Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Significant association between anemia and higher risk for COVID-19 mortality: A meta-analysis of adjusted effect estimates

Ying Wang [a], Lan Nan [b], Mengke Hu [a], Ruiying Zhang [a], Yuqing Hao [c], Yadong Wang [d], Haiyan Yang [a,*]

[a] Department of Epidemiology, School of Public Health, Zhengzhou University, Zhengzhou 450001, China
[b] Yusuf Hamied Department of Chemistry, University of Cambridge, UK.
[c] International College of Zhengzhou University, Zhengzhou 450052, China.
[d] Department of Toxicology, Henan, Center for Disease Control and Prevention, Zhengzhou 450016, China.

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ABSTRACT

Objective: This study aimed to evaluate whether there was a significant relationship between anemia and the risk for mortality among coronavirus disease 2019 (COVID-19) patients by a quantitative meta-analysis based on the adjusted effect estimates.
Methods: A systematic search was conducted in electronic databases to identify all published literature. A random-effects meta-analysis model was used to estimate the pooled effect size and 95% confidence interval (CI). Heterogeneity test, Begg's test, subgroup analysis and meta-regression were performed.
Results: Twenty-three articles with 573,928 COVID-19 patients were included in the quantitative meta-analysis. There was a significant association between anemia and an elevated risk of COVID-19 mortality (pooled effect size = 1.47, 95% CI [1.30–1.67]). We observed this significant association in the further subgroup analyses by age, proportion of males, sample size, study design, region and setting. Sensitivity analysis exhibited that our results were reliable. Begg's test showed that there was no publication bias. Meta-regression indicated that the tested variables might not be the source of heterogeneity.
Conclusion: Our meta-analysis based on risk factors-adjusted effect estimates indicated that anemia was independently associated with a significantly elevated risk for mortality among COVID-19 patients.

1. Introduction

Recently, Taneri et al. have performed a systematic review and meta-analysis to explore the prognostic value of biomarkers of anemia among patients with coronavirus diseases 2019 (COVID-19) [1]. They found non-significant difference in hemoglobin levels between survivors and non-survivors among COVID-19 patients, indicating that anemia might not be a risk predictor for COVID-19 mortality. This is an extremely interesting study, but the pooled effect size was estimated on the basis of un-adjusted effect in Taneri et al' study [1], which suggests that some confounding factors were not taken into account when the authors evaluated the association between anemia and COVID-19 mortality. To the best of our knowledge, a few variables such as age, sex and pre-existing chronic health conditions (hypertension, diabetes mellitus, cardiovascular disease and chronic liver disease, etc.) have been identified to influence the clinical outcomes of COVID-19 patients [2-8], which might confound the association between anemia and the risk for COVID-19 mortality. We therefore performed a meta-analysis based on the risk factors-adjusted effect estimates to investigate whether there was a significant association between anemia and higher risk for mortality from COVID-19.

2. Methods

We carried out a systematic search in the electronic databases of Web of Science, PubMed, Springer Link, Elsevier Sciencedirect, EMBASE, Cochrane Library and Scopus to identify all potential articles published on March 13, 2022. The keywords were utilized as follows: ("coronavirus disease 2019" or "COVID-19" or "severe acute respiratory syndrome coronavirus-2" or "SARS-CoV-2" or "2019 novel coronavirus" or "2019-nCoV") and ("non-survivor" or "deceased" or "death" or "fatality" or "mortality") and ("anemia" or "hemoglobin"). Eligible studies in English were included when they were peer-reviewed and presented the risk factors-adjusted effect estimates on the association between anemia and COVID-19 mortality. Preprints, review papers, comments, case reports, errata and studies presenting un-adjusted effect estimates

* Corresponding author at.: Department of Epidemiology, School of Public Health, Zhengzhou University, No. 100 of Science Avenue, Zhengzhou, 450001, China.
E-mail address: yhy@zzu.edu.cn (H. Yang).

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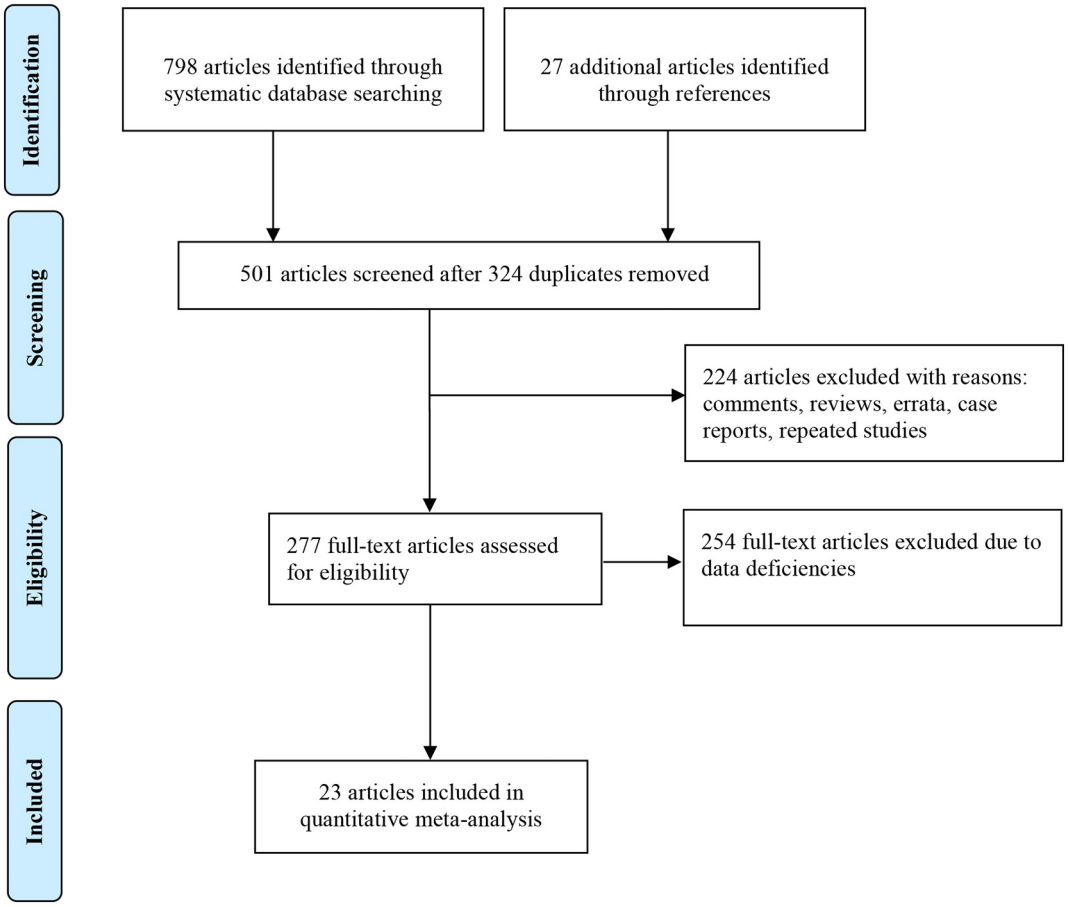

Fig. 1. Flow chart of the process of study selection.

on the association between anemia and COVID-19 mortality were excluded accordingly. Additional articles were eligibly included through looking into the reference lists of the included studies and relevant reviews. The detailed extraction of the each included article was completed independently by two authors using a standardized form. Discrepancies were arbitrated by a third author. The following information extracted from the eligible literature, including name of the first author, number of COVID-19 patients, the proportion of males, age (mean

Table 1
General information of the eligible studies included in this meta-analysis

Author	Country	Cases	Age#	Male (%)	Study design	Adjusted effect (95% CI)	Setting
Kim DH	Korea	5621	50.9	41.2	Retrospective study	2.08 (1.40–3.11)	All patients
Pilgram L	Lean European Open Survey	426	78.3	58.9	Retrospective study	3.21 (1.17–8.82)	All patients
Oh SM	USA	733	65 ± 16	50.8	Retrospective study	1.523 (1.008–2.303)	Hospitalized patients
Tremblay D	USA	2563	59 (42–71)	56.9	Prospective study	1.26 (1.06–1.51)	All patients
Bellmann-Weiler R	Austria	259	68 (53–80)	60.6	Retrospective study	5.063 (1.260–20.345)	Hospitalized patients
Khosravi B	Iran	121	60 ± 16	55.4	Retrospective study	3.86 (1.52–9.77)	Hospitalized patients
Tang O	USA	752	71.2 ± 51.7	39.9	Prospective study	1.12 (0.80–1.57)	All patients
Turgutalp K	Turkey	567	63 (53–71)	52.2	Retrospective study	0.541 (0.284–1.029)	Hospitalized patients
Le Borgne P	France	287	63.1 (50.0–73.0)	65.8	Retrospective study	5.14 (1.19–22.19)	Hospitalized patients
Lee J	Korea	4052	NR	38.7	Retrospective study	1.74 (1.10–2.77)	All patients
Faghih Dinevari M	Iran	1274	64.43 ± 17.16	55.41	Prospective study	1.68 (1.10–2.57)	Hospitalized patients
Giacomelli A	Italy	520	61 (52–70)	67	Prospective study	2.13 (1.21–3.76)	Hospitalized patients
Meisel E	Israel	333	63.6 ± 16.8	65.5	Retrospective study	1.50 (0.83–2.71)	Hospitalized patients
Kompaniyets L	USA	540,667	66 (53–77)	51.7	Retrospective study	1.17 (1.14–1.19)	Hospitalized patients
Hermel DJ	USA	473	61.23 ± 16.70	55.18	Retrospective study	1.74 (1.07–2.85)	Hospitalized patients
Bushman D	USA	1029	56 (23–64)	65.5	Case-control study	1.69 (1.01–2.80)	Hospitalized patients
Pagano L	Italy	3801	65 (54–74)	58.5	Retrospective study	2.022 (0.724–5.645)	All patients
Chojnicki M	Poland	322	77.5 ± 10.0	40.7	Prospective study	2.21 (1.33–3.68)	Hospitalized patients
Bernardo J	Portugal	544	68.9 ± 17.9	54.8	Retrospective study	0.972 (0.899–1.051)	Hospitalized patients
Alhasan KA	Saudi Arabia	229	52.8 ± 16.6	80.4	Retrospective study	2.31 (0.63–8.48)	Hospitalized patients
Kim YJ	Korea	5349	67.6	40.6	Retrospective study	1.917 (1.134–2.441)	All patients
Buso G	International RIETE registry	737	63.6	60.1	Retrospective study	1.14 (0.77–1.69)	All patients
AbuRuz S	United Arab Emirates	3269	44.3 ± 13.4	76.3	Retrospective study	1.76 (1.03–3.00)	Hospitalized patients

Note: # the age (years) was presented as mean ± standard deviation or median (interquartile range, IQR); CI, confidence interval; NR, not clearly reported; RIETE, Registro Informatizado de Enfermedad TromboEmbolica; USA, the United states of America.

± standard deviation (SD) or median (interquartile range)), study design, country or region, the number and percent of COVID-19 patients with anemia, adjusted effect size (95% confidence interval (CI)), death outcome and setting. This systematic meta-analysis was performed in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (Table S1) [9].

All statistical analyses were carried out by using R software with the "meta" package. Heterogeneity across studies was measured by I^2 statistic and standard Cochran's Q analysis. The pooled effect size with its 95% CI was calculated to measure the association between anemia and the risk for COVID-19 mortality by a random-effects meta-analysis model. The stability of the overall results was examined by the leave-one-out sensitivity analysis. Potential publication bias was evaluated by Begg's rank correlation analysis. Meta-regression and subgroup analyses were also conducted. Statistically significant difference was defined as $P < 0.05$.

3. Results

Fig. 1 showed the flow chart of related literature search and selection process. A total of twenty-three articles with 573,928 COVID-19 patients were eligibly included in this quantitative meta-analysis [10-32]. The characteristics of the eligible studies are summarized in Table 1.

The pooled effect size with 95% CI on the basis of risk factors-adjusted effect estimates is presented in Fig. 2A. We observed that there was a significant association between anemia and higher risk for COVID-19 mortality (pooled effect size = 1.47, 95% CI [1.30–1.67]). We also observed this significant association in the further subgroup analyses stratified by sample size (pooled effect size = 1.54, 95% CI [1.29–1.84] for ≥1000 cases and pooled effect size = 1.58, 95% CI [1.21–2.06] for <1000 cases), proportion of male patients (pooled effect size = 1.38, 95% CI [1.20–1.58] for ≥50% and pooled effect size = 1.72, 95% CI [1.32–2.25] for <50%), age (pooled effect size = 1.42, 95% CI [1.23–1.65] for age ≥ 60 years old and pooled effect size = 1.43, 95% CI [1.23–1.66] for age < 60 years old), region (pooled effect size = 1.17, 95% CI [1.15–1.20] for North America; pooled effect size = 1.68, 95% CI [1.29–2.19] for Asia and pooled effect size = 2.21, 95% CI [1.27–3.86] for Europe), study design (pooled effect size = 1.46, 95% CI [1.26–1.70] for retrospective studies and pooled effect size = 1.50, 95% CI [1.17–1.91] for prospective studies) and setting (pooled effect size = 1.45, 95% CI [1.24–1.70] for hospitalized patients and pooled effect size = 1.52, 95% CI [1.23–1.86] for all patients). The sensitivity analysis demonstrated that our results were reliable and robust (Fig. 2B). There was no potential publication bias detected in Begg's test (P = 0.196, Fig. 2C). Meta-regression suggested that the tested variables including sample size ($P = 0.720$), proportion of males ($P = 0.121$), age ($P = 0.628$), study design ($P = 0.907$), region ($P = 0.360$) and setting ($P = 0.783$) might not be the source of heterogeneity.

4. Discussion

Although the published literature has investigated the relationship between anemia and the risk for mortality among COVID-19 patients, their conclusions were inconsistent [15,17]. Our data based on risk factors-adjusted effect estimates showed that anemia was associated with a significantly elevated risk of COVID-19 mortality, which suggests that anemia might be an independent risk predictor for the fatal outcome of COVID-19 patients. Further subgroup analyses stratified by sample size, age, proportion of males, region, study design and setting also supported the overall results. COVID-19 patients had respiratory system damages and increased oxygen demand, and bore lower hemoglobin levels, and this situation further reduces the oxygen supply to the peripheral tissues, as the disease progresses, persistent hypoxic condition may lead to peripheral tissue ischemia or multiple organ failure [12]. This may explain the higher mortality among COVID-19 patients with anemia in comparison to those without anemia.

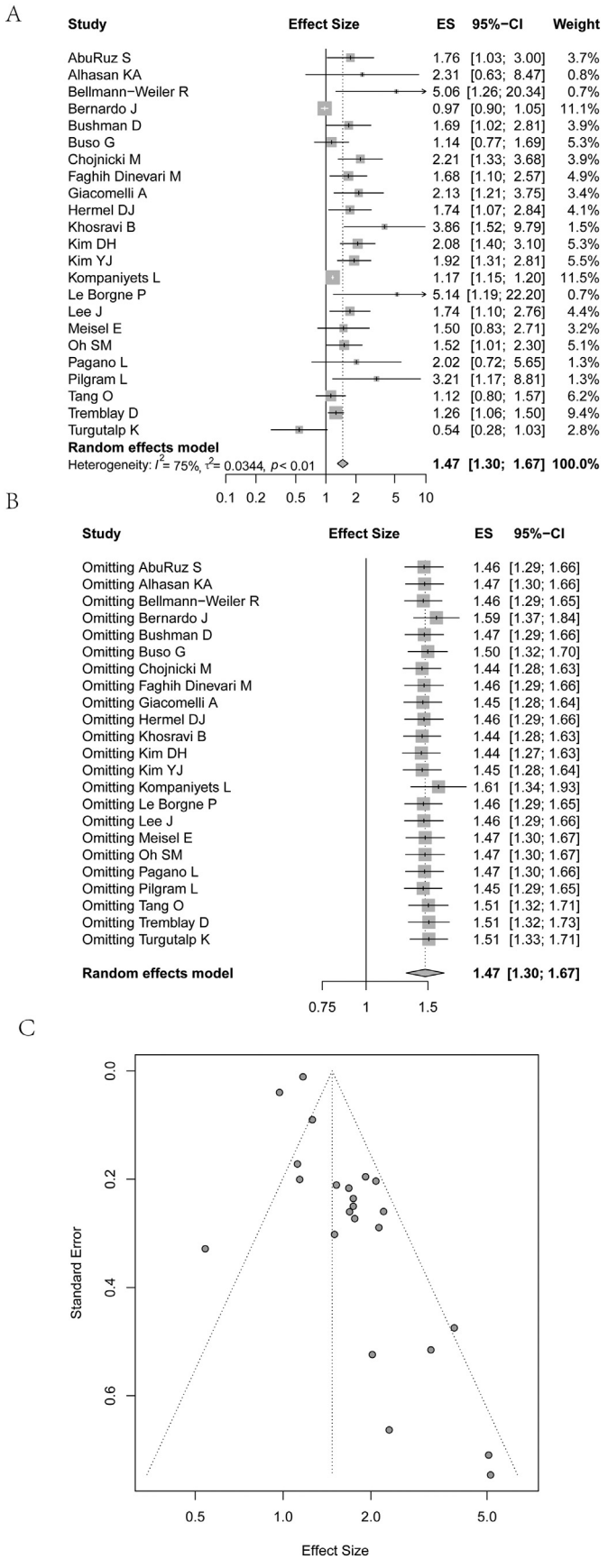

Fig. 2. The forest plots indicated that there was a significant association between anemia and an elevated risk for mortality among patients with coronavirus disease 2019 (COVID-19) on the basis of twenty-three studies with 573,928 cases (A); Leave-one-out sensitivity analysis demonstrated the stability of the overall results (B); Begg's test revealed that there was no obvious publication bias (C).

This current meta-analysis still has several limitations. Firstly, most of the included studies were retrospective. Thus, further meta-analyses based on prospective studies with large sample sizes are required to verify our findings. Secondly, the pooled effect sizes were calculated on the basis of adjusted effect estimates, but the risk factors adjusted in the included studies were not completely consistent. Thirdly, the definition of anemia (the level of hemoglobin) in the included literature was not fully consistent. Finally, the heterogeneity could not be ignored. Although we conducted meta-regression to explore the source of heterogeneity, no source of heterogeneity was found.

In conclusion, our meta-analysis based on risk factors-adjusted effect estimates showed that anemia was independently associated with a significantly higher risk for mortality among patients with COVID-19. Further well-designed studies with more eligible literature and large sample sizes are warranted to verify our current findings.

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Author contributions

Haiyan Yang and Yadong Wang conceptualized the study. Lan Nan, Ruiying Zhang, Yuqing Hao and Ying Wang performed literature search and data extraction. Mengke Hu, Lan Nan, Ying Wang and Yuqing Hao analyzed the data. Ying Wang and Ruiying Zhang wrote the manuscript. All the authors approved the final manuscript.

Data availability statement

The data that support the findings of this study are included in this article and available from the corresponding author upon reasonable request.

CRediT authorship contribution statement

Lan Nan: Writing – review & editing, Methodology, Investigation, Formal analysis. **Mengke Hu:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Ruiying Zhang:** Writing – review & editing, Methodology, Investigation. **Yuqing Hao:** Writing – review & editing, Methodology, Investigation. **Yadong Wang:** Writing – review & editing, Conceptualization. **Haiyan Yang:** Conceptualization.

Declaration of Competing Interest

All authors declare that they have no any potential conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajem.2022.06.030.

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