan J[9]	China	Chinese	2020.1.24-2020.2.23	223	46.5(16.1)	106	117		1(0.45%)
Argenziano MG[10]	USA	English	2020.3.1-2020.4.15	1000	61.7(17.5)	596	404		21(2.10%)

[a] Age data presented as median (IQR) or mean (SD). HIV: human immunodeficiency virus.

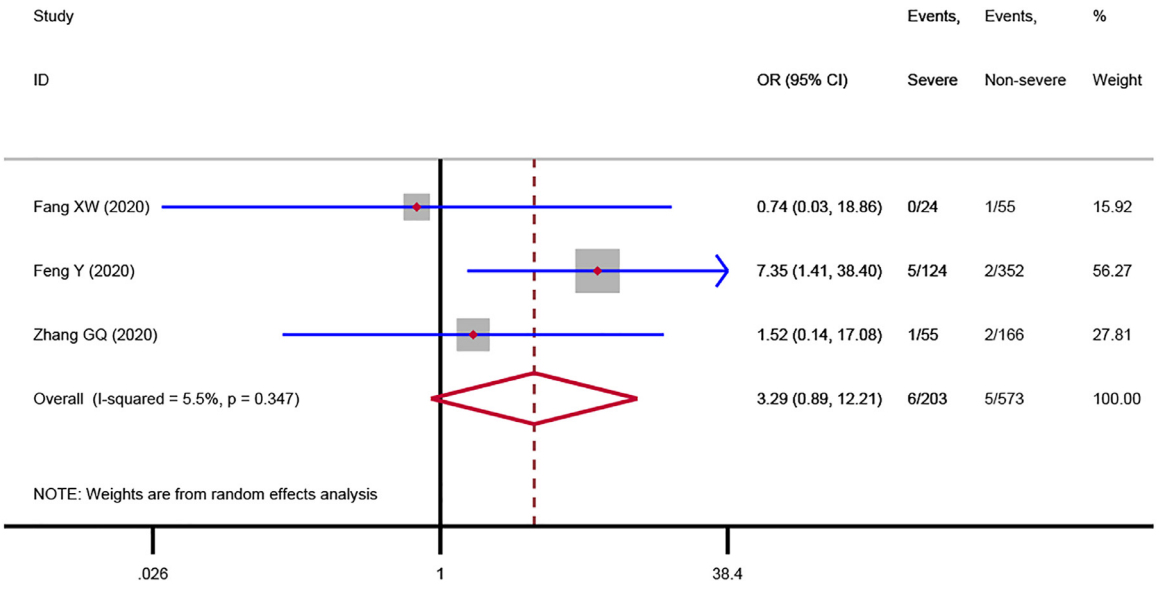

Fig. 1. Association between immunosuppression and severe COVID-19 disease

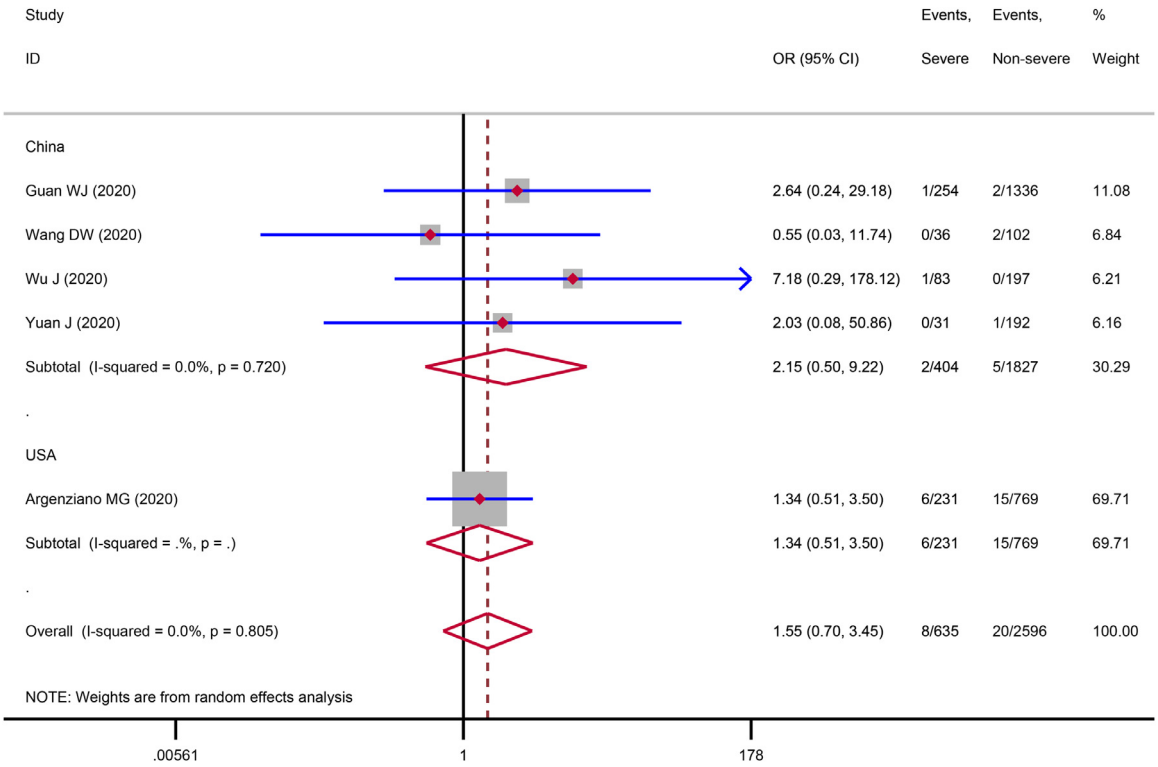

Fig. 2. Association between immunodeficiency and severe COVID-19 disease

patients with immunosuppression and immunodeficiency/HIV. Future researchers should focus on the treatment and management strategies for patients with immunosuppression and immunodeficiency/HIV during the COVID-19 pandemic, as well as the care and treatment strategies for COVID-19 patients with immunosuppression and immunodeficiency/HIV. However, our study was limited by small sample size, the results should be interpreted with caution. As more data becomes available, these findings should be re-analyzed to provide more reliable evidence.

In conclusion, immunosuppression and immunodeficiency were associated with increased risk of severe COVID-19 disease, although the statistical differences were not significant. Further high-quality studies are needed to provide robust evidence of the association between immunosuppression and immunodeficiency and COVID-19.

Declaration of Competing Interest

The authors declare that they have no competing interests.

Declarations

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