Association of immunological features with COVID-19 severity: a systematic review and meta-analysis

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Abstract

Background: We aim to explore the association of immunological features with COVID-19 severity.

Methods: We conducted a meta-analysis to estimate mean difference (MD) of immune cells and cytokines levels with COVID-19 severity in PubMed, Web of Science, Scopus, the Cochrane Library and the grey literature.

Results: A total of 21 studies with 2033 COVID-19 patients were included. Compared with mild cases, severe cases showed significantly lower levels of some immune cells, $CD3^+$ T cell ($\times 10^6$, MD, -413.87; 95%CI, -611.39 to -216.34), $CD4^+$ T cell ($\times 10^6$, MD, -203.56; 95%CI, -277.94 to -129.18), $CD8^+$ T cell ($\times 10^6$, MD, -128.88; 95%CI, -163.97 to -93.79), B cell ($\times 10^6$/L; MD, -23.87; 95%CI, -43.97 to -3.78) and NK cell ($\times 10^6$/L; MD, -57.12; 95%CI, -81.18 to -33.06), and significantly higher levels of some cytokines, TNF-α (pg/ml; MD, 0.34; 95%CI, 0.09 to 0.59), IL-5 (pg/ml; MD, 14.2; 95%CI, 3.99 to 24.4), IL-6 (pg/ml; MD, 13.07; 95%CI, 9.80 to 16.35), and IL-10 (pg/ml; MD, 2.04; 95%CI, 1.32 to 2.75), and significantly higher levels of some chemokines, MCP-1 (SMD, 3.41; 95%CI, 2.42 to 4.40), IP-10 (SMD, 2.82; 95%CI, 1.20 to 4.45) and eotaxin (SMD, 1.55; 95%CI, 0.05 to 3.05). However, no significant differences were found in other indicators, Treg cell ($\times 10^6$, MD, -0.13; 95%CI, -1.40 to 1.14), $CD4^+/CD8^+$ ratio (MD, 0.26; 95%CI, -0.02 to 0.55), IFN-γ (pg/ml; MD, 0.26; 95%CI, -0.05 to 0.56), IL-2 (pg/ml; MD, 0.05; 95%CI, -0.49 to 0.60), IL-4 (pg/ml; MD, -0.03; 95%CI, -0.68 to 0.62), GM-CSF (SMD, 0.44; 95%CI, -0.46 to 1.35), and RANTES (SMD, 0.94; 95%CI, -2.88 to 4.75).

Conclusion: Our meta-analysis revealed significant lower levels of immune cells ($CD3^+$ T, $CD4^+$ T, $CD8^+$ T, B and NK cells), significant higher levels of cytokines (TNF-α, IL-5, IL-6 and IL-10) and significant higher levels of chemokines (MCP-1, IP-10 and eotaxin) in severe cases compared with mild cases of COVID-19. Measurement of immunological features could help to assess disease severity for effective triage of COVID-19 patients.

Background

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has been spreading all over the world [1]. Till September 09, 2020, the SARS-CoV-2 has infected over 27 million patients and caused over 890,000 deaths [2]. The severity of COVID-19 may be strongly related to immune status of patients, but this is poorly understood. Therefore, it is necessary to explore the association of immunological features with COVID-19 severity, which may help to identify immune markers of disease severity for effective triage of COVID-19 patients.

Some studies focused on the association between immunologic features and COVID-19 severity, but the conclusions remain controversial. Chen et al. found that the SARS-CoV-2 infection may decrease primarily T lymphocytes, particularly $CD4^+$ and $CD8^+$ T cells [3]. Qin et al. showed that the increase in cytokines levels (tumor necrosis factor alpha (TNF-α), interleukin-5 (IL-5), IL-6 and IL-10) correlated with

COVID-19 course, especially in severe cases [4]. Sophie et al. demonstrated that increased serum concentrations of IFN-γ inducible protein-10 (IP-10/CXCL10) and granulocyte-macrophage colony-stimulating factor (GM-CSF) were associated with day-28 mortality of COVID-19 patients [5]. However, other studies have revealed that $CD4^+$ and $CD8^+$ T cell [4], some cytokines (IL-5, IL-6 and IL-10) [6] and some chemokines (GM-CSF and IP-10) [7] showed no significant differences between severe cases and mild cases. Thus, we presented a meta-analysis of 21 studies in order to assess the association between immune cells ($CD4^+$ T, $CD8^+$ T, $CD3^+$ T, Treg, B and NK cells), cytokines (TNF-α, interferon gamma (IFN-γ), IL-2, IL-4, IL-5, IL-6 and IL-10), chemokines (GM-CSF, RANTES, MCP-1, IP-10 and eotaxin) and COVID-19 severity respectively.

Methods

Search Strategy

We performed a systematic literature search to identify relevant studies published up to September 09, 2020 in PubMed, Web of Science, Scopus, the Cochrane Library and the grey literature. The following combined search terms were used: ("Novel coronavirus" OR "Coronavirus disease 2019" OR "Coronavirus 2019" OR "nCoV-2019" OR "2019-nCoV" OR "COVID-19" OR "SARS-CoV-2") and (("CD3+ T" OR "CD4+ T" OR "CD8+ T" OR "CD4+/CD8+" OR "Treg" OR "B cell" OR "NK cell") OR ("interferon gamma" OR "tumor necrosis factor alpha" OR "IL-2" OR "IL-4" OR "IL-5" OR "IL-6" OR "IL-10") OR ("chemokine" OR "chemokines" OR "RANTES" OR "GM-CSF" OR "Eotaxin" OR "MCP-1" OR "IP-10")).

Study selection

Inclusion criteria of the study were as follows: 1) studies with data on immune cells ($CD4^+$ T, $CD8^+$ T, $CD3^+$ T, $CD4^+/CD8^+$, Treg, B and NK cells), cytokines (IFN, TNF-α, IL-2, IL-4, IL-5, IL-6 and IL-10) and chemokines (GM-CSF, RANTES, MCP-1, IP-10 and eotaxin) with mean ± standard deviation (SD) or median (interquartile range, IQR); 2) patients could be grouped into severe cases and mild cases; and 3) studies with clear information on COVID-19 confirmation and included patients. And exclusion criteria were as follows: 1) studies without corresponding outcome of indicators; 2) studies without available full texts; 3) studies not published in English; 4) lack of mean ± SD or mean (IQR) of indicators; 5) reviews, editorials, case reports, and meta-analysis.

Two investigators developed the search strategy and one investigator conducted the primary systematic search for all studies meeting the predetermined inclusion criteria. The titles and abstracts of the retrieved articles were screened for duplicates and relevance to the topic. A second investigator checked study eligibility, quality assessment, and data extraction, for validity and consistency. Full-text reports of the identified citations were reviewed by both the primary and secondary investigators in order to select the final studies. Any discrepancy was resolved by consensus, and if necessary, by consultation with the third investigator.

Data extraction

The following data were extracted from each study: 1) the first author and year of publication; 2) study design; 3) the country where the study was conducted; 4) ages; 5) sample size; 6) sex; 7) the levels of immune cells ($CD4^+$ T, $CD8^+$ T, $CD3^+$ T, $CD4^+/CD8^+$, Treg, B and NK cells), and cytokines (IFN, TNF-α, IL-2, IL-4, IL-5, IL-6 and IL-10), and chemokines (GM-CSF, RANTES, MCP-1, IP-10 and eotaxin). Median (IQR) were converted to mean ± SD using mathematical formulas according to Hozo et al [8].

Quality assessment

Quality assessments of the studies were carried out based on the Newcastle-Ottawa Scale (NOS). The total NOS score ≥ 7 indicated a good research quality of the included study.

Data synthesis and analysis

Data entry and analysis were carried out with Review Manager 5.3 (The Cochrane Collaboration, Oxford, England). Heterogeneity of effect estimates within each group of studies were assessed by Q test and I^2 statistic, where $I^2 > 50\%$ or $p < 0.05$ indicated heterogeneity and the random-effects model was used. When $I^2 \leq 50\%$ or $p \geq 0.05$, the fixed-effects model was used. For continuous data, we calculated mean differences (MD) and 95% confidence intervals (CI) between severe cases and mild cases. To investigate the potential publication bias, we visually examined the funnel plots. For robustness of results, we performed sensitivity analysis by removing one study each time through sensitivity analysis.

Results

Search results and characteristics of included studies

Fig 1 provides the flow diagram for study selection. Based on the inclusion criteria, 75 full articles were retrieved and 21 of these were included in the final meta-analysis. Duplicate publications, reviews, editorials, case reports, and studies without median (IQR) and mean ± SD of indicators were excluded. Table 1 presents the characteristics of the 21 included studies, with 758 severe cases and 1275 mild cases of COVID-19 reported. All but one prospective study [9] of the studies included in this meta-analysis were retrospective studies, which were mostly performed in China. All studies were deemed of high quality with 7 or more NOS scores and details can be found in Table 2.

Association of immune cells with COVID-19 severity

Compared with mild cases, severe cases showed significantly lower levels of some immune cells, $CD3^+$ T cell ($\times 10^6$, MD, -413.87; 95%CI, -611.39 to -216.34; I^2, 100%; $p < 0.001$, Fig 2a), $CD4^+$ T cell ($\times 10^6$, MD, -203.56; 95%CI, -277.94 to -129.18; I^2, 99%; $p < 0.001$, Fig 2b), $CD8^+$ T cell ($\times 10^6$, MD, -128.88; 95%CI, -163.97 to -93.79; I^2, 99%; $p < 0.001$, Fig 2c), B cell ($\times 10^6$/L; MD, -23.87; 95%CI, -43.97 to -3.78; I^2, 87%; $p < 0.001$, Fig 2f), and NK cell ($\times 10^6$/L; MD, -57.12; 95%CI, -81.18 to -33.06; I^2, 92%; $p < 0.001$, Fig 2g). However, no significant differences were found in other indicators, $CD4^+/CD8^+$ ratio (MD, 0.26; 95%CI,

-0.02 to 0.55; I^2, 97%; $p < 0.001$, Fig 2d) and Treg cell ($\times 10^6$, MD, -0.13; 95%CI, -1.40 to 1.14; I^2, 90%; $p = 0.002$, Fig 2e).

Association of cytokines with COVID-19 severity

Compared with mild cases, severe cases showed significantly higher levels of some cytokines, TNF-α (pg/ml; MD, 0.34; 95%CI, 0.09 to 0.59; I^2, 98%; $p < 0.001$, Fig 2h), IL-5 (pg/ml; MD, 14.20; 95%CI, 3.99 to 24.4; I^2, 99%; $p < 0.001$, Fig 2l), IL-6 (pg/ml; MD, 13.07; 95%CI, 9.80 to 16.35; I^2, 100%; $p < 0.001$, Fig 2m), and IL-10 (pg/ml; MD, 2.04; 95%CI, 1.32 to 2.75; I^2, 99%; $p < 0.001$, Fig 2n). However, there were no significant differences found in other cytokines, IFN-γ (pg/ml; MD, 0.26; 95%CI, -0.05 to 0.56; I^2, 98%; $p < 0.001$, Fig 2i), IL-2 (pg/ml; MD, 0.05; 95%CI, -0.49 to 0.6; I^2, 100%; $p < 0.001$, Fig 2j), and IL-4 (pg/ml; MD, -0.03; 95%CI, -0.68 to 0.62; I^2, 100%; $p < 0.001$, Fig 2k).

Association of chemokines with COVID-19 severity

Compared with mild cases, severe cases showed significantly higher levels of some chemokines, MCP-1 (SMD, 3.41; 95%CI, 2.42 to 4.40; I^2, 71%; $p = 0.03$, Fig 2q), IP-10 (SMD, 2.82; 95%CI, 1.20 to 4.45; I^2, 91%; $p < 0.001$, Fig 2r), and eotaxin (SMD, 1.55; 95%CI, 0.05 to 3.05; I^2, 87%; $p = 0.01$, Fig 2s). However, there were no significant differences found in other chemokines, GM-CSF (SMD, 0.44; 95%CI, -0.46 to 1.35; I^2, 85%; $p = 0.001$, Fig 2o) and RANTES (SMD, 0.94; 95%CI, -2.88 to 4.75; I^2, 98%; $p < 0.001$, Fig 2p).

Sensitivity Analysis

Strong evidences of heterogeneity were found in all the comparisons (Fig 2). Sensitivity analyses showed that tour results were not obviously impacted by excluding any one specific study for “CD4+ T”, “CD8+ T”, “CD3+ T”, “CD4+/CD8+”, “Treg”, “B cell”, “NK cell”, “TNF-α” “IFN”, “IL-2”, “IL-4”, “IL-5”, “IL-6”, “IL-10” , “RANTES”, “MCP-1”, “IP-10” and “eotaxin” between the severe group and the mild group. But after excluding the study Chi et al. [24]on GM-CSF (SMD, 0.94; 95%CI, 0.58 to1.31), the sensitivity findings showed that there was a significant difference between pre- and post-sensitivity pooled SMD on its outcome, suggesting that it is better to keep this result in the meta-analysis. Hence, our sensitivity analysis indicates that most of our results are reliable and believable.

Publication bias

We assessed the publication bias of the literature by the funnel plots in all included studies of each indicator, respectively. Funnel plot analysis did not detect obvious publication bias as the shape of all funnel plots did not reveal any evidence of obvious asymmetry (Fig 3).

Discussion

It is necessary to explore the host immune response to SARS-CoV-2, which may help to identify immune markers of disease severity for effective triage of COVID-19 patients [25]. Our study mainly compared the

level differences of immune cells, cytokines and chemokines between mild and severe patients with COVID-19.

The variations of immune cells levels are inconsistent in different reports. Most of our included studies found significant lower levels of immune cells ($CD8^+$ T, $CD4^+$ T, $CD3^+$ T, B and NK cells) in severe cases compared with mild cases [3, 11, 15]. Only two studies reported no significant decrease in $CD8^+$ T cell level [4, 19], while one study reported higher levels of B cell [14] in severe cases. Synthesizing all the collected evidence, our meta-analysis results found that the levels of immune cells (CD8+ T, CD4+ T, CD3+ T, B and NK cells) were significantly lower in severe cases compared with mild cases, but Treg cell level and $CD4^+/CD8^+$ ratio showed no significant differences.

The mechanism underlying the association between the reduction of immune cells levels and COVID-19 severity remain to be determined. $CD8^+$ T cells exert their effects mainly through two mechanisms, including cytolytic activities against target cells and secretion of cytokines [20]. $CD4^+$ T cells could activate the $CD8^+$ T cell response to acute respiratory virus infection [25]. SARS-CoV-2 and associated autoimmune antibodies may lead to growth inhibition and apoptosis of hematopoiesis [26], which may decrease the production and maturation of immune cells [6].

With regard to cytokines, the conclusions of different studies are also inconsistent. With the exception of one study on IL-6 [6] and another study on TNF-α, most of our included studies found that of IL-6 and TNF-α levels were significantly higher in severe cases compared with mild cases [4, 16, 20, 27]. Some of our included studies found no significant differences in the levels of IL-2, IL-4, IL-5, and IFN-γ, while an nearly equivalent number of studies of each indicator found that they were significantly higher in severe cases. Synthesizing all the collected evidence, our meta-analysis results found that IL-5, IL-6, IL-10 and TNF-α levels were significantly higher in severe cases compared with mild cases. However, the levels of IL-2, IL-4, IFN-γ, Treg cell and $CD4^+/CD8^+$ ratio showed no significant differences.

In severely infected individuals, SARS-CoV-2 could induce excessive cytokine response, such as IL-6, IL-10, and TNF-α surge, known as cytokine storm. Cytokine storm could contribute to acute respiratory distress syndrome (ARDS) or multiple-organ dysfunction, leading to physiological deterioration and death [28]. Cytokines such as IL-10, IL-6, and TNF-α are also involved in T cell reduction. IL-6 contributes to host defense via stimulation of acute phase responses [29]. TNF-α is a pro-inflammatory cytokine that can promote T cell apoptosis [30]. Patients requiring ICU admission have significantly higher levels of IL-6, IL-10, and TNF-α. Further, the levels of IL-6, IL-10, and TNF-α inversely correlate with $CD4^+$ and $CD8^+$ T cell counts [31]. This fact is strengthened by our meta-analysis results.

SARS-CoV-2 infection is a potent inducer of proinflammatory chemokines that may be involved in the defense against viral infections [24]. Some studies reported higher concentrations of GM-CSF [5], IP-10 [5, 23, 24] , MCP-1 [23, 24] , eotaxin [7] and RANTES [23] between severe cases and mild cases. However, other studies have not showed significant differences in the concentrations of GM-CSF [7, 24], IP-10 [7], RANTES [24] , MCP-1 [7] , and eotaxin [24] . Synthesizing all the collected evidence, our meta-analysis

results found that MCP-1, IP-10 and eotaxin levels were significantly higher in severe cases compared with mild cases. However, the levels of GM-CSF and RANTES showed no significant differences. Through its binding to the chemokine receptor 3, IP-10 activates and recruits leucocytes, including T cells and monocytes, thereby perpetuating inflammation [32]. MCP-1-mediated migration of monocytes from the blood stream through the vascular endothelium is essential for routine immune surveillance of tissues, as well as in response to inflammation [33]. Abnormally elevated MCP-1, IP-10 and eotaxin levels may help to determine the severity of SARS-CoV-2 infections and may be predictors of clinical symptoms.

Limitations

Several limitations of our study should be considered. First, the number of studies and participants was not large enough for publication bias analysis of most indicators. Second, most of the included studies in this meta-analysis were retrospective. Third, the overall generalizability of the meta-analysis results should be interpreted with caution as most of included studies were conducted in China. It would be better to include as many studies with a broad geographic scope, to gain a more comprehensive understanding of immunological features of COVID-19 patients.

Conclusions

Our synthesized results revealed significant lower levels of immune cells ($CD3^+$ T, $CD4^+$ T, $CD8^+$ T, B and NK cells), significant higher levels of cytokines (TNF-α, IL-5, IL-6 and IL-10) and significant higher levels of chemokines (MCP-1, IP-10 and eotaxin) in severe cases compared with mild cases of COVID-19 patients. However, the levels of Treg cell, $CD4^+/CD8^+$ ratio, IL-2, IL-4, IFN-γ, GM-CSF and RANTES showed no significant differences. Measurement of immune cells and cytokines may help to identify immune markers of COVID-19 severity and contribute to the development of immunologic therapies and vaccine design of COVID-19.

Declarations

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Authors' contributions

Conception: ZZ, HJJ. Literature search: ZZ, HJJ. Selection of studies: ZX, ZC. Full texts search: ZZ, LS. Data extraction: GC. Data synthesis and analysis: ZZ, AG. Data interpretation: CL. Manuscript drafting: ZZ, HJJ. Manuscript editing and revision: LS, HJH. Manuscript final version approval: ZZ, QH, HJH. Guarantor of the review: HJJ, HJH.

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Availability of data and materials

All relevant data for this study are presented in tables, figures and supplementary materials.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Abbreviations

COVID-19: Coronavirus disease 2019; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; MD: Mean difference; IQR: Interquartile range; IL-2: interleukin-2; IL-4: Interleukin-4; IL-5: Interleukin-5; IL-6: Interleukin-6; IL-10: Interleukin-10; TNF-α: Tumor necrosis factor alpha; IFN-γ: Interferon gamma; NK cell: Natural killer cell; CI: Confidence interval; NOS: Newcastle-ottawa scale; ARDS: Acute respiratory distress syndrome; SD, Standard deviation; GM-CSF: Granulocyte-macrophage colony-stimulating factor; RANTES (CCL5): Regulated upon activation, normal T-cell expressed and secreted; IP-10 (CXCL10): IFN-γ Inducible protein-10; MCP-1 (CCL2): Monocyte chemoattractant protein-1.

References

1. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497–506. doi:10.1016/S0140-6736(20)30183-5.
2. World Health Organization. Coronavirus disease (COVID-19). Weekly Operational Update [accessed 9 September 2020]. Available from: https://www.who.int/docs/default-source/coronaviruse/weekly-updates/wou-9-september-2020-cleared-14092020.pdf?sfvrsn=68120013_2.
3. Chen G, Di Wu, Guo W, Cao Y, Huang D, Wang H, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. J Clin Invest. 2020;130:2620–9. doi:10.1172/JCI137244.
4. Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. Clin Infect Dis 2020. doi:10.1093/cid/ciaa248.

5. Hue S, Beldi-Ferchiou A, Bendib I, Surenaud M, Fourati S, Frapard T, et al. Uncontrolled Innate and Impaired Adaptive Immune Responses in Patients with COVID-19 ARDS. Am J Respir Crit Care Med 2020. doi:10.1164/rccm.202005-1885OC.
6. He R, Lu Z, Zhang L, Fan T, Xiong R, Shen X, et al. The clinical course and its correlated immune status in COVID-19 pneumonia. Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology. 2020;127:104361. doi:10.1016/j.jcv.2020.104361.
7. Zhao Y, Qin L, Zhang P, Li K, Liang L, Sun J, et al. Longitudinal COVID-19 profiling associates IL-1RA and IL-10 with disease severity and RANTES with mild disease. JCI Insight 2020. doi:10.1172/jci.insight.139834.
8. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol. 2005;5:13. doi:10.1186/1471-2288-5-13.
9. Du R-H, Liang L-R, Yang C-Q, Wang W, Cao T-Z, Li M, et al. Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2: a prospective cohort study. Eur Respir J 2020. doi:10.1183/13993003.00524-2020.
10. Chen R, Sang L, Jiang M, Yang Z, Jia N, Fu W, et al. Longitudinal hematologic and immunologic variations associated with the progression of COVID-19 patients in China. J Allergy Clin Immunol 2020. doi:10.1016/j.jaci.2020.05.003.
11. Jiang M, Guo Y, Luo Q, Huang Z, Zhao R, Liu S, et al. T cell subset counts in peripheral blood can be used as discriminatory biomarkers for diagnosis and severity prediction of COVID-19. The Journal of infectious diseases 2020. doi:10.1093/infdis/jiaa252.
12. Liu Y, Liao W, Wan L, Xiang T, Zhang W. Correlation Between Relative Nasopharyngeal Virus RNA Load and Lymphocyte Count Disease Severity in Patients with COVID-19. Viral Immunol 2020. doi:10.1089/vim.2020.0062.
13. Ma J, Yin J, Qian Y, Wu Y. Clinical characteristics and prognosis in cancer patients with COVID-19: A single center's retrospective study. The Journal of infection 2020. doi:10.1016/j.jinf.2020.04.006.
14. Sun D-W, Zhang D, Tian R-H, Li Y, Wang Y-S, Cao J, et al. The underlying changes and predicting role of peripheral blood inflammatory cells in severe COVID-19 patients: a sentinel? Clin Chim Acta 2020. doi:10.1016/j.cca.2020.05.027.
15. Wan S, Yi Q, Fan S, Lv J, Zhang X, Guo L, et al. Relationships among lymphocyte subsets, cytokines, and the pulmonary inflammation index in coronavirus (COVID-19) infected patients. Br J Haematol. 2020;189:428–37. doi:10.1111/bjh.16659.
16. Wang F, Yang Y, Dong K, Yan Y, Zhang S, Ren H, et al. CLINICAL CHARACTERISTICS OF 28 PATIENTS WITH DIABETES AND COVID-19 IN WUHAN, CHINA. Endocr Pract 2020. doi:10.4158/EP-2020-0108.
17. Zhang J, Yu M, Tong S, Liu L-Y, Tang L-V. Predictive factors for disease progression in hospitalized patients with coronavirus disease 2019 in Wuhan, China. Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology. 2020;127:104392. doi:10.1016/j.jcv.2020.104392.

18. Zheng Y, Xu H, Yang M, Zeng Y, Chen H, Liu R, et al. Epidemiological characteristics and clinical features of 32 critical and 67 noncritical cases of COVID-19 in Chengdu. Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology. 2020;127:104366. doi:10.1016/j.jcv.2020.104366.
19. Zhou Y, Zhang Z, Tian J, Xiong S. Risk factors associated with disease progression in a cohort of patients infected with the 2019 novel coronavirus. Ann Palliat Med. 2020;9:428–36. doi:10.21037/apm.2020.03.26.
20. Zhu Z, Cai T, Fan L, Lou K, Hua X, Huang Z, Gao G. Clinical value of immune-inflammatory parameters to assess the severity of coronavirus disease 2019. Int J Infect Dis. 2020;95:332–9. doi:10.1016/j.ijid.2020.04.041.
21. Pallotto C, Suardi LR, Esperti S, Tarquini R, Grifoni E, Meini S, et al. Increased CD4/CD8 ratio as a risk factor for critical illness in coronavirus disease 2019 (COVID-19): a retrospective multicentre study. Infectious Diseases. 2020;52:675–7. doi:10.1080/23744235.2020.1778178.
22. Urra JM, Cabrera CM, Porras L, Ródenas I. Selective CD8 cell reduction by SARS-CoV-2 is associated with a worse prognosis and systemic inflammation in COVID-19 patients. Clinical Immunology 2020. doi:10.1016/j.clim.2020.108486.
23. Li S, Jiang L, Li X, Lin F, Wang Y, Li B, et al. Clinical and pathological investigation of patients with severe COVID-19. JCI Insight 2020. doi:10.1172/jci.insight.138070.
24. Chi Y, Ge Y, Wu B, Zhang W, Wu T, Wen T, et al. Serum Cytokine and Chemokine Profile in Relation to the Severity of Coronavirus Disease 2019 in China. The Journal of infectious diseases. 2020;222:746–54. doi:10.1093/infdis/jiaa363.
25. Rogers MC, Lamens KD, Shafagati N, Johnson M, Oury TD, Joyce S, Williams JV. CD4+ Regulatory T Cells Exert Differential Functions during Early and Late Stages of the Immune Response to Respiratory Viruses. J Immunol. 2018;201:1253–66. doi:10.4049/jimmunol.1800096.
26. Yang M, Li CK, Li K, Hon KLE, Ng MHL, Chan PKS, Fok TF. Hematological findings in SARS patients and possible mechanisms (review). Int J Mol Med. 2004;14:311–5.
27. Zhang J, Yu M, Tong S, Liu L-Y, Tang L-V. Predictive factors for disease progression in hospitalized patients with coronavirus disease 2019 in Wuhan, China. Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology. 2020;127:104392. doi:10.1016/j.jcv.2020.104392.
28. Moore JB, June CH. Cytokine release syndrome in severe COVID-19. Science. 2020;368:473–4. doi:10.1126/science.abb8925.
29. Jones SA, Jenkins BJ. Recent insights into targeting the IL-6 cytokine family in inflammatory diseases and cancer. Nat Rev Immunol. 2018;18:773–89. doi:10.1038/s41577-018-0066-7.
30. Gupta S, Bi R, Kim C, Chiplunkar S, Yel L, Gollapudi S. Role of NF-kappaB signaling pathway in increased tumor necrosis factor-alpha-induced apoptosis of lymphocytes in aged humans. Cell Death Differ. 2005;12:177–83. doi:10.1038/sj.cdd.4401557.

31. Diao B, Wang C, Tan Y, Chen X, Liu Y, Ning L, et al. Reduction and Functional Exhaustion of T Cells in Patients With Coronavirus Disease 2019 (COVID-19). Front Immunol. 2020;11:827. doi:10.3389/fimmu.2020.00827.
32. Costela-Ruiz VJ, Illescas-Montes R, Puerta-Puerta JM, Ruiz C, Melguizo-Rodríguez L. SARS-CoV-2 infection: The role of cytokines in COVID-19 disease. Cytokine Growth Factor Rev 2020. doi:10.1016/j.cytogfr.2020.06.001.
33. Shi C, Pamer EG. Monocyte recruitment during infection and inflammation. Nat Rev Immunol. 2011;11:762–74. doi:10.1038/nri3070.

Tables

Table 1. Main characteristics and quality of the included studies.

Author	Study Design	Country	Age (years)	Sample size (Severe)	Sample size (Mild)	Sample size	Sex (male %)
Chen G. 2020 [3]	Retrospective	China	56 (50–65)	11	10	21	17 (81%)
Chen R. 2020 [10]	Retrospective	China	56±15	155	345	500	313 (57.1%)
Du R. 2020 [9]	Prospective	China	69±8	21	42	63	30 (47.6%)
He R. 2020 [6]	Retrospective	China	49 (34-62)	69	135	204	79 (38.7%)
Jiang M. 2020 [11]	Retrospective	China	46 (17-88)	17	86	103	58 (56.3%)
Liu Y. 2020 [12]	Retrospective	China	/	30	46	76	/
Ma J. 2020 [13]	Retrospective	China	62 (59–70)	17	20	37	20 (54%)
Qin C. 2020 [4]	Retrospective	China	58 (47-67)	27	17	44	235 (52%)
Sun D. 2020 [14]	Retrospective	China	65	11	25	36	29 (80.5%)
Wan S. 2020 [15]	Retrospective	China	46	21	102	123	66 (53.7%)
Wang F. 2020 [16]	Retrospective	China	69 ± 9	14	14	28	21 (75%)
Zhang J. 2020 [17]	Retrospective	China	38 (32-57)	93	18	111	46 (41.4%)
Zheng Y. 2020 [18]	Retrospective	China	49	26	63	89	/
Zhou Y. 2020 [19]	Retrospective	China	42	5	12	17	6 (35.3%)
Zhu Z. 2020 [20]	Retrospective	China	51	111	16	127	45 (35.4%)
Pallotto C. 2020 [21]	Retrospective	Italy	65	13	25	38	19 (50.0%)
Urra J.M. 2020 [22]	Retrospective	Spain	59	27	145	172	104 (60.5%)
Sophie H. 2020 [5]	Retrospective	France	66	38	36	74	60 (81.1%)
Li S. 2020 [23]	Retrospective	China	46	26	43	69	40 (60.0%)
Zhao Y. 2020 [7]	Retrospective	China	48	18	53	71	30 (42.3%)
Chi Y. 2020 [24]	Retrospective	China	46	8	22	30	/

Age is described as mean or mean ± SD or median (IQR).

Table 2. Newcastle-Ottawa Scale (NOS) of included studies

Included studies	Is the definition adequate?	Represent activeness of the cases	Selection of controls	Definition of controls	Comparability of both groups	Ascertainment of diagnosis	Same ascertainment method for both groups	Nonresponse rate	Total scores
Chen G. 2020 [3]	☆	☆	☆	☆	☆	☆	☆	☆	8
Chen R. 2020 [10]	☆	☆	☆	☆	☆	☆	☆	☆	8
Du R. 2020 [9]	☆	☆	☆	☆	☆	☆	☆	☆	8
He R. 2020 [6]	☆	☆	☆	☆	☆	☆	☆	☆	8
Jiang M. 2020 [11]	☆	☆	☆	☆	☆	☆	☆	☆	8
Liu Y. 2020 [12]	☆	☆	☆	☆	/	☆	☆	☆	7
Ma J. 2020 [13]	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Qin C. 2020 [4]	☆	☆	☆	☆	☆	☆	☆	☆	8
Sun D. 2020 [14]	☆	☆	☆	☆	☆	☆	☆	☆	8
Wan S. 2020 [15]	☆	☆	☆	☆	☆	☆	☆	☆	8
Wang F. 2020 [16]	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Zhang J. 2020 [17]	☆	☆	☆	☆	☆	☆	☆	☆	9
Zheng Y. 2020 [18]	☆	☆	☆	☆	☆	☆	☆	☆	8
Zhou Y. 2020 [19]	☆	☆	☆	☆	☆	☆	☆	☆	8
Zhu Z. 2020 [20]	☆	☆	☆	☆	☆	☆	☆	☆	8
Pallotto C. 2020 [21]	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Urra J.M. 2020 [22]	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Sophie H. 2020 [5]	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Li S. 2020 [23]	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Zhao Y. 2020 [7]	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Chi Y. 2020 [24]	☆	☆	☆	☆	☆	☆	☆	☆	8

Figures

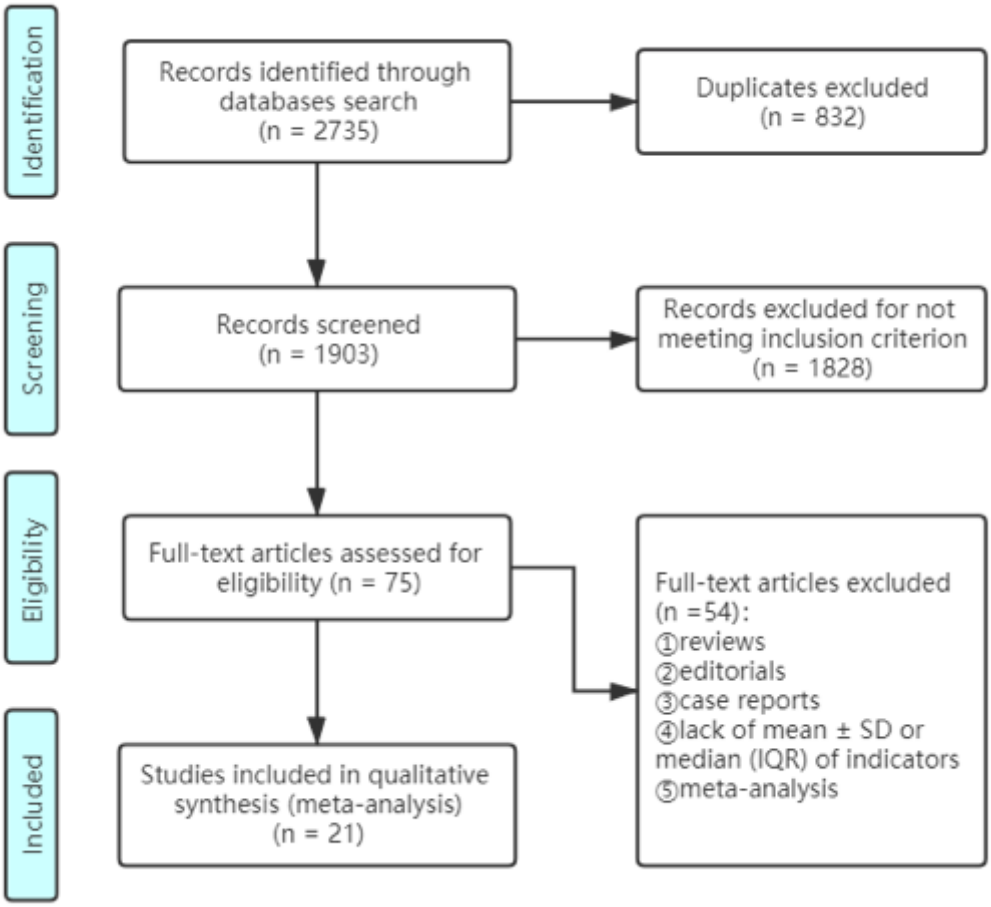


Figure 1

Flow diagram for studies selection

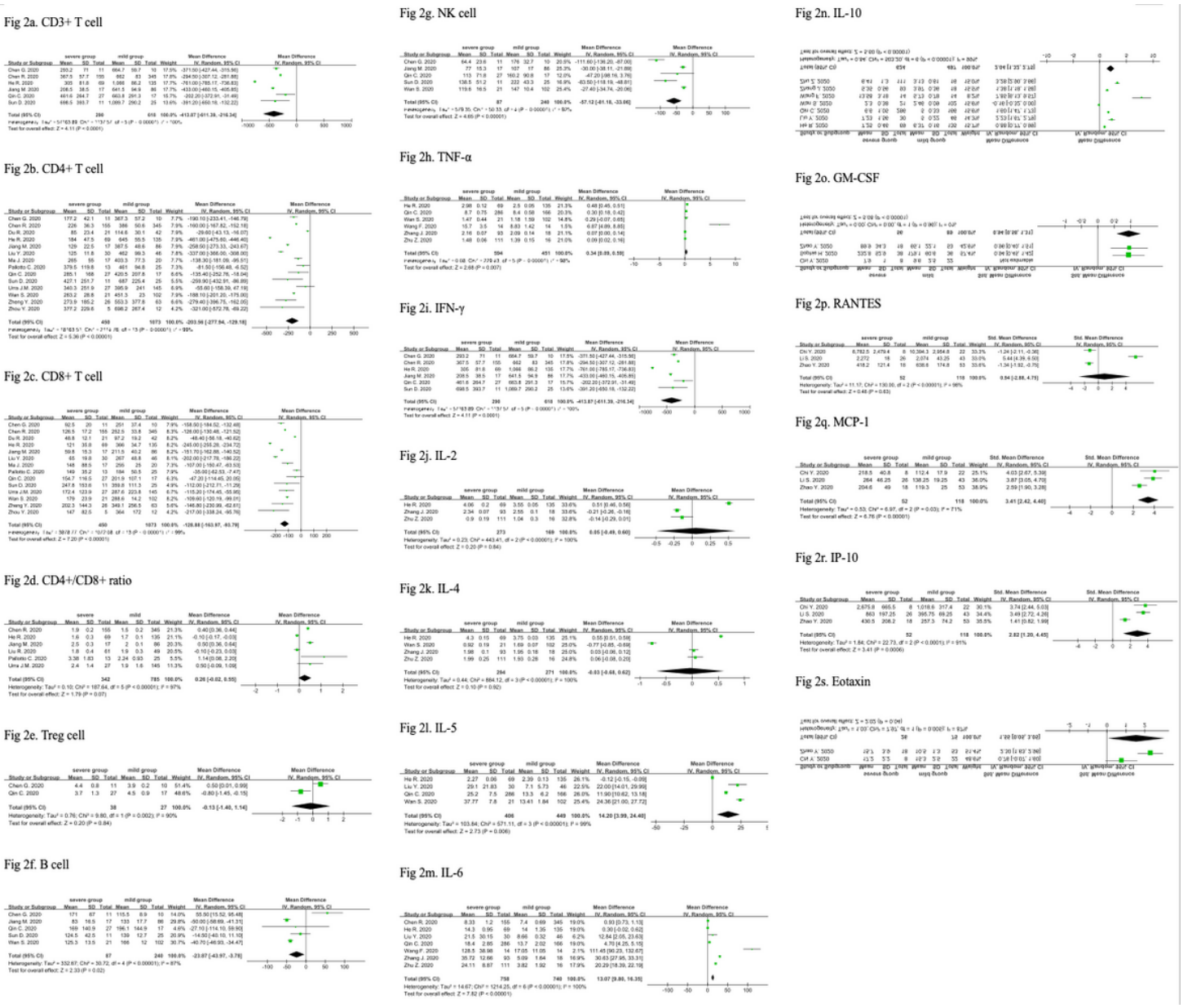


Figure 2

Mean difference of immunological features with COVID-19 severity.

Fig 3a. CD3+ T cell

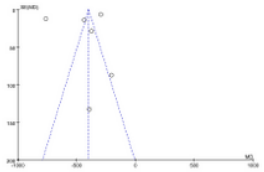


Fig 3b. CD4+ T cell

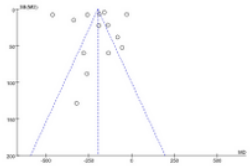


Fig 3c. CD8+ T cell

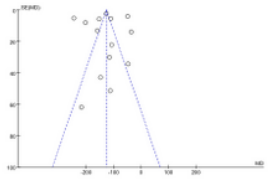


Fig 3d. CD4+/CD8+ ratio

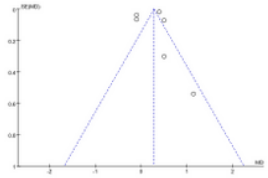


Fig 3e. Treg cell

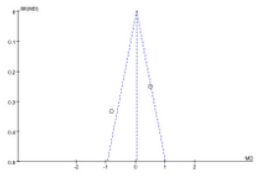


Fig 3f. B cell

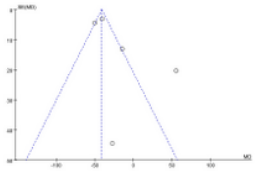


Fig 3g. NK cell

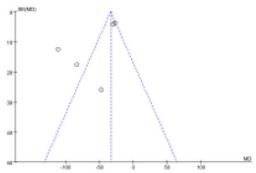


Fig 3h. TNF-α

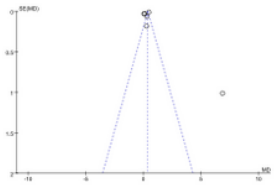


Fig 3i. IFN-γ

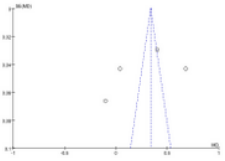
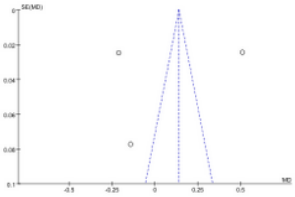


Fig 3j. IL-2



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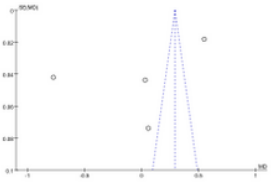
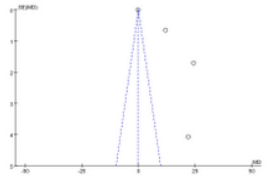


Fig 3l. IL-5



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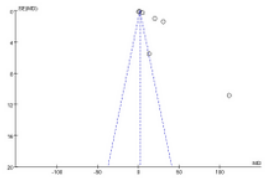

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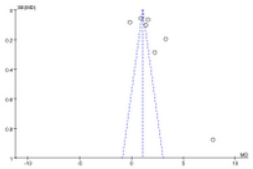


Fig 3o. GM-CSF

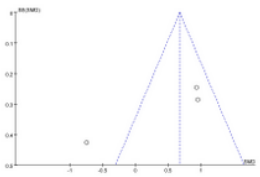


Fig 3p. RANTES

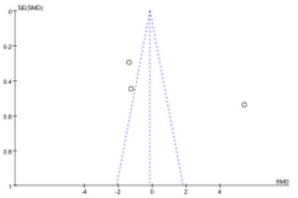
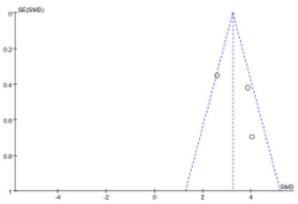


Fig 3q. MCP-1



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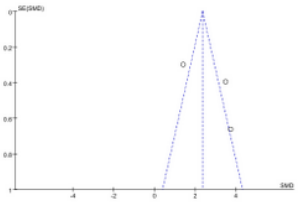

Fig 3s. Eotaxin

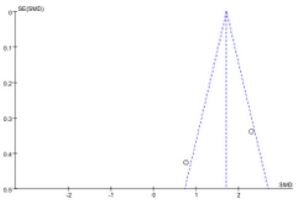

Figure 3

Funnel plots of immunological features with COVID-19 severity.