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 and Web of Science.

Results

A total of 16 studies with 1689 COVID-19 patients were included. Compared with mild cases, severe cases showed significantly lower levels of 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, -225.89; 95%CI, -306.36 to -145.43), CD8+ T cell ($\times 10^6$, MD, -138.59; 95%CI, -176.36 to -100.82), 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 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). However, no significant differences were found in other indicators, 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), Treg cell ($\times 10^6$, MD, -0.13; 95%CI, -1.40 to 1.14), and CD4+/CD8+ ratio (MD, 0.17; 95%CI, -0.14 to 0.49).

Conclusion

Our meta-analysis revealed significant lower levels in immune cells (CD3+ T, CD4+ T, CD8+ T, B and NK cells) and significant higher levels in cytokines (TNF-α, IL-5, IL-6 and IL-10) 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 June 16, 2020, the SARS-CoV-2 has infected over 8 million patients and caused over 440,000 deaths. 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 [2]. 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 [3]. However, other studies revealed no significant differences in CD4\(^+\) and CD8\(^+\) T cell [3] and some cytokines (IL-5, IL-6 and IL-10) [4] between severe cases and mild cases. Thus, we presented a meta-analysis of 15 studies in order to assess the association between immune cells (CD4\(^+\) T, CD8\(^+\) T, CD3\(^+\) T, Treg, B, and NK cells) and cytokines (TNF-α, interferon gamma (IFN-γ), IL-2, IL-4, IL-5, IL-6 and IL-10) and COVID-19 severity.

## Methods

### Search Strategy

We performed a systematic literature search to identify relevant studies published up to June 16, 2020 in PubMed and Web of Science. The following combined search terms were used: 1) (“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”); 2) (“Novel coronavirus” OR “Coronavirus disease 2019” OR “Coronavirus 2019” OR “nCoV-2019” OR “2019-nCoV” OR “COVID-19” OR “SARS-CoV-2”) and (“interferon gamma” OR “tumor necrosis factor alpha” OR “IL-2” OR “IL-4” OR “IL-5” OR “IL-6” OR “IL-10”).

### Study selection

Inclusion criteria of the study were as follows: 1) it provided data on 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) with mean ± standard deviation (SD) or median (interquartile range, IQR); 2) patients could be grouped into severe cases and mild cases; and 3) it provided clear information on COVID-19 confirmation and included patients.

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 COVID-19 severity.
IL-4, IL-5, IL-6 and IL-10). Median (IQR) were converted to mean ± SD using mathematical formulas according to Hozo et al [5].

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 ≤50% or p ≥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, 36 full articles were retrieved and 15 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 15 included studies, with 628 severe cases and 951 mild cases of COVID-19 reported. All but one prospective study of the studies included in this meta-analysis were retrospective studies, which were 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 immune cells, CD3^+ T cell (×10^6, MD, -413.87; 95%CI, -611.39 to -216.34; I^2, 100%; p<0.001, Fig 2a), CD4^+ T cell (×10^6, MD, -225.89; 95%CI, -306.36 to -145.43; I^2, 99%; p<0.001, Fig 2b), CD8^+ T cell (×10^6, MD, -138.59; 95%CI, -176.36 to -100.82; I^2, 99%; p<0.001, Fig 2c), B cell (×10^6/L; MD, -23.87; 95%CI, -43.97 to -3.78; I^2, 87%; p<0.001, Fig 2f), and NK cell (×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, 0.17; 95%CI, -0.14 to 0.49; I^2, 98%; p<0.001, Fig 2d) and Treg cell (×10^6, MD, -0.13; 95%CI, -1.40 to 1.14; I^2, 90%; p<0.001, Fig 2e).
Association of cytokines with COVID-19 severity

Compared with mild cases, severe cases showed significantly higher levels of 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 2i), 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).

Sensitivity Analysis

Strong evidences of heterogeneity were found in all the comparisons (Fig 2). Sensitivity analyses demonstrated that the results were not obviously altered by excluding any one specific study and therefore our results were reliable and believable.

Publication bias

Given that the number of included studies for each indicator was not large enough, we did not assess the publication bias.

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 [18]. Our study mainly compared the level differences of immune cells and cytokines 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 [2, 8, 12]. Only two studies reported no significant decrease in CD8^+ T cell level [3, 16], while one study reported higher levels of B cell [11] 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) 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 [17]. CD4^+ T cells could activate the CD8^+ T cell response to acute respiratory virus infection [18]. SARS-CoV-2 and associated
autoimmune antibodies may lead to growth inhibition and apoptosis of hematopoiesis [19], which may decrease the production and maturation of immune cells [4].

Regarding cytokines, the conclusions of different studies are also inconsistent. With the exception of one study on IL-6 [4] 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 [3, 13, 17, 20]. 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 [21]. 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 [22]. TNF-α is a pro-inflammatory cytokine that can promote T cell apoptosis [23]. 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 [24]. This fact is strengthened by our meta-analysis results.

**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, all but one prospective trial of the studies included in this meta-analysis were retrospective studies. Third, the overall generalizability of the meta-analysis results should be interpreted with caution as all 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 in immune cells (CD3+ T, CD4+ T, CD8+ T, B and NK cells) and significant higher levels in cytokines (TNF-α, IL-5, IL-6 and IL-10) in severe cases compared with mild cases of COVID-19 patients. However, the levels of IL-2, IL-4, IFN-γ, Treg cell and CD4+/CD8+ ratio 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.

**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;

Declarations

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.

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Authors’ contributions

Conception: ZZ, HJ. Literature search: ZZ, HJ. 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, HJ. Manuscript editing and revision: LS. Manuscript final version approval: ZZ, QH. Guarantor of the review: HJ.

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### Tables

Table 1. Main characteristics and quality of the included studies.
Age is described as mean ± SD or median (IQR)

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

| Author          | Study Design | Country | Age (years) | Sample size (Severe) | Sample size (Mild) | Sample size (Male) | Quality |
|-----------------|--------------|---------|-------------|----------------------|--------------------|--------------------|---------|
| Chen G. 2020[2] | Retrospective | China   | 56.0        | 11                   | 10                 | 21                 | 17      | 8       |
| Chen R. 2020[6] | Retrospective | China   | 56.0±14.    | 155                  | 345                | 500                | 313     | 8       |
| Du R. 2020[7]   | Prospective  | China   | 69.7±7.7    | 21                   | 42                 | 63                 | 30      | 8       |
| He R. 2020[4]   | Retrospective | China   | 49 (34-)    | 69                   | 135                | 204                | 79      | 8       |
| Jiang M. 2020[8] | Retrospective | China   | 46 (17-)    | 17                   | 86                 | 103                | 58      | 8       |
| Liu Y. 2020[9]  | Retrospective | China   | /           | 30                   | 46                 | 76                 | /       | 7       |
| Ma J. 2020[10]  | Retrospective | China   | 62          | 17                   | 20                 | 37                 | 20      | 8       |
| Qin C. 2020[3]  | Retrospective | China   | 58 (47-)    | 27                   | 17                 | 44                 | 235     | 8       |
| Sun D. 2020[11] | Retrospective | China   | 65          | 11                   | 25                 | 36                 | 29      | 8       |
| Wan S. 2020[12] | Retrospective | China   | 46          | 21                   | 102                | 123                | 66      | 8       |
| Wang F. 2020[13]| Retrospective | China   | 68.6 ±     | 14                   | 14                 | 28                 | 21      | 8       |
| Zhang J. 2020[14]| Retrospective | China   | 38 (32-)    | 93                   | 18                 | 111                | 46      | 9       |
| Zheng Y. 2020[15]| Retrospective | China   | 49.4        | 26                   | 63                 | 89                 | /       | 8       |
| Zhou Y. 2020[16]| Retrospective | China   | 42          | 5                    | 12                 | 17                 | 6       | 9       |
| Zhu Z. 2020[17] | Retrospective | China   | 50.9        | 111                  | 16                 | 127                | 45      | 9       |

Figures
Figure 1

Flow diagram for studies selection
### aCD5 Test

| Study of Substance | Mean | SD | Total | Weight | (t) | P Value |
|-------------------|------|----|-------|--------|-----|---------|
| Ctrl 2015         | 1.16 | 0.1 | 158.5 | 118.5  | -1.72 | 0.086   |
| Ctrl 2015         | 1.72 | 0.1 | 208.5 | 208.5  | -2.12 | 0.035   |
| Ctrl 2016         | 1.16 | 0.1 | 158.5 | 158.5  | -1.72 | 0.086   |
| Total             |      |     |       |        |      |         |
| DOS               |      |     |       |        |      |         |
| Ctrl 2015         | 1.16 | 0.1 | 158.5 | 118.5  | -1.72 | 0.086   |
| Ctrl 2015         | 1.72 | 0.1 | 208.5 | 208.5  | -2.12 | 0.035   |
| Ctrl 2016         | 1.16 | 0.1 | 158.5 | 158.5  | -1.72 | 0.086   |
| Total             |      |     |       |        |      |         |
| bCD4 Test         |      |     |       |        |      |         |

### cCD5 Test

| Study of Substance | Mean | SD | Total | Weight | (t) | P Value |
|-------------------|------|----|-------|--------|-----|---------|
| Ctrl 2015         | 1.16 | 0.1 | 158.5 | 118.5  | -1.72 | 0.086   |
| Ctrl 2015         | 1.72 | 0.1 | 208.5 | 208.5  | -2.12 | 0.035   |
| Ctrl 2016         | 1.16 | 0.1 | 158.5 | 158.5  | -1.72 | 0.086   |
| Total             |      |     |       |        |      |         |
| DOS               |      |     |       |        |      |         |
| Ctrl 2015         | 1.16 | 0.1 | 158.5 | 118.5  | -1.72 | 0.086   |
| Ctrl 2015         | 1.72 | 0.1 | 208.5 | 208.5  | -2.12 | 0.035   |
| Ctrl 2016         | 1.16 | 0.1 | 158.5 | 158.5  | -1.72 | 0.086   |
| Total             |      |     |       |        |      |         |
| dCD4 CDS ratio    |      |     |       |        |      |         |

### eCD8 Test

| Study of Substance | Mean | SD | Total | Weight | (t) | P Value |
|-------------------|------|----|-------|--------|-----|---------|
| Ctrl 2015         | 1.16 | 0.1 | 158.5 | 118.5  | -1.72 | 0.086   |
| Ctrl 2015         | 1.72 | 0.1 | 208.5 | 208.5  | -2.12 | 0.035   |
| Ctrl 2016         | 1.16 | 0.1 | 158.5 | 158.5  | -1.72 | 0.086   |
| Total             |      |     |       |        |      |         |
| DOS               |      |     |       |        |      |         |
| Ctrl 2015         | 1.16 | 0.1 | 158.5 | 118.5  | -1.72 | 0.086   |
| Ctrl 2015         | 1.72 | 0.1 | 208.5 | 208.5  | -2.12 | 0.035   |
| Ctrl 2016         | 1.16 | 0.1 | 158.5 | 158.5  | -1.72 | 0.086   |
| Total             |      |     |       |        |      |         |
| F4/80             |      |     |       |        |      |         |

### gCD8 Test

| Study of Substance | Mean | SD | Total | Weight | (t) | P Value |
|-------------------|------|----|-------|--------|-----|---------|
| Ctrl 2015         | 1.16 | 0.1 | 158.5 | 118.5  | -1.72 | 0.086   |
| Ctrl 2015         | 1.72 | 0.1 | 208.5 | 208.5  | -2.12 | 0.035   |
| Ctrl 2016         | 1.16 | 0.1 | 158.5 | 158.5  | -1.72 | 0.086   |
| Total             |      |     |       |        |      |         |
| DOS               |      |     |       |        |      |         |
| Ctrl 2015         | 1.16 | 0.1 | 158.5 | 118.5  | -1.72 | 0.086   |
| Ctrl 2015         | 1.72 | 0.1 | 208.5 | 208.5  | -2.12 | 0.035   |
| Ctrl 2016         | 1.16 | 0.1 | 158.5 | 158.5  | -1.72 | 0.086   |
| Total             |      |     |       |        |      |         |
| hCD8 Test         |      |     |       |        |      |         |

### iNK Cell Test

| Study of Substance | Mean | SD | Total | Weight | (t) | P Value |
|-------------------|------|----|-------|--------|-----|---------|
| Ctrl 2015         | 1.16 | 0.1 | 158.5 | 118.5  | -1.72 | 0.086   |
| Ctrl 2015         | 1.72 | 0.1 | 208.5 | 208.5  | -2.12 | 0.035   |
| Ctrl 2016         | 1.16 | 0.1 | 158.5 | 158.5  | -1.72 | 0.086   |
| Total             |      |     |       |        |      |         |
| DOS               |      |     |       |        |      |         |
| Ctrl 2015         | 1.16 | 0.1 | 158.5 | 118.5  | -1.72 | 0.086   |
| Ctrl 2015         | 1.72 | 0.1 | 208.5 | 208.5  | -2.12 | 0.035   |
| Ctrl 2016         | 1.16 | 0.1 | 158.5 | 158.5  | -1.72 | 0.086   |
| Total             |      |     |       |        |      |         |
| hTRF-a             |      |     |       |        |      |         |

### jIL-2 Test

| Study of Substance | Mean | SD | Total | Weight | (t) | P Value |
|-------------------|------|----|-------|--------|-----|---------|
| Ctrl 2015         | 1.16 | 0.1 | 158.5 | 118.5  | -1.72 | 0.086   |
| Ctrl 2015         | 1.72 | 0.1 | 208.5 | 208.5  | -2.12 | 0.035   |
| Ctrl 2016         | 1.16 | 0.1 | 158.5 | 158.5  | -1.72 | 0.086   |
| Total             |      |     |       |        |      |         |
| DOS               |      |     |       |        |      |         |
| Ctrl 2015         | 1.16 | 0.1 | 158.5 | 118.5  | -1.72 | 0.086   |
| Ctrl 2015         | 1.72 | 0.1 | 208.5 | 208.5  | -2.12 | 0.035   |
| Ctrl 2016         | 1.16 | 0.1 | 158.5 | 158.5  | -1.72 | 0.086   |
| Total             |      |     |       |        |      |         |
| hIL-4             |      |     |       |        |      |         |

### nIL-5 Test

| Study of Substance | Mean | SD | Total | Weight | (t) | P Value |
|-------------------|------|----|-------|--------|-----|---------|
| Ctrl 2015         | 1.16 | 0.1 | 158.5 | 118.5  | -1.72 | 0.086   |
| Ctrl 2015         | 1.72 | 0.1 | 208.5 | 208.5  | -2.12 | 0.035   |
| Ctrl 2016         | 1.16 | 0.1 | 158.5 | 158.5  | -1.72 | 0.086   |
| Total             |      |     |       |        |      |         |
| DOS               |      |     |       |        |      |         |
| Ctrl 2015         | 1.16 | 0.1 | 158.5 | 118.5  | -1.72 | 0.086   |
| Ctrl 2015         | 1.72 | 0.1 | 208.5 | 208.5  | -2.12 | 0.035   |
| Ctrl 2016         | 1.16 | 0.1 | 158.5 | 158.5  | -1.72 | 0.086   |
| Total             |      |     |       |        |      |         |
Figure 2

Mean difference of immunological features with COVID-19 severity. Weights were calculated from binary random-effects model analysis.