

# Immune status could be associated with severity in COVID-19 patients

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<http://dx.doi.org/10.1590/1806-9282.66.S2.13>

**KEYWORDS:** *Coronavirus Infections/immunology. Meta-analysis. Immunocompetence. Immunologic Factors.*

Dear Editor,

Corona Virus Disease 2019 (COVID-19) is a highly contagious disease that has caused outbreaks across the globe. As of May 21, 2020, a total of 5,027,732 confirmed COVID-19 cases have been reported in 188 countries, with an average mortality of 6.54%<sup>1</sup>. The current relationship between COVID-19 disease severity and immune function status is unclear. As far as we know, this study is the first meta-analysis to compare immune status and immunoglobulin efficacy in severe vs. non-severe patients with COVID-19.

An extensive electronic search of PubMed, Embase, and Cochrane Library was conducted without date limitations (until May 6, 2020), using the keywords "COVID-19", "2019-nCoV", "SARS-CoV-2",

"Novel Coronavirus", "Feature", "Immune", etc. Two authors independently screened articles, assessed qualities, and performed data extraction. Any discrepancies during these steps were regularly resolved by consulting with a third reviewer. Severe COVID-19 infection was defined as severe pneumonia, acute respiratory distress syndrome (ARDS), treatment with mechanical ventilation or intensive care unit (ICU), and/or death. Dichotomous variables were estimated with Odds Ratios (OR) and 95% confidence interval (CI). Continuous data (using mean and standard deviation - SD) were compared and the mean difference (MD) was calculated with 95% CI, and a P-value <0.05 was considered statistically

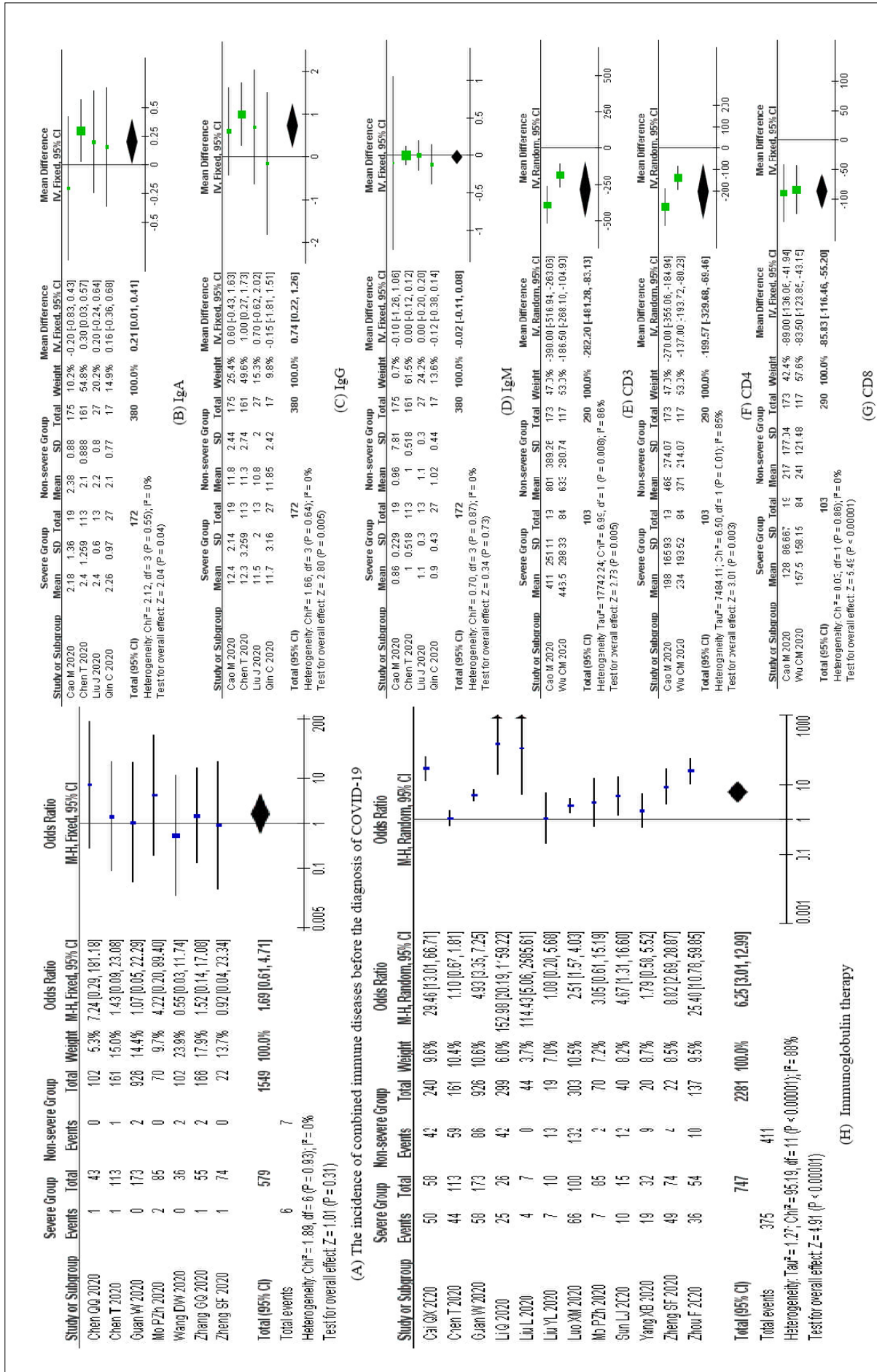
DATE OF SUBMISSION: 26-Jun-2020

DATE OF ACCEPTANCE: 11-Jul-2020

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**FIGURE 1.** META-ANALYSIS RESULTS OF THE OUTCOMES: (A) THE INCIDENCE OF COMBINED IMMUNE DISEASES BEFORE THE DIAGNOSIS OF COVID-19; (B) IGA; (C) IGG; (D) IGM; (E) CD3; (F) CD4; (G) CD8; (H) IMMUNOGLOBULIN THERAPY.

significant. The random-effects model was used if  $I^2 > 50\%$ . The publication bias was evaluated by visual inspection of the funnel plot. Our meta-analysis was carried out using Review Manager software version 5.3 (Cochrane Collaboration).

Nineteen studies<sup>2-20</sup> were enrolled in our analysis. All studies originated from China and involved 4,011 confirmed COVID-19 patients in total. The incidence of combined immune diseases before the diagnosis of COVID-19 was not significantly associated with an enhanced risk of severe COVID-19 (OR: 1.69, 95% CI: 0.61-4.71,  $P=0.31$ ). Immune globulin A (IgA) and immune globulin G (IgG) were found to be increased in COVID-19 patients in the severe group [IgA: MD=0.21, 95%CI (0.01, 0.41),  $P=0.04$ ; IgG: MD=0.74, 95%CI (0.22, 1.26),  $P=0.005$ ]. Immune globulin M (IgM) was not found to be correlated with the severity of COVID-19 (MD: -0.02, 95% CI: -0.11, 0.08,  $P=0.73$ ). Our study revealed that a decrease in the mean cluster of differentiation (CD)3, CD4 and CD8 was significantly associated with an increased likelihood of severity [CD3: MD=-282.2, 95%CI (-481.28, -83.13),  $P=0.005$ ; CD4: MD=-199.57, 95%CI (-329.68, -69.46),  $P=0.003$ ; CD8: MD=-85.83, 95%CI (-116.46, -55.20),  $P<0.0001$ ]. Immunoglobulin therapy is significantly more effective in severe COVID-19 patients (OR: 6.25, 95% CI: 3.01-12.99,  $P<0.0001$ ). Based on a visual inspection of the funnel plots, no evidence of publication bias was found. More details of our meta-analysis are presented in Figure 1.

This meta-analysis provides evidence that hypo-immune states could be associated with a more severe form of COVID-19, and that immunoglobulins are more effective against severe COVID-19. Our results are consistent with some previous descriptive reviews<sup>21-23</sup>. In addition, this study has important clinical implications. First, it can potentially help in disease assessment as the COVID-19 pandemic continues to affect multiple countries. Second, it reminds us of the

relevance of early initiation of immunoglobulin therapy, which is effective in improving the prognosis of severe and critical type patients.

This study has its limitations. First, most of the studies included are retrospective and lack a prospective design. Second, some of the outcomes in this study had a high I<sup>2</sup> value, which represents heterogeneity. This might be explained by the small sample size, limited data, and different patient populations.

Based on our results, a hypimmune status might be an important sign of COVID-19 severity, guiding clinicians to identify severe patients earlier and faster and alerting clinicians that immunoglobulins have better efficacy in critically ill patients. Further, more high-quality literature is needed to better support this conclusion.

### Acknowledgments

The National Natural Science Foundation of China (No. 81370494 and No. 31471330) funded this manuscript.

### Ethical approval

All analyses were based on previously published studies, thus no ethical approval and patient consent are required.

### Author's Contribution

Chuan Liu conceptualized and designed the study, drafted the initial manuscript, and approved the final manuscript as submitted. Jiahui Yang, Wancong Wang, and Yang Mi obtained the data, carried out the analyses. Youcai Tang and Pengyuan Zheng critically reviewed the manuscript and approved the final manuscript as submitted.

### Conflict of Interest

The authors declare no conflict of interest.

**PALAVRAS CHAVE:** Infecções por Coronavirus/imunologia. Metanálise. Imunocompetência. Fatores Imunológicos.

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