Received: 17 June 2020 | Revised: 30 June 2020 | Accepted: 5 July 2020

DOI: 10.1111/ijlh.13298

ISLH International Journal of Laboratory Hematology WILEY

LETTER TO THE EDITOR

Is neutrophilia associated with mortality in COVID-19 patients? A meta-analysis and meta-regression

Dear Editors,

Coronavirus disease 2019 (COVID-19) is spreading rapidly around the world. There are many published studies exploring the risk factors of severe and mortal COVID-19 patients. Huang et al reported that the elevated leukocyte counts and decreased lymphocyte counts were significantly associated with the severity of COVID-19. Although neutrophil counts were not uniformly reported in that study, they thought that neutrophilia was more specific to severe patients than leukocytosis.[1] To our knowledge, a number of studies have investigated the association of neutrophil counts with the mortality of COVID-19; however, the conclusions among studies are inconsistent.[2-6] On this basis, we explored the relationship between neutrophil counts and mortality of COVID-19 by quantitative meta-analysis and meta-regression.

We completed our meta-analysis by strictly following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Table S1).[7] We conducted an electronic search of PubMed, Web of Science, and EMBASE to identify potential studies published between January 1, 2020, and May 22, 2020, using the following terms: ("clinical" OR "laboratory" OR "neutrophil") AND ("coronavirus" OR "2019-nCoV" OR "SARS-CoV-2" OR "COVID-19") AND ("outcome" OR "mortality"). In addition, the references of included studies were also reviewed to screen out additional eligible studies by two researchers (Li Shi and Ying Wang), respectively. Extracted data included authors, study design, locations, number of cases, percentages of male, the median or mean of age, and neutrophil counts and corresponding units in the non-survival and survival groups. The Agency for Healthcare Research and Quality (AHRQ) score checklist was used for assessing the quality of included studies in this meta-analysis.[8] The quality assessment of the studies was divided into low (0-3), moderate (4-7), or high (8-11).

The inclusion criteria involved (a) studies presented in English; (b) patients with laboratory-confirmed and clinically diagnosed COVID-19 pneumonia; and (c) clear report about neutrophil counts in the non-survival and survival groups. Case reports, meta-analysis, review, and studies with overlapping data were excluded.

Considering the inherent differences among studies, we calculated the pooled standardized mean difference (SMD) and corresponding 95% confidence interval (CI) for continuous variables by using random-effects model to evaluate the relationship between changes in neutrophil counts and mortality of COVID-19 patients. When the mean and standard deviation could not be extracted directly from studies, we estimated them according to Wan et al's[9] method by utilizing sample size, median and interquartile range (IQR), or median and range. The I^2 statistic and Cochran's Q statistic were used to quantify the heterogeneity across studies.[10] For the Cochran's Q statistic, significant heterogeneity across studies was deemed as a P-value <.10. For the I^2 statistic, significant heterogeneity across studies was regarded as I^2> 50%. In addition, we also provided the prediction interval, which was helpful for assessing whether the variation across studies was clinically significant.[11,12] We used age and gender as covariates to conduct a restricted-maximum likelihood random-effects meta-regression. Sensitivity analysis was used not only to identify sources of heterogeneity but also to assess the robustness of the results. For assessing small-study effects, we chose Begg's test and regression-based Egger's test. All calculations were performed in Stata 16.0. Two-tailed P-values <.05 were considered statistically significant.

At the beginning, there were 648 records in the search results, 100 duplicates were deleted, and the remaining 548 studies were screened. Finally, 10 observational studies[2-6,13-17] including nine retrospective studies and one prospective study were enrolled in this meta-analysis through careful screening of titles, abstracts, and full texts. There were a total of 1473 COVID-19 cases including 372 nonsurvivors and 1101 survivors. Baseline characteristics of the included studies are shown in Table 1. Neutrophil counts were clearly reported upon admission in most studies except for Du et al, He et al and Wang et al. Objectively speaking, their studies presumably reported neutrophil counts on admission. In addition, all included studies were of high or moderate quality with an AHRQ score ≥6 (Table S2).

The combined results revealed that higher neutrophil counts were detected in the non-survival COVID-19 patients compared with the survival COVID-19 patients (SMD = 0.93, 95% CI = 0.63-1.24; I^2 = 76.3%, Q = 42.12, P < 0.001; prediction interval = −0.12-1.99) (Figure. 1A). The results of sensitivity analysis suggested that removing any individual study of the included studies had no significant effect on the association between changes in neutrophil counts and mortality of COVID-19-infected patients (Figure. 1B). Due to the limitations of the data reported in the included studies, we only used age and gender as covariates for meta-regression. The results of meta-regression analysis indicated that the relationship between changes in neutrophil counts and increased risk of mortality in COVID-19-infected patients was not obviously affected by age (P = 0.628) (Figure. 1C) and gender (P = 0.222) (Figure. 1D). Begg's test (P = 1.839) and regression-based Egger's test (P = 0.058)

TABLE 1 Characteristics of the included studies

Author	Study design	Location	Case	Male (%)	Age, years	Quality score [a]	Non-survival		Survival	
							n	Neutrophils, × 10^9/L	n	Neutrophils, ×10^9/L
Chen T et al. PMID: 32217556	Retrospective	China	274	171 (62.4)	62 (median)	6	113	9.0 (5.4-12.7)	161	3.2 (2.4-4.5)
Chen Tielong et al. PMID: 32279081	Retrospective	China	55	34 (61.8)	74 (median)	6	19	5.5 (2-21)	36	4.3 (1-13)
Du R et al. PMID: 32269088	Prospective	China	179	97 (54.2)	57.6 (mean)	8	21	7.7 (3.0-11.5)	158	3.9 (2.6-6.1)
He W et al. PMID: 32332856	Retrospective	China	13	7 (53.8)	35 (median)	6	8	0.7 (0.2-6.5)	5	2.7 (1.1-6.8)
Wang D et al. PMID: 32354360	Retrospective	China	107	57 (53.3)	51 (median)	8	19	5.4 (3.2-8.5)	88	2.8 (2.0-3.9)
Wang K et al. PMID: 32361723	Retrospective	China	296	140 (47.3)	47.32 (mean)	8	19	6.4 (3.2-10.0)	277	3.0 (2.0-4.4)
			44	24 (54.5)	55.2 (mean)	8	14	5.8 (5.0-8.4)	30	3.4 (2.0-5.0)
Wang L et al. PMID: 32240670	Retrospective	China	339	166 (49.0)	69 (median)	7	65	7.65 (4.35-11.74)	274	4.01 (2.63-5.97)
Wu C et al. PMID: 32167524	Retrospective	China	84	60 (71.4)	58.5 (median)	9	44	7.43 (5.15-10.60)[b]	40	5.91 (3.39-9.70)[b]
Yan Y et al. PMID: 32345579	Retrospective	China	48	33 (68.8)	69.4 (mean)	9	39	8.04 (5.36-12.49)	9	3.23 (2.26-5.38)
Martín-Moro F et al. PMID: 32379921	Retrospective	Spain	34	19 (55.9)	72.5 (median)	6	11	7.4 (0-64.2)[c]	23	4.8 (0-41.1)[c]

Note: All values are n (%), or median (IQR).

[a]Quality scores obtained by using an 11-item checklist suggested by the Agency for Healthcare Research and Quality.

[b]The unit of neutrophils is × 10^9/mL.

[c]The values are median (range).

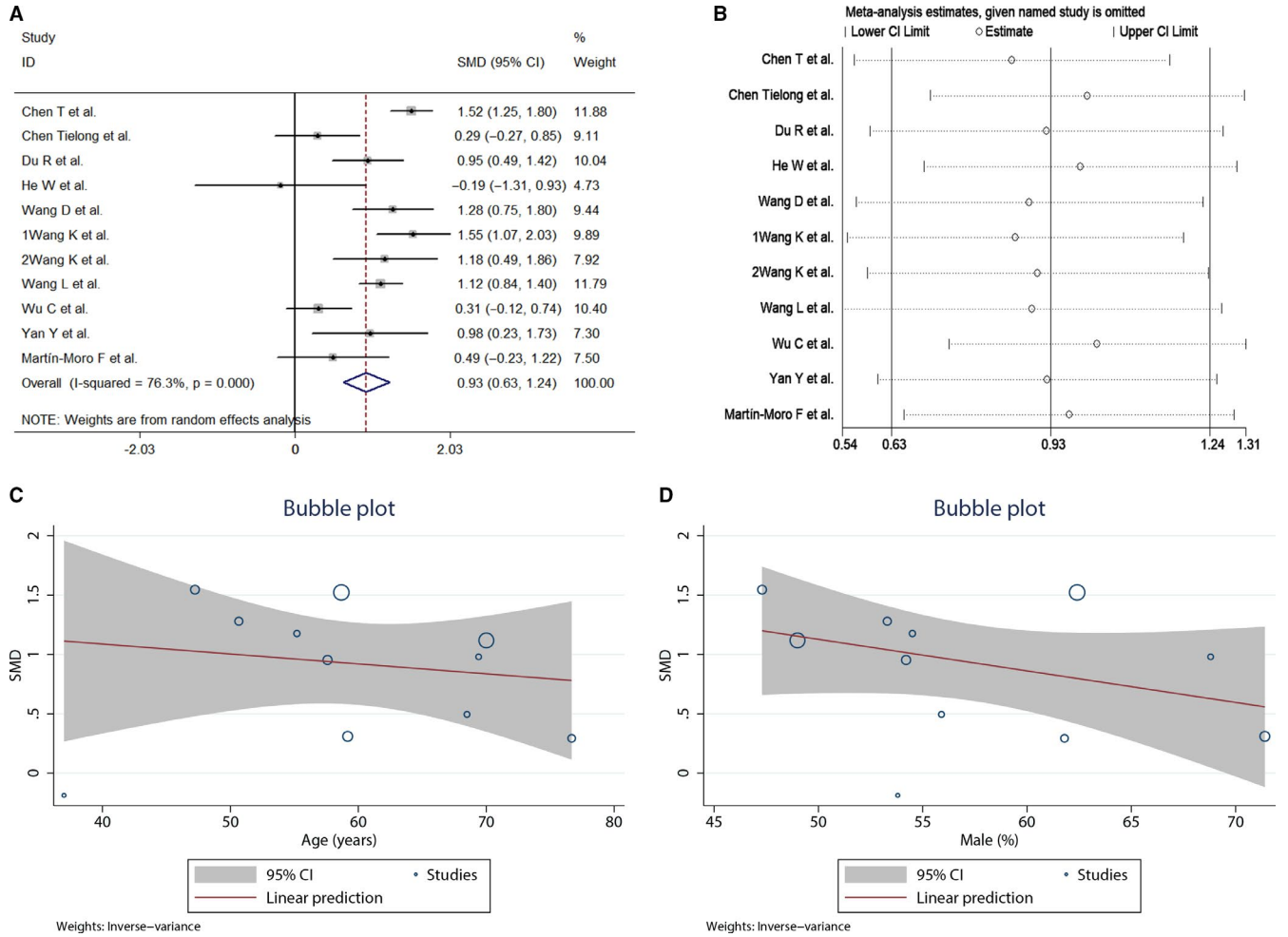

FIGURE 1 The pooled standardized mean difference (SMD) and corresponding 95% confidence interval (CI) (A), sensitivity analysis (B), and meta-regression for age (C) and gender (D) to evaluating the association between changes in neutrophil counts and mortality of COVID-19-infected patients

demonstrated no small-study effects for the relationship between neutrophil counts and increased risk of mortality in COVID-19 patients.

Our current study demonstrated that the elevated neutrophil counts were significantly correlated to the mortality of COVID-19 patients. However, there was high heterogeneity in our study. To find sources of heterogeneity, we conducted a meta-regression. Considering the relationship between age and gender and mortality in COVID-19 patients,[18] we selected age and gender as covariables based on the available data provided by the included studies. Although meta-regression did not identify the sources of heterogeneity, sensitivity analysis indicated that our results were reliable and robust. Besides, the prediction interval showed that values were possible on both sides of the null (prediction interval = −0.12-1.99). Hence, interpretation of our results in some settings or different study populations should be taken with caution. There are still some other limitations to our meta-analysis. This meta-analysis was based on only 10 published studies with 1473 COVID-19 cases. Therefore, future studies with larger sample size are needed to support our results. Besides, most of the studies were from China and only one was from Spain, so the scope of our findings might be limited. In conclusion, neutrophilia is a risk factor for mortality of COVID-19 patients, and our results are required to be verified by a study analyzing the adjusted effect estimates in the future.

KEYWORDS

COVID-19, meta-analysis, mortality, neutrophil

CONFLICTS OF INTEREST

All authors report that they have no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Li Shi, Haiyan Yang, and Yadong Wang conceptualized the study. Li Shi, Ying Wang, Xuan Liang, and Wenwei Xiao extracted the data. Li Shi and Ying Wang analyzed the data. Li Shi, Ying Wang, Guangcai Duan, Haiyan Yang, and Yadong Wang contributed to methodology. Li Shi, Xuan Liang, and Wenwei Xiao contributed software; Li Shi,

Ying Wang, Haiyan Yang, and Yadong Wang wrote and reviewed the manuscript. All the authors approved the final manuscript.

FUNDING INFORMATION

This study was supported by a grant from the National Natural Science Foundation of China (No. 81973105).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.