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Association between the peripheral blood eosinophil counts and COVID-19

A meta-analysis

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Abstract

Background: The conclusions about the relationship between eosinophil counts and the severity of coronavirus disease 2019 (COVID-19) were controversial, so we updated the evidences and reassessed it.

Methods: We searched the PubMed, Cochrane library, Excerpta Medica Database, and Web of Science to compare the eosinophil counts about non-severe disease group (mild pneumonia, moderate pneumonia, non-critical disease and recovery group) and severe disease group (severe pneumonia, critical pneumonia, critical disease and death group) in COVID-19.

Results: A total of 1228 patients from 10 studies were included. Compared with non-severe group, severe group had strikingly lower average eosinophil counts (SMD 0.65, 95% confidence intervals [CI] 0.29–1.01; $P < .001$). The result of subgroup analysis of different countries showed SMD 0.66, 95% CI 0.26–1.06; $P < .001$. Another subgroup analysis between mild-moderate pneumonia versus severe-critical pneumonia showed SMD 0.69, 95% CI 0.25–1.13; $P < .001$, and no significant risk of publication bias (Begg test 0.063 and Egger test 0.057) in this subgroup. The heterogeneity was substantial, but the sensitivity analyses showed no significant change when individual study was excluded, which suggested the crediblity and stablity of our results.

Conclusions: The eosinophil counts had important value as an indicator of severity in patients with COVID-19.

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Abbreviations: 95% CI = 95% confidence intervals, COVID-19 = coronavirus disease 2019.

Keywords: coronavirus disease 2019, eosinophils, non-severe disease, severe disease, meta-analysis

1. Introduction

A new form of respiratory and systemic disorder named coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2,[1,2] a new and more infectious virus than that of severe acute respiratory syndrome and Middle East respiratory syndrome. The clinical symptoms of COVID-19 are fever, cough, fatigue, extremity pain, and gastrointestinal symptoms.[3] Severe patients often experience progressive dyspnea and/or refractory hypoxemia 1 week after onset, and rapidly develop acute respiratory distress syndrome, septic shock, multiple organ failure and other manifestations.[4,5] There is no doubt that it has become one of the most concerned issues today because of its extremely high transmission capacity and mortality rate. According to Guidelines for the Diagnosis and Treatment of COVID-19, the clinical typing of COVID-19 are 4 types: mild, moderate, severe and critical pneumonia. So far, over 64 million people has infected and caused over 1,480,000 deaths (as of December 2, 2020) over the world. Since it breaks out, the global economy is badly disrupted and global health care systems is suffered a multitude of challenges.

One of the first lines to against virus, the eosinophil should be noticed.[6] A previous systematic literature included 3 studies showed that the peripheral blood eosinophil counts may not be associated with the progression of COVID-19.[7] However, several related clinical studies had been conducted since then, these findings were not entirely consistent. Yang et al thought the low percentage of eosinophil was not a biomarker of pneumonia severity.[8] While more scholars got the conclusions that the eosinophil counts were helpful to predict the severe COVID-19 cases.[9–20] Considering these divergent conclusions, it is worth exploring whether eosinopenia is related to the severity of the disease in COVID-19, so we meta-analyze the relevant literature.

2. Methods and analysis

2.1. Study inclusion/exclusion criteria

We included cohort studies and case-control studies to assess the relationship between eosinophil counts and the severity of COVID-19. Exclusion criteria:

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This study does not require ethical approval as the meta-analysis is based on published research, and the original data are anonymous.

The authors have no funding and conflicts of interests to disclose.

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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1. overlapping or duplicate studies;
2. insufficient necessary data for detailed analysis;
3. review articles, meta-analysis articles, case reports, letters, conference summary;
4. animal research and basic research.

2.1.1. Participants. The study population included laboratory-confirmed with COVID-19, without limitation of age, gender, or racial.

2.1.2. Interventions. The experimental group (the severe disease group) included the severe pneumonia, critical pneumonia, critical disease and death group.

2.1.3. Comparisons. The control group (the non-severe disease group) were the mild pneumonia, moderate pneumonia, non-critical disease and recovery group.

2.1.4. Outcomes

2.1.4.1. Main outcome. Evaluated the relationship between eosinophil counts and the severity of COVID-19.

2.1.4.2. Additional outcomes. The subgroup analysis in different countries and another subgroup analysis between mild-moderate pneumonia vs severe-critical pneumonia were assessed.

2.2. Search strategy

We performed electronic searches in PubMed, Cochrane Library, EMBASE and Web of Science to search published studies without date (until 23 Aug, 2020) or language restrictions, using the following terms: (a) "Eosinophils" OR "White Blood Cells" OR "Leukocytes" OR "Granulocytes"; combined with (b) "2019 nCoV" OR "2019 novel coronavirus" OR "new coronavirus"

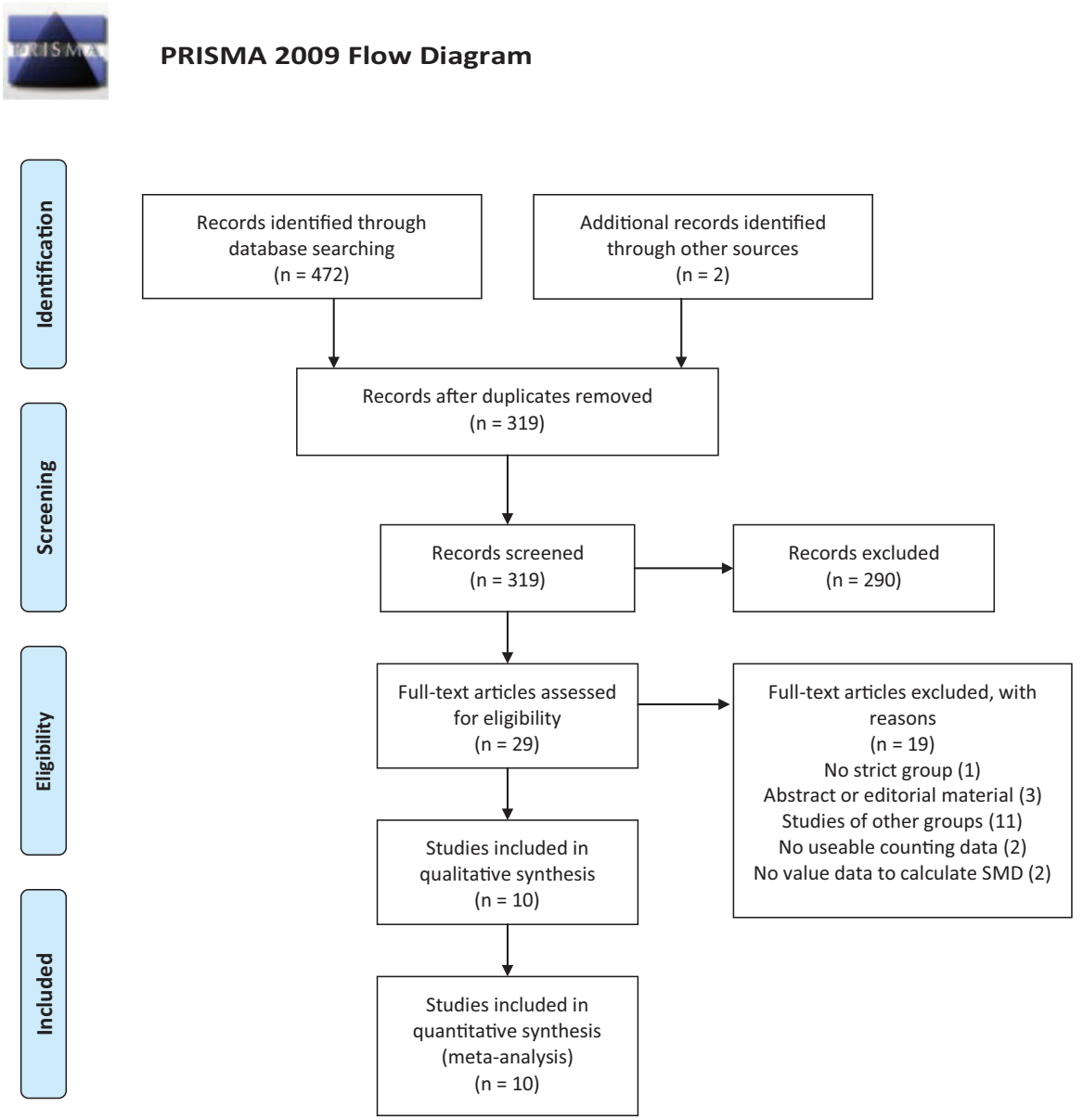

Figure 1. PRISMA 2009 Flow Diagram.

Table 1

Basic characteristics of included studies.

Author	Year	Country	Age	Men (%)	Disease severity and primary data#		Score##
					Non-severe group	Severe group	
J. Chen	2020	China	45.81 ± 14.84	87 (51.5%)	Common group (n = 145):0.03 (0.02-0.06)	Severe group (n = 24):0.01 (0.00-0.02)	********
D. Liao	2020	China	63.33 ± 14.88	206 (54.0%)	Moderate disease(n = 149):0.04(0.01–0.10)	Severe disease(n = 145):0.05 (0.01–0.11) Critical disease(n = 86):0.01 (0–0.03)	********
D. W. Sun	2020	China	63.86 ± 12.71	29 (50.9%)	Non-severe type (n = 12):0.160 (0.123–0.228)	Severe type (n = 45):0.030(0.005–0.050)	********
S. Sun	2020	China	49.33 ± 12.01	60 (51.7%)	Common (n = 89):0.03 (0.01–0.05)	Severe (n = 27):0.01 (0.00–0.02)	********
Y. Sun	2020	China	45.5 ± 17.59	Not reported	Mild disease (n = 8):0.14 ± 0.06 Moderate disease (n = 36):0.03 ± 0.04	Severe disease (n = 10):0.01 ± 0.00 Critically ill (n = 9):0.09 ± 0.14	********
C. Z. Wang	2020	China	39 ± 10.44	23 (51.1%)	Moderate (n = 35):0.04 ± 0.06	Severe (n = 10):0.00 ± 0.01	********
J. J. Zhang	2020	China	56.5 ± 11.88	71 (50.7%)	Nonsevere patients (n = 82):0.02 (0.008-0.05)	Severe patients (n = 56):0.01 (0.0-0.06)	********
G. Q. Qian	2020	China	47.87 ± 15.37	37 (40.7%)	mild (n = 82):0.02(0.01-0.06)	severe (n = 9):0.01(0-0.01)	********
Z. Wang	2020	China	46.33 ± 20.44	32 (46.0%)	SpO2 ≥ 90%(n = 55):0.01(0.00-0.02)	SpO2 ≤ 90%(n = 14):0.00(0.00-0.01)	********
M. S. Asghar	2020	Pakistan	52.58 ± 15.68	69 (69.0%)	Recovery (n = 78):1.72 ± 1.64	Death (n = 22):0.73 ± 1.09	

#Reported variously as mean ± SD or median, and interquartile range (IQR) values.## Newcastle–Ottawa Quality Assessment Scale (NOS) for quality estimation of literature.

OR "novel coronavirus" OR "novel corona virus" OR "SARS CoV-2" OR "Wuhan corona virus " OR "COVID-19" without date (until August 23, 2020) or language restrictions. Searches were re-run prior to the final analysis. The flow chart of search result was presented in Figure 1.

2.3. Screening

The articles found in the search were imported into Endnote X9 software. Duplicates were eliminated. Two investigators (RH and LCX) independently screened the titles and abstracts due to the inclusion and exclusion criteria, the irrelevant articles were removed. Finally, the eligible articles were chosen by full-text screening. Disagreements were resolved by discussion between these 2 authors and the third author (JPH) resolved any disagreements.

2.4. Data extraction

For all the eligible studies, 2 reviewers (RH and LCX) independently extracted the information: the first author, year, study country, demographic information (age and sex), disease severity, study size and outcomes. If the data given in the original article was nonconsistent forms, we would use Wan's calculation formula to convert the data to mean ± SD.[21]

2.5. Risk of bias assessment

Two reviewers (RH and LCX) independently took the Newcastle–Ottawa Quality Assessment Scale[22] for quality estimation of literature. Nine questions would be evaluated, and each satisfactory answer were received 1 point, the maximum score was 9. If the score ≥7, we considered the article was high methodological quality. Two reviewers (RH and LCX) cross-checked the assessing process and the final score were obtained after discussing with the third reviewer (JPH).

1. Selection: Representativeness of the exposed cohort; Selection of the non-exposed cohort; Ascertainment of exposure (the proof of COVID-19 and the eosinophil counts measurement); Demonstration that outcome of interest was not present at start of study.
2. Comparability: Comparability of cohorts on the basis of the design or analysis. (a) Study controls for the eosinophil counts; (b) Study controls for any additional factor (age, gender, exposure history, comorbidity, etc).
3. Outcome: Assessment of outcome; was follow-up long enough for outcomes to occur? (death or recurrence); Adequacy of follow-up of cohorts.

2.6. Statistical analysis

2.6.1. Assessment of heterogeneity and data syntheses. The standard mean differences and corresponding 95% confidence intervals (CIs) were calculated. Heterogeneity presumption was investigated using the Q-test and I^2 statistic. If there was significant heterogeneity among studies ($P < .05$ or $I^2 > 50\%$), a random-effects model was used; otherwise, a fixed-effects mode was applied. Two-sided $P < .05$ was considered statistically significant. Analyses were conducted using Stata 15.0 statistical software packages.

2.6.2. Subgroup and sensitivity analyses. If there was significant heterogeneity among studies, the subgroup analysis of different countries and another subgroup analysis between mild-moderate pneumonia vs severe-critical pneumonia were assessed. Sensitivity analysis were performed by sequentially omitting each trial.

2.6.3. Assessment of reporting bias. Egger test and Begg test were created to estimate publication bias with the strict definition of clinical classification about COVID-19(mild-moderate pneumonia vs severe-critical pneumonia).

3. Results

3.1. Description of studies

At the beginning, 12 articles were finally eligible according to the search strategies,[9–20] but 2 articles were unable to extract value data to calculate SMD[14,18] and finally we included 10 articles assessed 1228 patients considered in this meta-analysis. The sample size ranged from 9 to 231. All the studies were originated from Asia. The details of these articles included in the meta-analysis were summarized in Table 1.

3.2. Results of the meta-analysis

A comparison of the peripheral blood eosinophil counts for non-severe and severe disease in COVID-19 was performed in 10

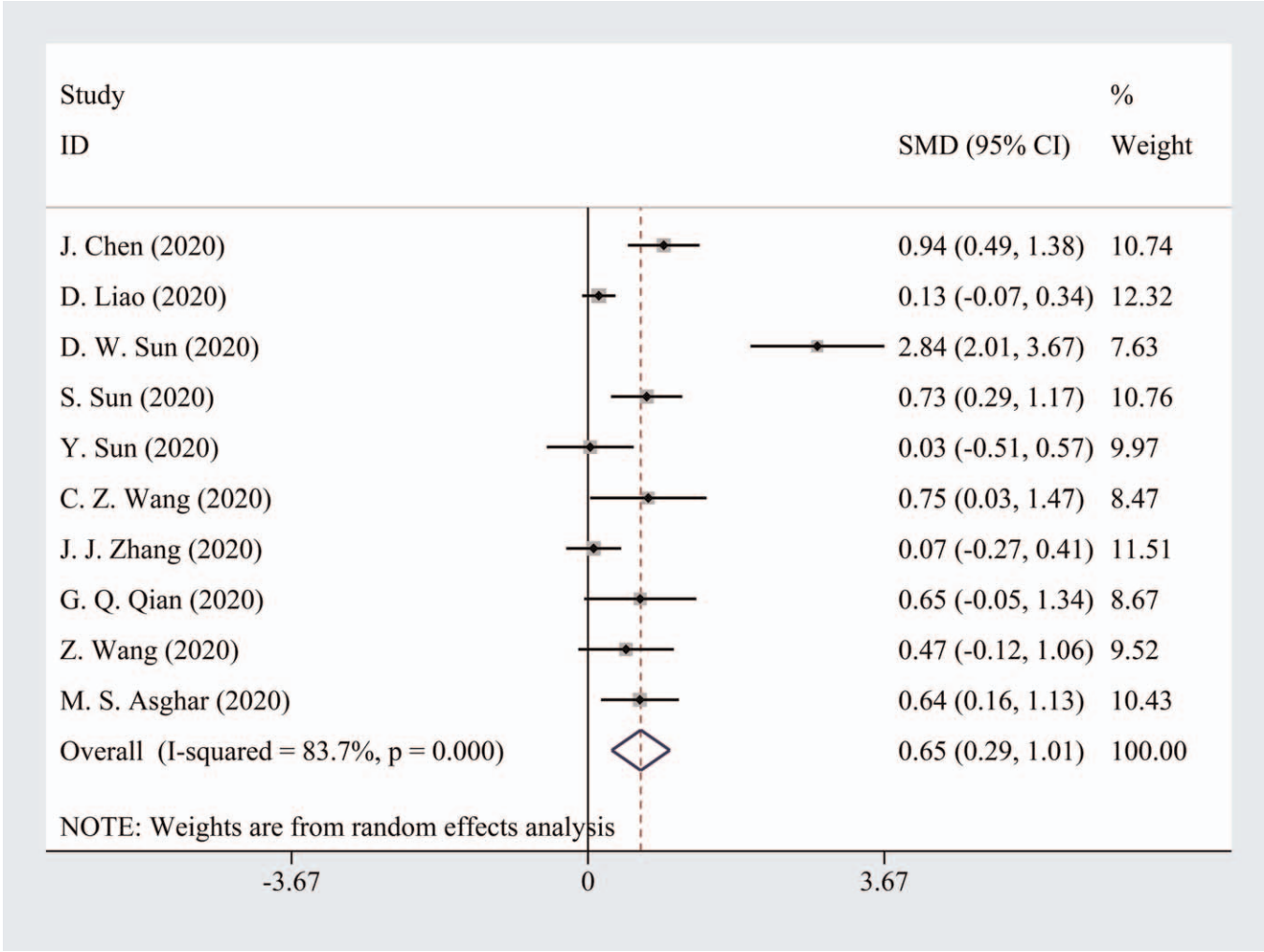

Figure 2. Forest of the peripheral blood eosinophil counts between patients with non-severe and severe disease group. SMD = standard mean difference.

studies. Compared with non-severe disease group, severe disease group had strikingly lower average eosinophil counts (SMD 0.65, 95% CI 0.29–1.01; $P < .001$, $I^2 = 83.7\%$) (Fig. 2). Considering the high heterogeneity, 2 subgroups were studied. Between different countries, the result showed SMD 0.66, 95% CI 0.26–1.06; $P < .001$, $I^2 = 85.2\%$ (Fig. 3). Another subgroup was according to the strict definition of clinical classification about COVID-19 (mild-moderate pneumonia vs severe-critical pneumonia), the result showed SMD 0.69, 95% CI 0.25–1.13; $P < .001$, $I^2 = 87.1\%$ (Fig. 4). The sensitivity analyses showed no significant change when individual study was excluded using random-effects model, which suggested the crediblity and stablity of our results (Fig. 5). Begg funnel plot and Egger test were used to assess publication bias in the interested subgroup, the Begg funnel plot showed no evidence of significant publication bias ($P = .063$) nor did Egger ($P = .057$) (Fig. 6).

4. Discussion

In the present study, we updated the evidences and observed that the peripheral blood eosinophil counts levels in patients with severe disease group were significantly lower than those with non-severe disease group in COVID-19. On the basis of this meta-analysis, we suggest that the eosinophil counts levels have important value as an indicator of severity in patients with COVID-19. It may also be used to monitor the progression of this disease as early as possible.

Despite eosinophils are the second least granulocyte subpopulation in the peripheral blood, the scientific community is getting increasingly interested in it because of its complex pathophysiological roles to against bacterial and viral pathogens. Evidences are showing that eosinophils protect body from viral infections, especially against RNA viruses.[23] The TLR7 receptor, which recognizes viruses and recognizes single stranded RNA (ssRNA), is one of the most important viral receptors in eosinophils, demonstrating the role of eosinophils in virus recognition is unarguable.[6]

COVID-19 is becoming one of the worst infection disease outbreaks known, it is transmitted by droplets, aerosol, contact and fecal-oral route infection, and tend to transmit among family clusters[24,25] or cause outbreaks in hospitals. It is important to identify the key clinical features of COVID-19 patients, which

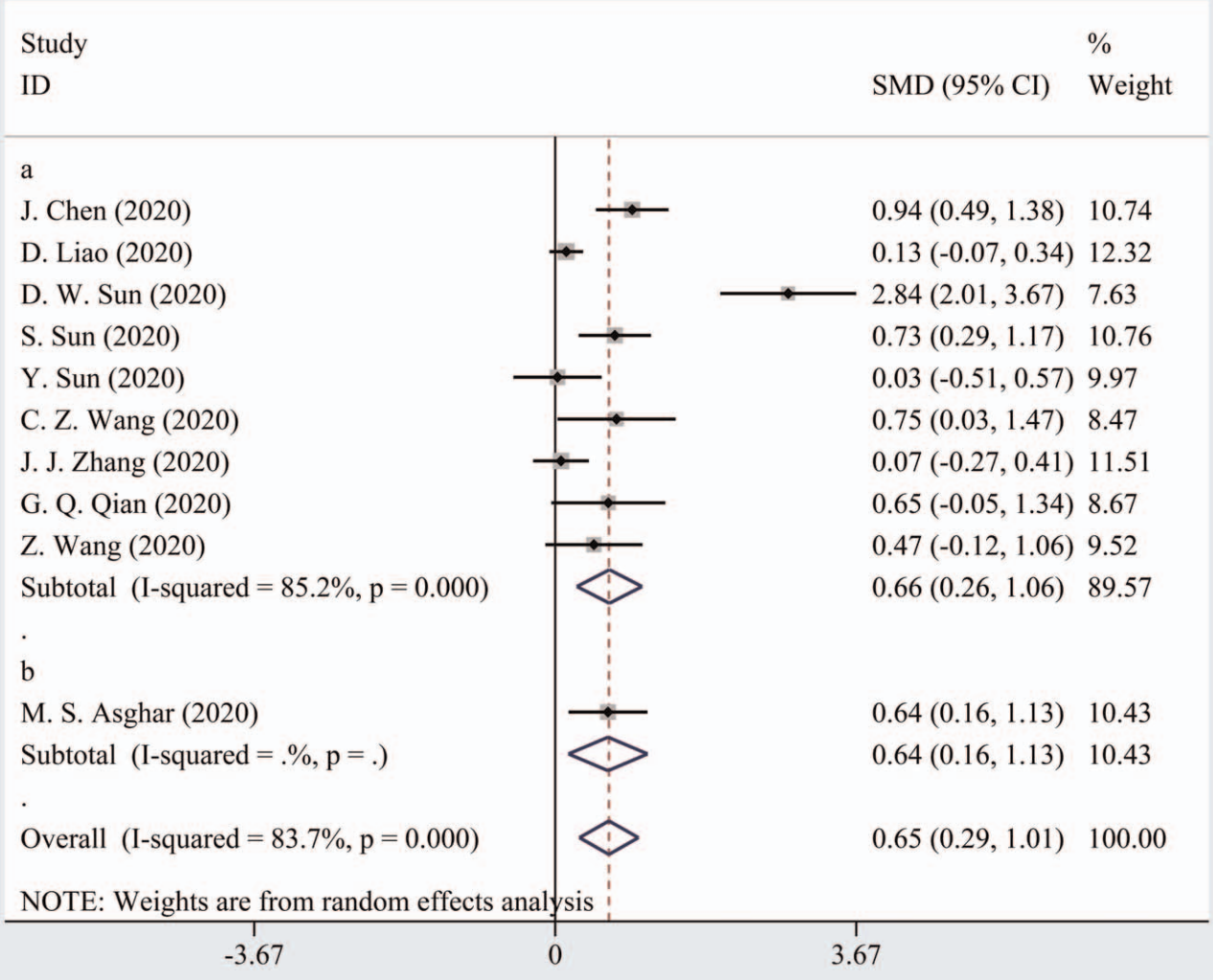

Figure 3. Forest of the peripheral blood eosinophil counts between patients with different countries. SMD = standard mean difference.

may help to detect and isolate the infected individuals as early as possible, and minimize the spread of the disease. Some scholars had studied the cases of COVID-19 and showed that the severe disease had abnormalities in many laboratory parameters, and some of them can be used as predictors of disease severity, such as levels of lactate dehydrogenase,[26,27] lymphocyte and subset counts,[27–31] interleukin-6,[32,33] procalcitonin,[34] D-dimer,[35] C-reactive protein[27,33] and so on. But compared to other biomarkers, the eosinophil was often overlooked, it had long been thought to be associated with allergy diseases and parasitic infections traditionally. Actually, it was versatile cell, and some scholars believed it was positioned centrally within immune and inflammatory networks, its new roles as neoplasm surveillance, tissue remodeling and the restructuring of adipose tissue were emerging.[36] The eosinophil cells may act as a positive predictor in early stages during the coronavirus infection.[37]

It has been reported previously that in infected patients, increased inflammation leads to lower counts of eosinophils.[38] Increased count of eosinophils was associated with a better prognosis for COVID-19, including the lower incidence of complications and mortality. While the recovery of lymphocytes had no effect on the prognosis.[39] In surviving acute lung injury patients, the number of eosinophils in the lungs showed an increased compared to the non-survivors.[40] Similarly, the number of peripheral blood eosinophils also increased in surviving acute respiratory distress syndrome patients. Therefore, the scholars further investigated its molecular mechanism and found that in the initiation of acute lung injury, $CD101^{-}$ eosinophils increased more rapidly and briefly than the neutrophils and secreted Protectin-D1 through Alox15-mediated to reduce the accumulation of inflammatory cells and reduce inflammatory factors, thus playing a role in fighting lung inflammation.[41]

Whether the glucocorticoids can save the lives of patients with severe in COVID-19 is still controversial. The hormones can prevent the release of eosinophils in the bone marrow and reduce

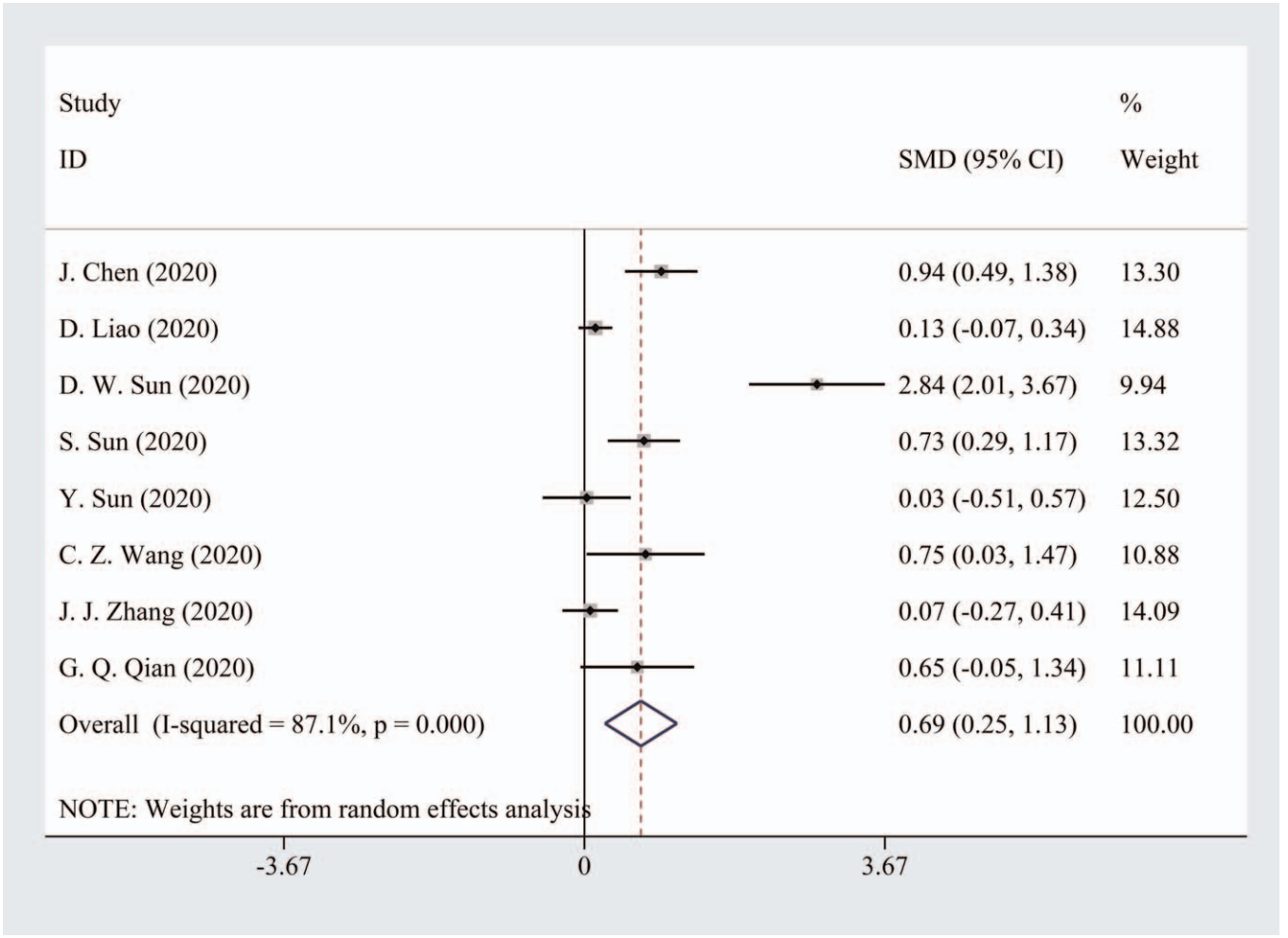

Figure 4. Forest of the peripheral blood eosinophil counts between patients with the strict definition of clinical classification about COVID-19(mild-moderate pneumonia versus severe-critical pneumonia). SMD = standard mean difference.

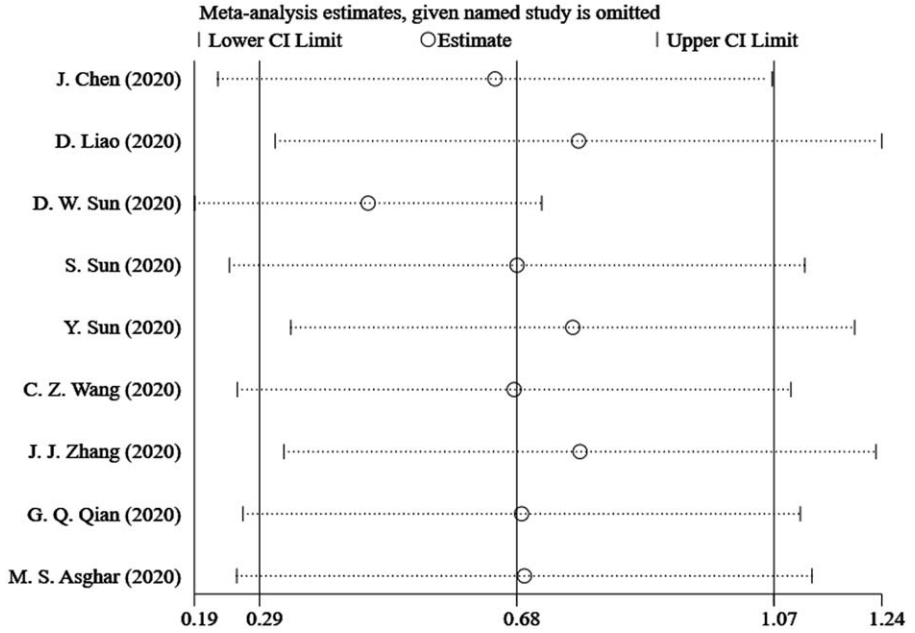

Figure 5. Sensitivity analysis of the peripheral blood eosinophil counts between patients with non-severe and severe disease group.

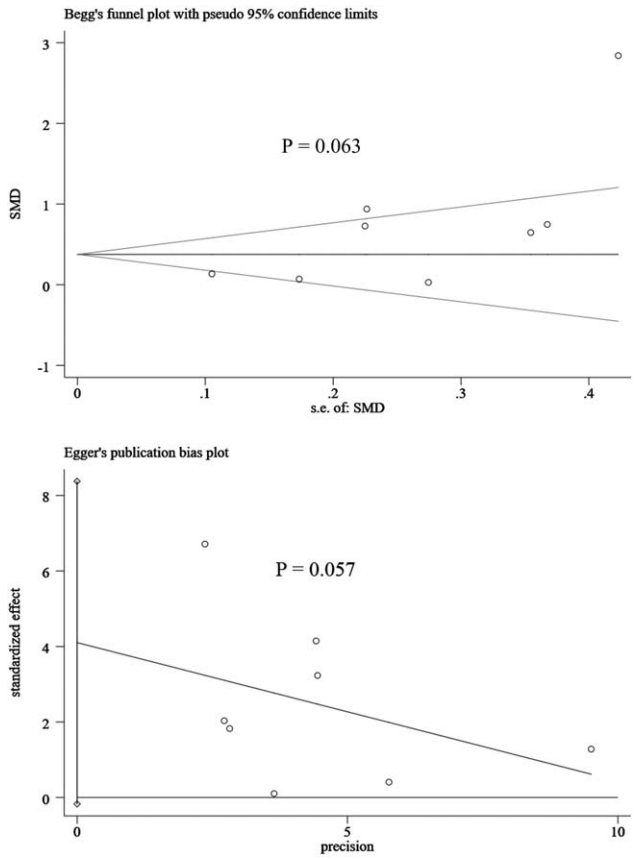

Figure 6. Begg test and Egger test for publication bias with the strict definition of clinical classification about COVID-19(mild-moderate pneumonia versus severe-critical pneumonia).

them in the peripheral blood. Given that the eosinophils play a "protective role" in the onset of COVID-19, early use of hormones will quickly inhibit their proliferation, differentiation, migration and "protective effect" against diseases.

Several limitations of our study should be discussed. Firstly, the number of studies included was relatively low although the definition of clinical classification about COVID-19 was not strict, which may reduce the reliability of results. Secondly, the data collection may be insufficient because only English language papers were included. Thirdly, because of the small sample size, it may not strongly confirm the association between eosinophil counts levels and severity of COVID-19, which needed more studies. Fourthly, the studies included in this analysis were all performed in Asia, and the results may not be representative of other parts of the world. The significant heterogeneity in these studies could not be neglected. The possible reasons for the observed heterogeneity were the difference in underlying comorbidities, different patient population, co-infection with other diseases and the variation in follow-up. The looser inclusion criteria resulted the variety of control interventions, which may also lead to heterogeneity. However, when we chose the random-effects model and performed subgroup analysis according to the strict definition, the marked heterogeneity was still remained.

In spite of the limitations mentioned above, the subgroup analysis and its sensitivity were remained consistent, demonstrating that eosinophil counts levels might be useful as an important parameter to recognize patients with severe COVID-19 in the disease course. If eosinophils are activated, they may have the potential to treat viral respiratory diseases.[42] We believe this analysis will contribute to the development of anti-COVID-19 drugs.

Author contributions

Writing – original draft: Rong Huang, Liangcai Xie, Junpeng He, Hong Dong, Tianchun Liu.

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