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A systematic review and meta-analysis on the association between lymphocyte subsets and the severity of COVID-19

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Abstract

Introduction: Prominent prognostic parameters that reflect the severity of coronavirus disease 2019 (COVID-19) to adopt an appropriate therapeutic approach are not fully identified. This systematic review and meta-analysis aimed to explore the association between lymphocyte variation and disease severity in COVID-19 individuals.
Methods: We searched Web of Science, Scopus, PubMed, EMBASE and WHO website to retrieve studies investigating lymphocyte subset counts in non-severe and severe cases of COVID-19. The pooled standardized mean difference (SMD) between two groups and the pooled average count of each lymphocyte subset were assessed by employing a random-effect model.
Results: Thirty-nine investigations on 5,087 participants, including 3,578 non-severe patients and 1,509 severe patients, were included. The pooled analysis showed that non-severe patients had higher total T lymphocytes (SMD = 1.01; 95% CI: 0.82, 1.20; I^2 = 75.7%), T helper cells (SMD = 1.07; 95% CI: 0.85, 1.28; I^2 = 85.4%), T cytotoxic cells (SMD = 1.07; 95% CI: 0.82, 1.32; I^2 = 87.1%), B cells (SMD = 0.72; 95% CI: 0.45, 0.98; I^2 = 79.7%), and natural killer cells (SMD = 0.65; 95% CI: 0.47, 0.84; I^2 = 63.1%) than severe patients and the average count of the corresponding lymphocyte signatures in non-severe patients/severe patients were 878.88/448.40, 493.12/268.96, 311.91/158.91, 177.09/110.37, and 155.02/103.09 cells/μL, respectively.
Conclusion: Lymphopenia may be a dilemma in COVID-19 management because over-activation of lymphocytes may lead to cytokine storm or acute respiratory distress syndrome (ARDS). In contrast, lymphopenia may increase SARS-CoV-2 amplification and COVID-19 severity. Therefore, novel therapies targeting lymphocyte proliferation or contraction may counterbalance lymphocyte counts in these patients.

Introduction

In December 2019, individuals infected with a novel kind of viral pneumonia were reported in Wuhan, China. Novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified to cause coronavirus disease 2019 (COVID-19) (1). The clinical manifestations of most patients with COVID-19 range from mild to severe symptoms. Lymphocyte subsets play important roles in the integrity and regulation of the immune system. Viral infections, especially SARS-CoV-2 infection, can dysregulate lymphocyte counts and function. Patients with COVID-19 showed

Key point

This meta-analysis showed reduced level of total T cells, CD4+ T cells, CD8+ T cells, B cells, and NK cells in severe cases of COVID-19 compared to non-severe cases. By considering the decrease or increase of these immune cells in patients with severe COVID-19, the appropriate diagnosis, prognosis, follow-up, targeted therapy, and response to the treatment will be more achievable in these patients.

contradictory patterns of natural killer (NK) cells, CD4+ T cells, CD8+ T cells, and B cells (2,3). T cells play an important role in virus eradication where CD4+ T cells (T helper cells) help other immune cells, especially activated CD8+ T cells (T cytotoxic cells) produce cytokines and eliminate molecules to combat the virus. Moreover, CD4+ T cells help B cells and macrophages enhance their capacity to eliminate pathogens by antibody production and phagocytosis, respectively (3). Viral infections usually induce lymphocytosis, especially CD8+ T cell responses; however, contradictory findings have been reported regarding lymphopenia and interferonopathy in individuals with severe COVID-19; therefore, this systematic review and meta-analysis aimed to explore the association among lymphocyte variation and disease severity in COVID-19 patients.

Methods

Protocol registration

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for this systematic review and the research question was determined with PICO framework as follows: what is the alteration of lymphocyte subsets (O) in severe patients (I) compared to non-severe patients (C) with COVID-19 infection (P).

Search strategy and study selection

PubMed, Web of Science, Scopus, EMBASE and WHO were searched for related studies on "lymphocyte", "severity", and "COVID-19" from the emergence of COVID-19 to 1 April 2021. Two authors (H.D. and H.A.) independently reviewed the titles and abstracts of the retrieved articles and then all selected articles by two authors were again screened based on the full text of manuscripts. Two authors (H.D. and H.A.) had discussed the disagreements in eligibility of studies, and if they did not reach a consensus, the third author (A.K.) made a decision.

Inclusion and exclusion criteria

All studies investigating any lymphocyte subset including T cell, B cell, NK cell (natural killer cell), CD4+ T helper cell and CD8+ T cytotoxic cells in the severe and non-severe patients infected with COVID-19 were included in this study. Exclusion criteria were case reports, case series, reviews, editorials, comments, expert opinions, nonhuman studies, studies that did not report the immune signatures quantitatively, studies that did not clarify the severity status of patients, and studies on the pediatric population or patients with any medications/conditions that induced immunosuppression or changed immune cell counts.

Data extraction

Two authors independently extracted the following data from the included studies; authors' name, title, country of population, study design, date of publication, total sample size, the sample size of each group, subgroup definition, number and percentage of gender, average age, and its dispersion, average lymphocyte subsets count and their dispersions. Finally, two authors compared the extraction files of each other and solved the mismatches with a third author consulted in a case of conflict.

Quality assessment

The risk of bias assessment of the included studies was conducted with the Newcastle-Ottawa Quality Assessment Scale (NOQAS) and conducted by two authors, independently. In this part, no disagreement was left after two authors had reviewed and discussed their files.

Statistical analysis

All statistical analyses were conducted in STATA software (version 14.1). First, we extracted the mean count of lymphocyte subsets and their dispersion in non-severe and severe groups of COVID-19 individuals directly or indirectly by calculating the mean and standard deviation (SD) from median and interquartile range (IQR). Second, we computed standardized mean difference (SMD) between the two groups. Finally, we carried out a meta-analysis employing the random-effects model to pool the SMDs of each lymphocyte subset. Besides, we meta-analyzed each lymphocyte subset count to determine the pooled lymphocyte subsets count in non-severe and severe groups. We demonstrated the pooled SMDs and pooled lymphocyte subset counts in the forest plots. The Cochran Q test and I^2 index were applied to test the heterogeneity. P value<0.05 was considered to be significant in all statistical tests.

Results

Study selection and baseline characteristics

We retrieved a total of 5,877 documents through searching international databases. Besides, we found 15 eligible documents by manually searching the reference list of the incorporated articles. Finally, 39 articles (4-42) met the inclusion and exclusion criteria that were extracted for qualitative and quantitative analysis. Figure 1 shows the PRISMA diagram of the study. A total of 5087 participants with COVID-19 were included in our meta-analysis,

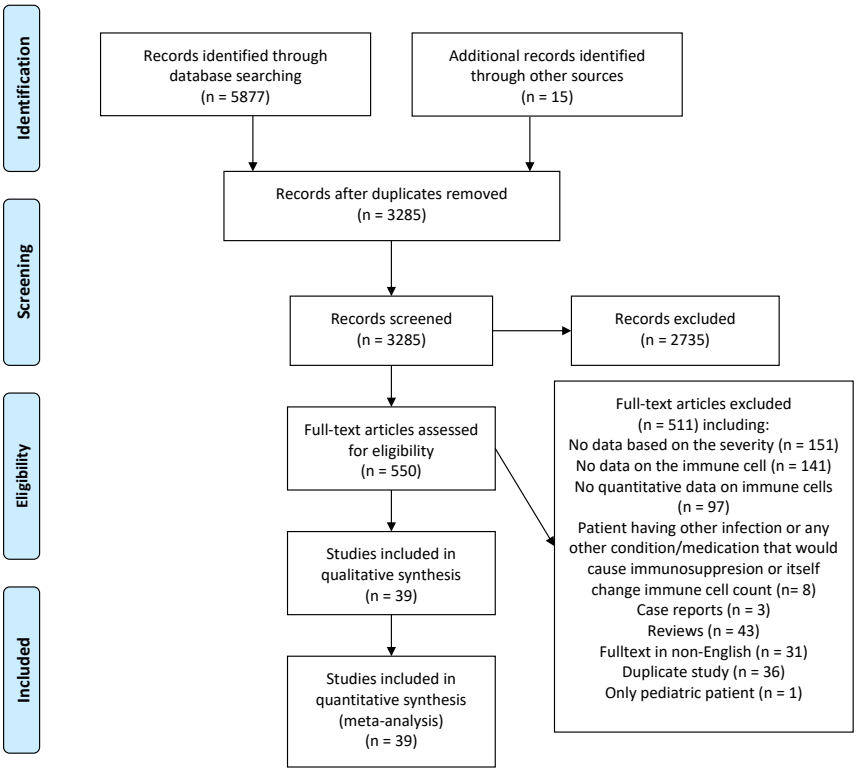

Figure 1. The PRISMA flowchart of the included studies.

including 3578 non-severe patients and 1509 severe patients. The sample sizes of the included studies ranged from 21 to 500, with 10 to 345 in the non-severe group and 5 to 155 in the severe group. The mean age of participants ranged from 42.3 years to 65.5 years. Table 1 shows the baseline characteristics of the study population.

Total T lymphocyte variation

The meta-analysis on 27 studies (4-6,8-10,15,16,18-20, 22,24-27,29-32,35-39,41,42) which assessed absolute T lymphocyte count in non-severe and severe cases showed that non-severe individuals had significantly higher total T cell count than severe patients (SMD = 1.01; 95% CI: 0.82, 1.20; I^2 = 75.7%, *P* value < 0.001). Besides, we found that the average T cell count in non-severe patients was 878.88 cells/μL (95% CI: 818.08, 939.69) and in severe patients was 448.40 cells/μL (95% CI: 396.10, 500.71). The forest plots of pooled SMD for total T cell and pooled average T cell count in non-severe and severe groups are shown in Figure 2.

$CD4^+$ T cell variation

Thirty-nine studies (4-42) explored the count of $CD4^+$ T cells in non-severe and severe patients. The pooled analysis showed that non-severe patients significantly had higher $CD4^+$ T cell count than severe patients (SMD=1.07; 95% CI: 0.85, 1.28; I^2 = 85.4%, *P* value<0.001). In this instance, non-severe patients had a pooled $CD4^+$ T cell count of 493.12 cells/μL (95% CI: 470.87, 515.38), and severe patients had a pooled $CD4^+$ T cell count of 268.96 cells/μL (95% CI: 239.56, 298.37). The forest plots of pooled SMD for $CD4^+$ T cells and pooled average $CD4^+$ T cell count in non-severe and severe groups are shown in Figure 3.

$CD8^+$ T cell variation

Around 35 studies (4-10,12,13,15-34,37-42) explored the count of $CD8^+$ T cells in non-severe and severe patients. The pooled SMD of $CD8^+$ T cells between groups showed that non-severe patients significantly had higher $CD8^+$ T cell count than severe patients (SMD = 1.07; 95% CI: 0.82, 1.32; I^2 = 87.1%, *P* value < 0.001). In this instance, non-severe patients had a pooled $CD8^+$ T cell count of 311.91 cells/μL (95% CI: 295.70, 328.12) and severe patients had a pooled $CD8^+$ T cell count of 158.91 cells/μL (95% CI: 140.05, 177.77). The forest plots of pooled SMD for $CD8^+$ T cells and pooled average $CD8^+$ T cell count in non-severe and severe groups are shown in Figure 4.

B cell variation

Twenty-two studies (4,6,9-11,13,15,16,18,19,22,24-26, 29-31,35,36,38,39,42) explored the count of B cells in non-severe and severe patients. The pooled SMD for B cells count was 0.72 with 95% CI of 0.45 to 0.98 (I^2 = 79.7%, *P* value < 0.001). Thus, the absolute B cells count was significantly higher in non-severe cases than those in severe patients. Further analysis showed that the pooled average B cells count in non-severe patients was 177.09 cells/μL (95% CI:163.06, 191.11) while in those severe

Table 1. Baseline characteristics of included studies

Author, Year	Country	Study design	Sample size (n)	Subgroup definition	Male, n (%)	Age, mean (SD) (years)	Lymphocyte subsets
Chen et al (4), 2020	China	Retrospective cross-sectional	21	10 Moderate/ 11 severe	17 (81%)	55.9 (8)	T, NK, B, Th, Ts cells
Liu et al (5) 2020	China	Retrospective cross-sectional	110	49 Moderate/ 61 severe	60 (54.5%)	63.5 (13.8)	T, NK, Th, Ts cells
Xu et al (6) 2020	China	Retrospective cross-sectional	125	80 Mild/ 45 severe	69 (55%)	60.5 (15.1)	T, NK, B, Th, Ts cells
Yang et al (7) 2020	China	Retrospective cross-sectional	39	14 Moderate/ 25 severe	11 (29%)	57.6 (6.6)	Th, Ts cells
Chen et al (8) 2020	China	Cohort (historical/ retrospective)	500	345 Mild, moderate/155 severe	285 (57%)	65 (12.7)	T, Th, Ts cells
Zhang et al (9) 2020	China	Cohort (historical/ retrospective)	310	5Asymptomatic/ 293 mild/ 12 severe	NR	NR	T, NK, B, Th, Ts cells
Qin et al (10) 2020	China	Retrospective cross-sectional	44	17 Non-severe/ 27 severe	NR	57.1 (13.7)	T, NK, B, Th, Ts cells
Zheng et al (11) 2020	China	Cohort (historical/ retrospective)	68	55 Mild/ 13 severe	36 (53%)	47.1 (48.6)	B, Th cells
liu et al (12) 2020	China	Cohort (historical/retrospective)	76	46 Mild/30 severe	NR	NR	Th, Ts cells
Wan et al(13) 2020	China	Cohort (prospective)	123	102 Mild/ 21 severe	66 (54%)	46.1 (13.4)	NK, B, Th, Ts cells
Yang P et al (14) 2020	China	Cohort (historical/ retrospective)	133	65 Mild/ 68 severe	72 (54%)	50.8 (15.7)	Th cells
jiang et al (15) 2020	China	Case-Control	103	86 Mild, moderate/ 17 severe	58 (56%)	49.7 (10.5)	T, NK, B, Th, Ts cells
Liu et al (16) 2020	China	Retrospective cross-sectional	39	21 Mild, moderate/ 18 severe, critical	NR	51.7 (14.4)	T, NK, B, Th, Ts cells
Wei et al (17) 2020	China	Retrospective cross-sectional	167	137 Non-severe/ 30 severe	95 (57%)	42.3 (14.9)	Th, Ts cells
Sun et al (18) 2020	China	Retrospective cross-sectional	54	8 Mild/ 36 moderate/ 10 severe	31 (58%)	47.1 (41.9)	T, NK, B, Th, Ts cells
He et al (19) 2020	China	Retrospective cross-sectional	204	135 Non-severe/ 69 severe	79 (39%)	49 (16.2)	T, NK, B, Th, Ts cells
Feng et al (20) 2020	China	Retrospective cross-sectional	240	214 Moderate/ 26 severe	134 (56%)	51.5 (18.5)	T, Th, Ts cells
Ma J et al (21) 2020	China	Retrospective cross-sectional	37	17 Mild/ 20 severe, critical	20 (54%)	64 (7)	Th, Ts cells
Li S et al (22) 2020	China	Retrospective cross-sectional	69	43 Non-severe/ 26 severe	40 (58%)	47.5 (19.3)	T, NK, B, Th, Ts cells
Yang F et al (23) 2020	China	Retrospective cross-sectional	52	33 Mild/ 19 severe, critical	NR	NR	Th, Ts cells
Li X et al (24) 2020	China	Retrospective cross-sectional	215	159 Non-severe/ 56 severe	127 (59%)	44.5 (23.2)	T, NK, B, Th, Ts cells
Han M et al (25) 2020	China	Retrospective cross-sectional	154	122 Mild/ 32 severe	86 (56%)	42.5 (14.7)	T, NK, B, Th, Ts cells

Table 1. Continued

Author, Year	Country	Study design	Sample size (n)	Subgroup definition	Male, n (%)	Age, mean (SD) (years)	Lymphocyte subsets
Liu J et al (26) 2020	China	Retrospective cross-sectional	156	62 Moderate/ 94 severe	75 (48%)	65.5 (13)	T, NK, B, Th, Ts cells
Xiong et al (27) 2020	China	Retrospective cross-sectional	116	61 Non-severe/ 55 severe	81 (70%)	58 (18.5)	T, Th, Ts cells
Kalpakci et al (28) 2020	Turkey	Retrospective cross-sectional	40	20 Non-severe/ 20 severe	20 (50%)	63.6 (14)	Th, Ts cells
Zou et al (29) 2020	China	Retrospective cross-sectional	121	69 Non-severe/ 52 severe	66 (55%)	64.4 (12.4)	T, NK, B, Th, Ts cells
He et al (30) 2020	China	Retrospective cross-sectional	53	32 Mild/ 21 severe	NR	NR	T, NK, B, Th, Ts cells
Wu et al (31) 2020	China	Retrospective cross-sectional	60	31 Mild/ 29 severe	37 (62%)	57.8 (17.2)	T, NK, B, Th, Ts cells
Wu et al (32) 2020	China	Cohort (historical/retrospective)	201	117 Not ARDS/ 84 ARDS	128 (64%)	52.2 (11.9)	T, Th, Ts cells
Chen et al (33) 2020	China	Retrospective cross-sectional	123	13Asymptomatic/ 16mild/ 89 moderate/ 5 severe	65 (53%)	45.3 (17)	Th, Ts cells
Zhou et al (34) 2020	China	Cohort (prospective)	83	66 Non-severe/ 17 severe	42 (51%)	46.7 (14)	Th, Ts cells
Jin et al (35) 2020	China	Cohort (prospective)	146	106 Non-severe/ 40 severe	77 (53%)	46.7 (53.5)	T, NK, B, Th, cells
Yi et al (36) 2020	China	Retrospective cross-sectional	100	51 Non-severe/ 49 severe	63 (63%)	54.1 (15)	T, NK, B, Th, cells
Xie et al (37) 2020	China	Retrospective cross-sectional	373	322 Non-severe/ 51 severe	197 (53%)	NR	T, Th, Ts cells
Liu et al (38) 2020	China	Retrospective cross-sectional	50	10Mild/ 32 moderate/ 8 severe	28 (55%)	NR	T, NK, B, Th, Ts cells
d'Alessandro et al (39) 2020	Italy	Retrospective cross-sectional	54	40 Non-severe/ 14 severe	33 (61%)	64.8 (12.2)	T, NK, B, Th, Ts cells
Wang et al (40) 2020	China	Retrospective cross-sectional	130	104 Not ARDS/ 26 ARDS	61 (47%)	47.1 (18.9)	Th, Ts cells
Huang et al (41) 2020	China	Cohort (prospective)	89	70 Moderate/ 19 severe	NR	NR	T, Th, Ts cells
Cai et al (42) 2020	China	Cohort (prospective)	41	19 Non-severe/ 22 severe	21 (51%)	59.6 (13.4)	T, NK, B, Th, Ts cells

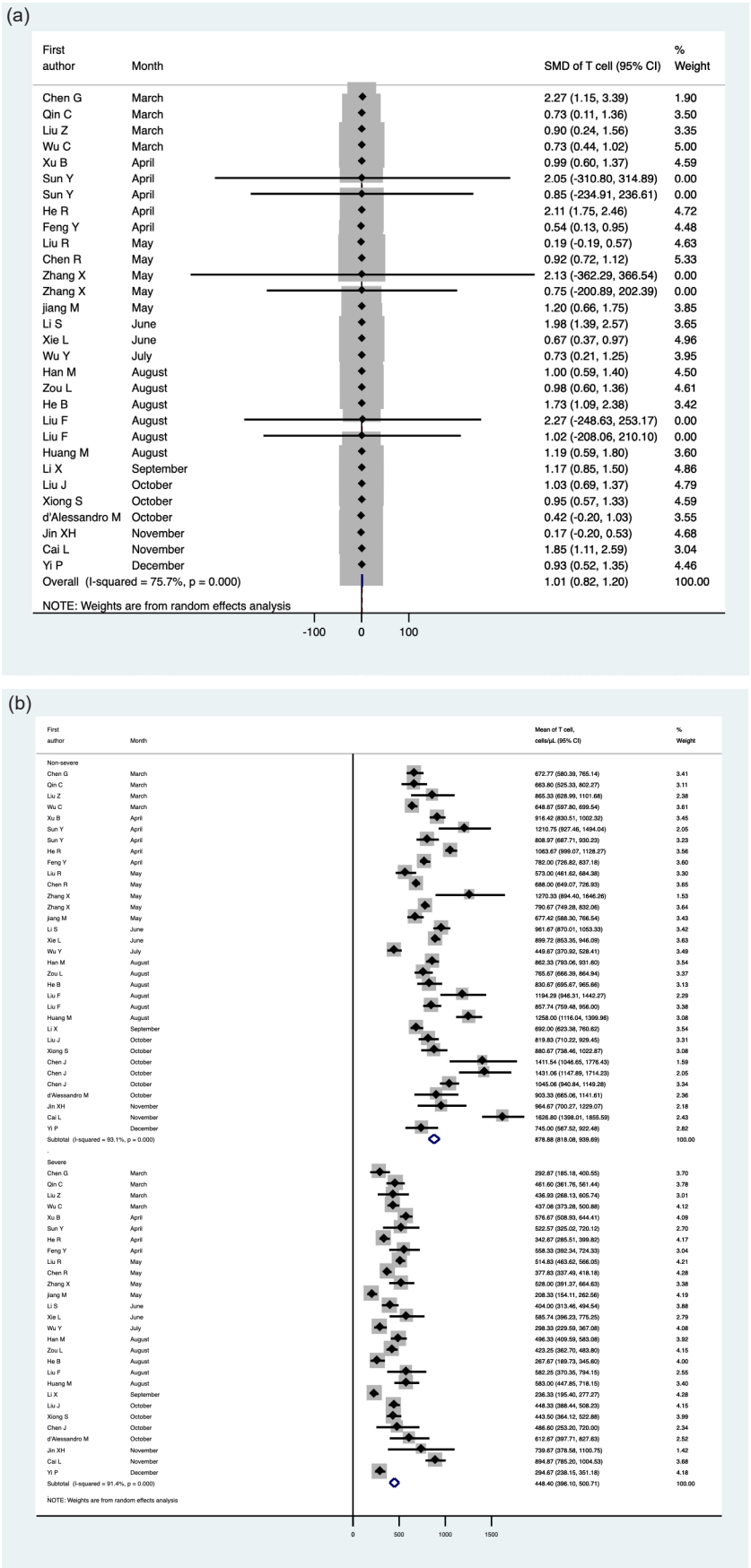

Figure 2. The forest plot of pooled effect on the standardized mean difference (SMD) of total T cell between non-severe and severe groups (a) and average T cell count in non-severe and severe groups (b).

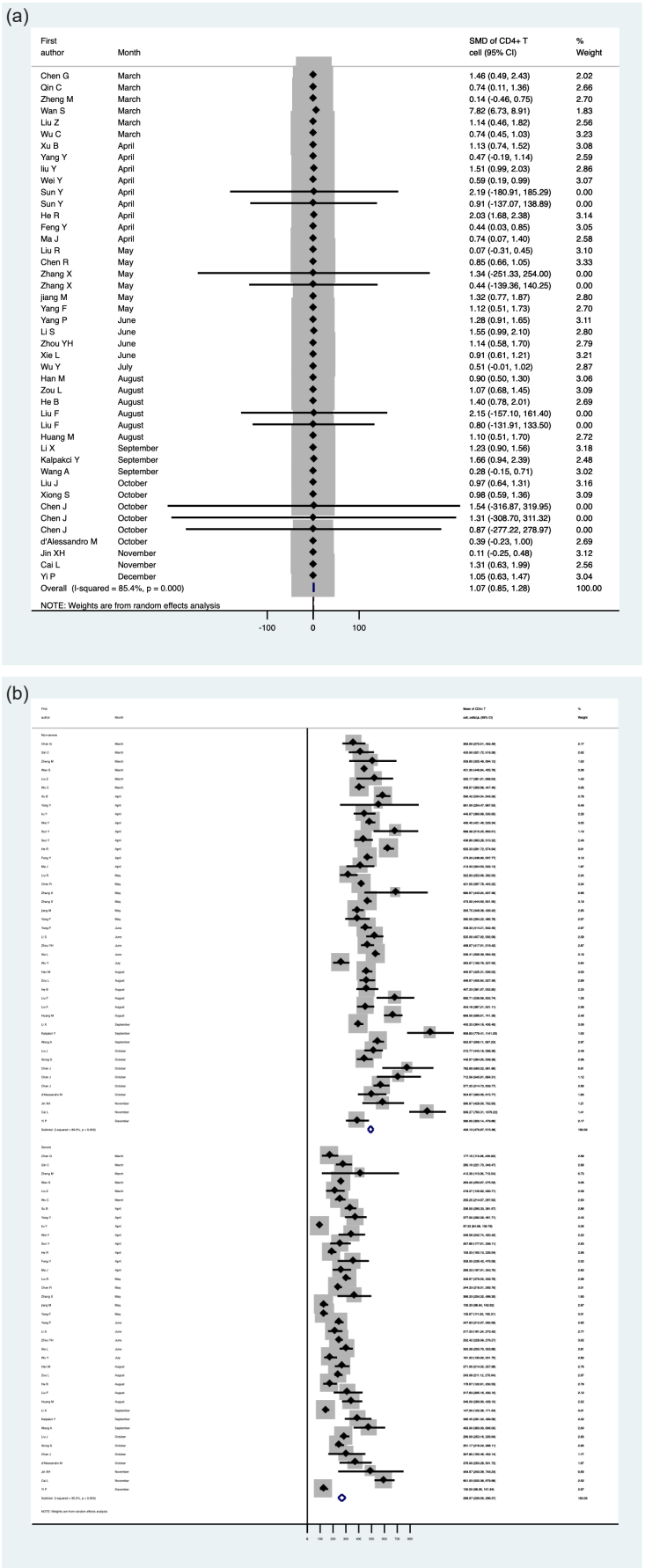

Figure 3. The forest plot of pooled effect on the standardized mean difference (SMD) of CD4+ T cell between non-severe and severe groups (a) and average CD4+ T cell count in non-severe and severe groups (b).

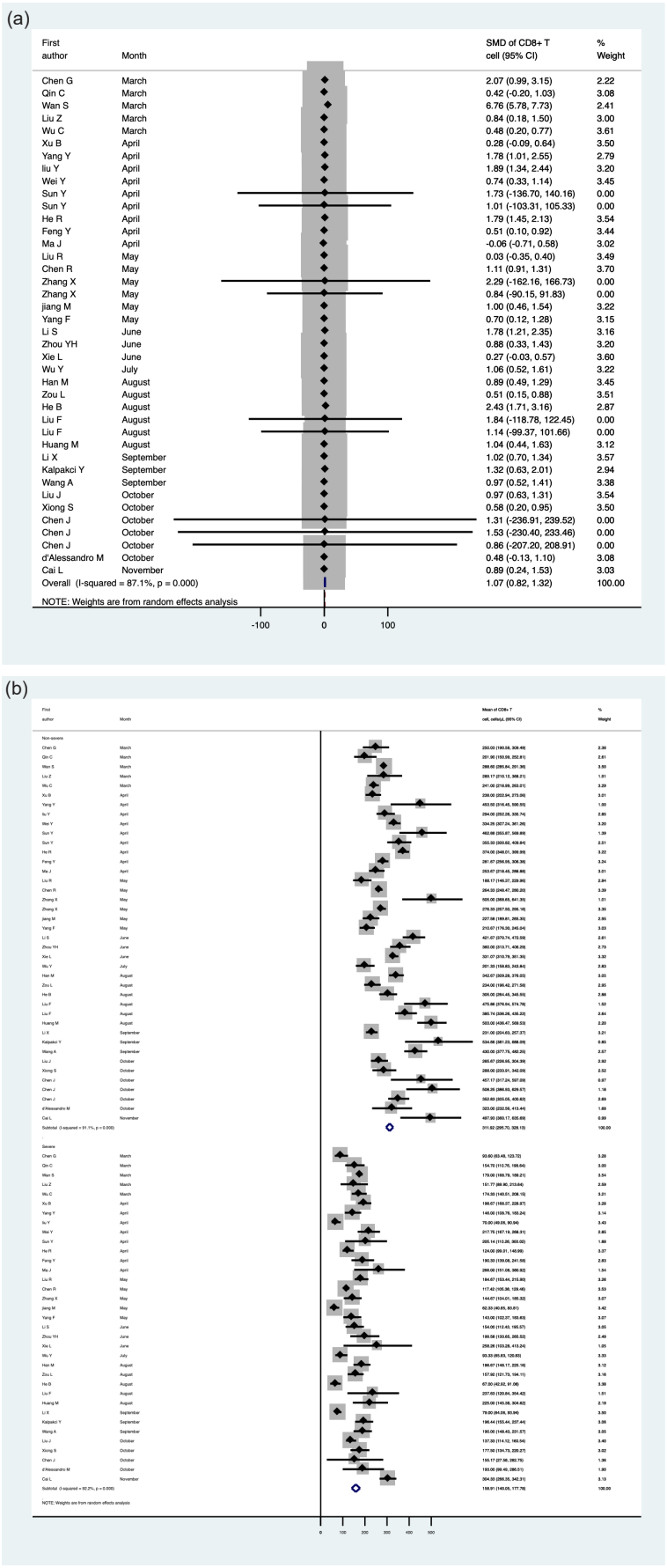

Figure 4. The forest plot of pooled effect on the standardized mean difference (SMD) of CD8+ T cell between non-severe and severe groups (a) and average CD8+ T cell count in non-severe and severe groups (b).

patients was 110.37 cells/μL (95% CI:100.38, 120.36). The forest plots of pooled SMD for B cells and the pooled average B cell count in non-severe and severe groups are shown in Figure 5.

Natural killer cell variation

Twenty-two studies (4-6,9,10,13,15,16,18,19,22,24-26,29-31,35,36,38,39,42) explored the count of NK cells in non-severe and severe patients. The pooled SMD analysis showed that non-severe patients had higher NK cells count than severe COVID-19 patients (SMD = 0.65; 95% CI: 0.47, 0.84; $I^2 = 63.1\%$, P value < 0.001). In this instance, non-severe patients had pooled average NK cells count of 155.02 cells/μL (95% CI:143.46, 166.58) while severe patients had pooled average NK cells count of 103.09 cells/μL (95% CI:90.09, 116.10; Figure 6).

Discussion

Nowadays, researchers are extensively searching to find more robust predicting factors in COVID-19 (43). Several studies have investigated the profiles of immune cells and mediators during different phases of COVID-19 in various populations that resulted in different outcomes, possibly due to the different ethnicity, the technique of assessment, and clinical and paraclinical characteristics of the patients (2,44). Therefore, we conducted this systematic review and meta-analysis to explore the association among lymphocyte variation and disease severity because identification of lymphocyte variation may provide more accurate insight for adopting therapeutic approaches in patients with different clinical stages.

A bulk of evidence showed that although T cell counts were normal or even slightly higher in patients with mild symptoms, total T lymphocytes, $CD4^+$, $CD8^+$ T lymphocytes, B lymphocytes and natural killer cells were usually below the normal range in COVID-19 patients resulting in lymphopenia that was associated with disease severity and mortality in COVID-19 individuals (45,46). In the present systematic review and meta-analysis, we demonstrate that non-severe patients had a significantly higher total T cell count than severe patients. Correspondingly, the pooled analysis showed that non-severe patients had significantly higher $CD4^+$ and $CD8^+$ T cell, natural killer cell and B cell counts than severe patients. Although these findings are consistent with previous studies (45,46), inflammatory cytokine levels were not evaluated to correlate disease severity and cytokine storm, which might serve as a signature of severe COVID-19. A systematic meta-analysis of immune signatures in patients with COVID-19 showed that $CD3^+$, $CD4^+$, $CD8^+$ T cells, $CD4^+CD25^+CD127^-$Treg cells, $CD19^+$ B cells and $CD16^+CD56^+$ NK cells were significantly decreased in severe COVID-19 patients than in non-severe ones (47). In addition, many other studies established that the total counts of lymphocyte subsets, both B and T cells, were significantly lower in both individuals with severe and non-severe COVID-19 (48,49). Several studies showed that lymphocytes were diminished in COVID-19 patients, whereas no significant difference was observed in NK cell counts (50,51). Contradictory results on NK cells necessitate further studies to shed more light on this issue. Huang et al (52), in a recent meta-analysis, demonstrated that lymphopenia correlated with poor outcomes and higher mortality in COVID-19 patients; therefore, inducing lymphocyte proliferation to increase or apoptosis to decrease (IL-7 and PD1/PD-L1 inhibitors) lymphocyte counts may help retrieve lymphocyte population in patients with severe COVID-19 for reducing COVID-19 mortality.

Most hospitalized patients have shown suboptimal, excessive, or inappropriate T cell responses in association with severe disease. Consequently, several discrete patterns of T cell responses may be found in different patients, indicating each patient is faced with different clinical outcomes. Thereby customizing therapeutic approaches may be beneficial to decrease the mortality of severe to critically ill cases with COVID-19 (53). On the other hand, a decrease of lymphocytes can be used as the prognostic factor for COVID-19 patients in the clinical setting. The lymphocytic cells cut point in our study can guide further studies to determine which patients should be warned to be a severe case of COVID-19 and cared cautiously. As antivirals, immunoglobulin, and glucocorticoids treatments have not shown a significant improvement in the survival of COVID-19 severe patients (54), immunotherapeutic strategies can be a promising treatment option for enhancing the lymphocytes. Novel therapeutic options as NK cell-based therapy, mesenchymal stem cell (MSC)-based therapy, and regulatory T cell-based therapy have been lately introduced, and trials are going on to assess these treatment strategies(55).

COVID-19 affects lymphocytes through direct and/or indirect mechanisms. The direct mechanism may be related to SARS-CoV-2 cytotoxicity, in which the virus actively replicates within infected lymphocytes (56,57). The indirect mechanism is attributed to the large production of inflammatory cytokines that potentially induce lymphocyte apoptosis (57). In addition, constitutive stimulation by a virus may cause T cell exhaustion in which T cells diminish or lose their capacity of cytokine production and effector functions (58). Similarly, SARS-CoV2-related exhaustion in lymphocytes may be due to some inhibitory cytokines, e.g., IL-10, that is significantly increased in COVID-19 patients (59). However, the exact mechanism(s) of lymphocyte reduction in individuals with severe COVID-19 remain to be completely clarified.

The present study had limitations that were common in all meta-analysis studies. We did not determine the impact of age, gender, cytokine levels, inflammatory mediators, predisposing comorbidities, effective anti-cytokine therapy

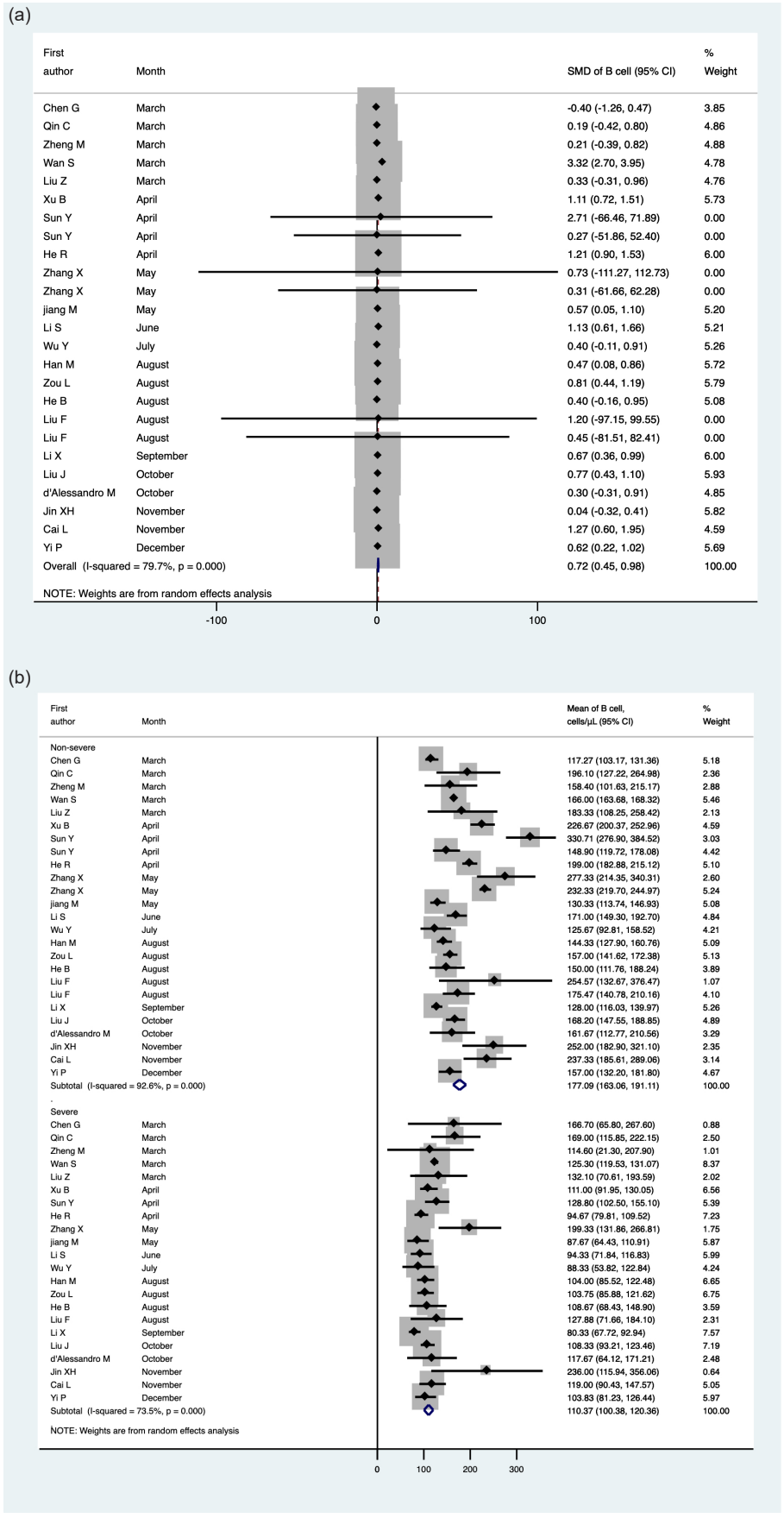

Figure 5. The forest plot of pooled effect on the standardized mean difference (SMD) of B cell between non-severe and severe groups (a) and average B cell count in non-severe and severe groups (b).

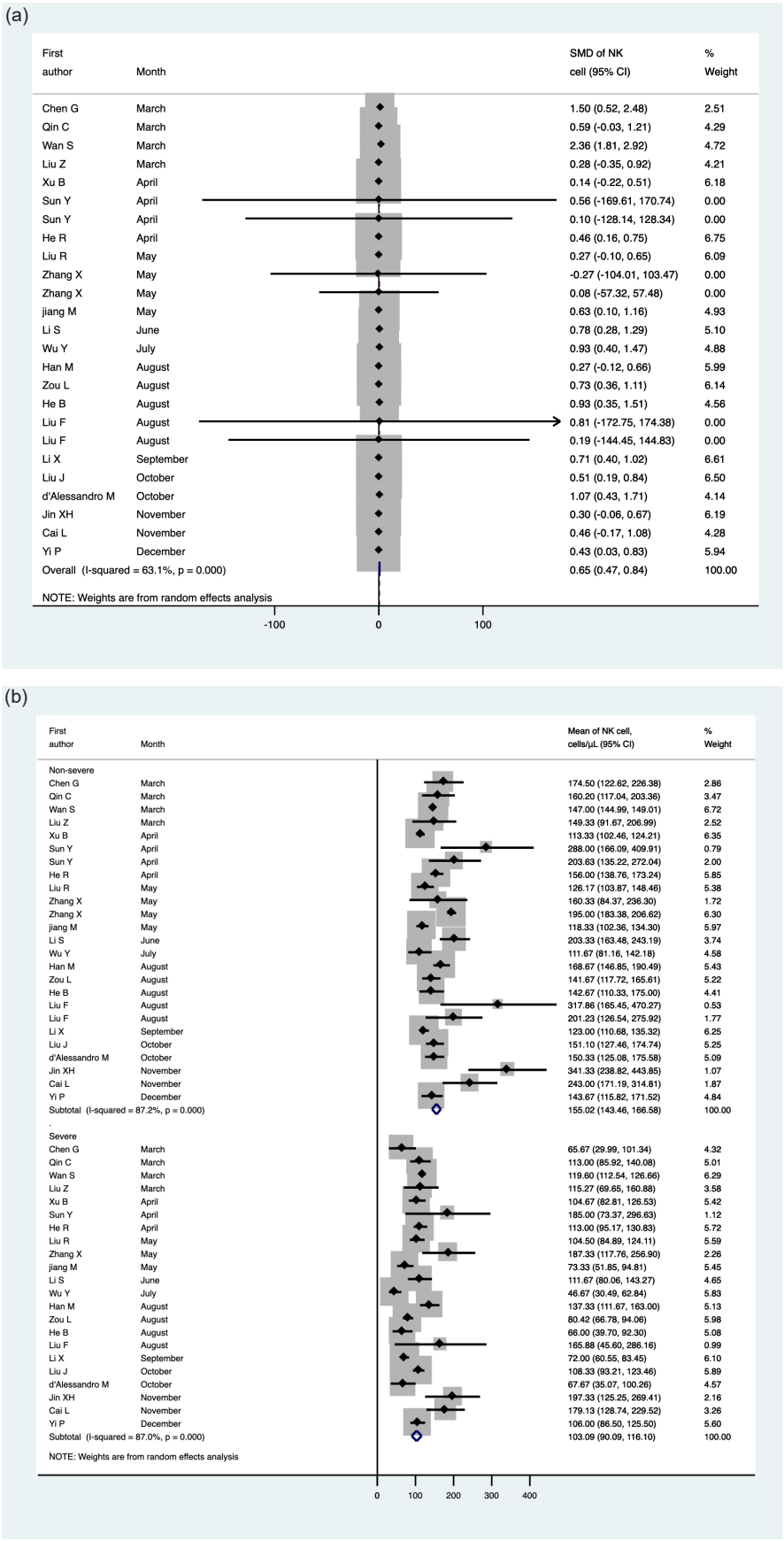

Figure 6. The forest plot of pooled effect on the standardized mean difference (SMD) of NK cell between non-severe and severe groups (a) and average NK cell count in non-severe and severe groups (b).

and ongoing critical trials on COVID-19 outcome; thus, further studies on severe patients, especially those who suffer from cytokine storm and ARDS(acute respiratory distress syndrome), are needed to elucidate the association between these determinants and COVID-19 severity or mortality. Furthermore, the sample population of some studies was small that may decrease the power of the studies. Finally, most of them were carried out in China, and measurements may have biased populations.

Conclusion

A severe type of COVID-19 may compromise the function and decrease the number of lymphocyte subsets. Thus, it is essential to identify prognostic inflammatory indicators, especially lymphocyte counts, to predict the disease severity and hospitalization. The current systematic review and meta-analysis indicated that severe COVID-19 cases had significantly lower lymphocyte counts, including CD4+ and CD8+ T cell, natural killer and B cells, than non-severe patients. COVID-19 outcome may be complicated by lymphopenia because over-activation of lymphocytes may result in cytokine storm or ARDS. On the other hand, lymphopenia may increase SARS-CoV-2 viral load and the intensity of COVID-19. Therefore, novel therapeutic strategies such as targeting lymphocyte proliferation or contraction (IL-7 and PD1/PD-L1 inhibitors, respectively) may help retrieve lymphocyte counts in patients with severe COVID-19.

Authors' contribution

AK, HD, and HA were the principal investigators of the study. HD and HA were included in preparing the concept and design. HD, HA, and PP managed the analyses of the study. All authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

Conflicts of interest

The authors declare that they have no conflict of interests.

Ethical issues

Ethical issues (including plagiarism, data fabrication and double publication) were completely observed by the authors.

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