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LETTER TO THE EDITOR

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Neutrophil-to-lymphocyte ratio is independently associated with COVID-19 severity: An updated meta-analysis based on adjusted effect estimates

As the current epidemic caused by coronavirus disease 2019 (COVID-19) progresses, prognostic markers that might be associated with adverse outcomes of COVID-19 patients caught the researchers' attention. Neutrophil-to-lymphocyte ratio (NLR) is an easily accessible value that has been known to correlate with inflammation and prognosis in several conditions. Recently, a meta-analysis by Chan et al[1] have reported that higher levels of NLR were observed in patients with severe COVID-19 compared with nonsevere disease (standard mean difference (SMD) = 2.80, 95% confidence interval (CI): 2.12-3.48, $P < .001$). However, the findings of Chan et al's[1] study were based on unadjusted effect estimates. Two other meta-analyses on this topic also reported unadjusted effect estimates.[2,3] It was worth noting that a univariate analysis indicated that NLR was an important risk factor significantly associated with COVID-19 severity. However, inconsistent conclusions were drawn from a multivariate analysis.[4-6] For example, in the article of Zhang et al,[4] univariate analysis showed that NLR was a risk factor for the disease severity of COVID-19 (odds ratio (OR) = 1.55, 95% CI: 1.18-2.03), while multivariate analysis demonstrated that NLR was not significantly associated with COVID-19 severity (OR = 1.17, 95% CI: 0.85-1.60). Similarly, Wang et al[5] reported that NLR was significantly associated with COVID-19 severity in univariate analysis (OR = 1.44, 95% CI: 1.23-1.68), but this significant association disappeared in a multivariate analysis (OR = 0.99, 95% CI: 0.97-1.01). Similar findings were also observed in Wang et al's study.[6] This meant that various factors such as age, gender, and other confounders (such as diabetes, hypertension, cerebrovascular diseases, and chronic obstructive pulmonary disease, etc.)[7-11] might affect the association between NLR and COVID-19 severity. So, an updated meta-analysis based on published studies reporting adjusted effect estimates is needed to clarify the association between NLR and COVID-19 severity.

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. We carried out an electronic search in PubMed, Web of Science, and EMBASE until October 23, 2020. The following keywords were used: ((“COVID-19” or “2019-nCoV” or “SARS-CoV-2” or “coronavirus disease 2019”) and (“NLR” or “neutrophil-to-lymphocyte ratio” or “neutrophil/lymphocyte”) and (“clinical progression” or “mortality” or “severity”)). Articles that reported the relationship between NLR and COVID-19 severity (including severe, critical, or mortal outcomes) using multivariate analysis model were selected. Reviews, erratum, duplicated papers, comments, and articles reporting the relationship between NLR and COVID-19 severity using univariate analysis model were excluded. Heterogeneity was evaluated by I^2 statistic. The combined effect with 95% CI was estimated by fixed-effects model ($I^2 < 50\%$ in heterogeneity test) or random-effects model ($I^2 > 50\%$ in heterogeneity test). We used Begg's test and Egger's test to assess publication bias, and sensitivity analysis to evaluate the stability of our results. Subgroup analyses by effect estimate, study design, sample size, country, and age were also performed. We estimated the mean and standard deviation according to Wan et al[12] when sample size, median, and interquartile range (IQR) were provided. We used STATA 11.2 to conduct all calculations, and $P < .05$ was considered significant.

The flow diagram of study selection is shown in Figure S1, and the PRISMA checklist is shown in Table S1. Initially, 530 articles were identified. After carefully reading titles, abstracts, and full texts, 496 articles were excluded. Finally, 34 studies with 25 074 COVID-19 patients were included. The main characteristics of the included studies are shown in Table 1. We observed that there was a significant association between elevated NLR and an increased risk for COVID-19 severity on the basis of adjusted effect estimates (pooled effect = 1.12, 95% CI: 1.08-1.16; $I^2 = 86.0\%$, $P < .001$; random-effects model; Figure 1A). When the disease outcomes were restricted to death, the significant association between NLR and death among COVID-19 patients still existed (pooled effect = 1.11, 95% CI: 1.06-1.17; Figure 1B). We observed consistent results in the subgroup analyses by effect estimates (OR = 1.15, 95% CI: 1.08-1.21 and hazard ratio (HR) = 1.12, 95% CI: 1.05-1.19; Table S2 and Figure S2), sample size (≥500: pooled effect = 1.86, 95% CI: 1.29-2.68 and <500: pooled effect = 1.09, 95% CI: 1.05-1.13; Table S2 and Figure S3), and age (≥60: pooled effect = 1.23, 95% CI: 1.14-1.32 and <60: pooled effect = 1.05, 95% CI: 1.01-1.09; Table S2 and Figure S4). Further subgroup analysis by countries indicated that the significant association between NLR and COVID-19 severity was found in China (pooled effect = 1.11, 95% CI: 1.07-1.16), Turkey (pooled effect = 2.56, 95% CI: 1.65-3.95), and Spain (pooled effect = 1.83, 95% CI: 1.13-2.96), but not in the USA (pooled effect = 1.38, 95% CI: 0.77-2.50), Italy (pooled effect = 1.38, 95% CI: 0.97-1.97), or UK (pooled effect = 1.02, 95% CI: 0.98-1.06; Table S2 and Figure S5). The subgroup analysis by study design showed that the significant

TABLE 1 Characteristics of the included studies

Author	Country	Cases (n)	Age (years)	Male n (%)	Study design	Outcomes	Adjusted effect estimate (95% CI)	Confounders
Yan X	China	1004	60.97 ± 14.97	493 (49.1)	R	Death	OR 44.351 (4.627, 425.088)	High-sensitivity CRP, NT-proBNP, BUN, HTN, respiratory failure, digestive system disease, cerebrovascular disease
Piano S	Italy	565	66 ± 15	357 (63)	R	ICU	OR 1.38 (0.97, 1.98)	Age, gender, Charlson comorbidity index, SOFA score, respiratory rate, heart rate, CRP, serum ALB, bilateral consolidation at X-ray, abnormal liver function tests
Chen L	China	1859	59 (45, 68)	925 (50)	R	Death	HR 3.3 (2.1, 5.19) HR 0.44 (0.02, 10.09) HR 14.06 (3.23, 61.21) HR 0.49 (0.17, 1.44)	Age, smoking history, temperature value at admission, admission platelet concentration, aPTT on admission, Log_{10}D-dimer, Log_{10}Scr
Zhang C	China	80	51.16 ± 17.476	33 (41.25)	R	Severity	OR 1.17 (0.85, 1.6)	Age, cardiac disease, HTN, more than 2 kinds of diseases, WBC, neutrophil, LYM%, NEU%, FiB, CRP, TBIL, ALB, GFR, CK-MB, myoglobin
Wang F	China	323	46 (33, 59)	154 (47.7)	A	Disease progression	OR 0.99 (0.97, 1.01)	T lymphocyte, CRP, IL-6, ESR
Ye W	China	349	62(21, 69)	173 (49.60)	R	Death	HR 1.01 (0.99, 1.03) HR 1 (0.99, 1.01)	Age, D-dimer on admission, peak D-dimer, peak NLR Age, D-dimer on admission, peak D-dimer, NLR on admission
Cheng B	China	456	54.97 ± 18.59	211 (46.27)	R	Any in-hospital disease progression	OR 1.132 (1.042, 1.23)	Age, male, HTN, diabetes, CKD, CVD, neural system diseases, neutrophil count, lymphocyte count, PCT, CRP
Yang Q	China	176	49.93 ± 15.35	82 (46.60)	R	Death	HR 1.103 (1.06, 1.148)	Scr, BUN, sex, T2DM, serum ALB, CRP, Age, AST, HTN, D-dimer
Liao D	China	380	64 (53, 73)	206 (54)	R	Death	OR 5.39 (1.7, 17.13)	D-dimer, thrombocytopenia, prolonged PT
Ok F	Turkey	139	55.5 ± 18.5	62 (44.6)	R	Severity	OR 2.21 (1.2, 4.3)	Age, gender, history of HTN, History of heart disease, BUN/Cr ratio, WBC, MLR, CRP
Zhang S	China	828	62 (51, 69)	447 (53.99)	A	Death	HR 2.63 (1.55, 4.4)	Age, direct bilirubin, LDH level
Lian J	China	232	67.25 ± 6.89	109(47.0)	P	Critical illness	HR 1.136 (1.094, 1.18)	Age, heart disease, multiple mottling, ground-glass opacity
Chen FF	China	681	65 (54, 72)	362 (53.2)	R	Death	OR 1.057 (1.01, 1.107)	Age, acute myocardial injury, CRP, LDH, CD3 count, arbidol, ribavirin
Knopp P	UK	217	80 ± 6.8	134 (62)	P	Death	HR 0.86 (0.47, 1.59) HR 0.54 (0.29, 1) HR 1.23 (0.67, 2.25)	Age, sex, cough, fever, dyspnea, gastrointestinal, imaging abnormalities, falls, reduced mobility, delirium, CRP

(Continues)

TABLE 1 (Continued)

Author	Country	Cases (n)	Age (years)	Male n (%)	Study design	Outcomes	Adjusted effect estimate (95% CI)	Confounders
Berenguer J	Spain	4035	70 (56, 80)	2433 (61)	R	Death	HR 1.41 (1.17, 1.69) HR 2.38 (1.99, 2.84)	Age, sex, HTN, chronic heart disease, diabetes, chronic pulmonary disease, obesity, CKD stage 4, liver cirrhosis, chronic neurological disorder, cancer, dementia, headache, myalgia/arthralgia, anosmia, cough, sputum production, dyspnea, chest pain, vomiting/nausea, altered consciousness, low SaO_2, WBC count, neutrophil count, platelets, prolonged APTT, INR, eGFR, ALT, CRP
Pakos IS	USA	242	66.03 ± 14.75	123 (51)	R	Death	OR 1.038 (1.003, 1.074)	Age, BMI, sex, African American (Caucasian, Hispanic, Others), COPD, asthma, DM, HTN, HF, CKD, AMC, platelets
Li C	China	203	57.63 ± 14.10	120 (59.1)	R	Severity Death	OR 1.21 (0.55, 2.64) HR 4.33 (0.65, 28.95)	WBC, lymphocyte, CRP, fibrinogen, D-dimer, CK, LDH Sex, age, WBC, lymphocyte, CRP, fibrinogen, D-dimer, CK, LDH
Gormez S	Turkey	247	51.3 ± 14.2	154 (62.3)	R	The composite of need for ICU, mechanical ventilation, or occurrence of death	OR 2.9 (1.6, 5.26)	Age, Sex, D-dimer, CRP, ACEIs/ARBs, HTN
Li C	China	104	59 ± 12.9	65 (62.5)	R	Death	HR 1.04 (1.01, 1.06)	Age, GLU, IL-6, PCT, INR
Wang W	China	123	68 (56.5, 78.0)	60 (48.7)	R	Death	OR 1.156 (1.07, 1.25)	Age, comorbidities, lymphocyte, PLR, IL-6, CRP, CT score, need nutrition support, electrolyte imbalance
Liu G	China	134	65.54 ± 11.28	76 (56.7)	R	Severe & extremely severe COVID-19 or not	OR 6.429 (2.103, 19.655)	NR
Liu C	China	156	NR	NR	R	Death	OR 0.28 (0.01, 5.48) OR 33.37 (1.56, 714.58)	Age, sex, gastrointestinal cancer, lung cancer, urogenital cancer, cancer stage, receipt of antitumor treatment, WBC count, lymphocyte count, COPD, dyspnea, fatigue
Wang X	China	131	64 (56, 71)	56 (42.7)	R	Death	OR 1.513 (1.101, 2.263)	AST, albumin, creatine kinase, Scr
Ruiz SJ	Spain	115	67.2 (77.2, 59)	68 (59.1)	R	Death	OR 1.02 (1.01, 1.12) OR 4.21 (1.4, 12.69)	LDH at hospital admission, CRP at hospital admission Age
Wang R	China	450	58 (41, 70)	206 (45.8)	P	Death	OR 0.868 (0.711, 1.059)	Age, sex, HTN, CVD, chronic respiratory disease, heart rate, respiratory rate, WBC, PNI, PLR, ALT, AST, ALP, LDH, BUN, Scr, CRP, INR, PT, APTT, D-dimer

(Continues)

TABLE 1 (Continued)

Author	Country	Cases (n)	Age (years)	Male n (%)	Study design	Outcomes	Adjusted effect estimate (95% CI)	Confounders
Xu JB	China	76	59.11 ± 14.55	46 (60.53)	R	Death	HR 0.82 (0.07, 10.13)	Age, sex, Cancer, ARDS, hypohepatia, renal insufficiency, HF, shock, PCT, CRP
Zhou J	China	118	71.68 ± 7.15	53 (44.9)	R	Death	OR 1.4 (1.2, 1.6)	Age, sex, disturbance of consciousness, abnormal gait, HTN, coronary heart disease, diabetes, chronic bronchitis, pulmonary emphysema, renal failure, chronic liver disease, carcinoma, albumin, urea nitrogen, LDH, D-dimer
Ioannou GN	USA	10 131	63.6 ± 16.2	9221 (91.0)	A	Death	HR 1.48 (1.11, 1.96) HR 1.71 (1.29, 2.25) HR 1.83 (1.36, 2.46) HR 2.88 (2.12, 3.91)	Age, sex, race, ethnicity, COVID-19–related deaths per million residents, urban vs rural, BMI at index date, diabetes, cancer, HTN, coronary artery disease, congestive HF, cerebrovascular disease, dialysis, CKD, cirrhosis, asthma, COPD, obstructive sleep apnea, obesity hypoventilation, alcohol dependence, hyperlipidemia, smoking, Charlson comorbidity index score, fever, cold, chills, myalgia, fatigue, cough, dyspnea, sore throat, nausea, diarrhea, abdominal pain, headache
Xu R	China	315	64 (48, 70)	158 (50.1)	R	Critical illness developed	OR 1.167 (1.055, 1.291)	Age, comorbidity diseases (HTN, diabetes, coronary heart disease, malignant tumor, CKD, some other disease), D-dimer, CRP, platelet count
Wang S	China	140	48 (29, 75)	51 (36.4)	R	Death	OR 1.15 (0.12, 11.05) OR 11.79 (2.05, 67.94)	Age, HTN, dyspnea, CRPR
Song CY	China	79	54 (45, 63)	49 (62.0)	R	Severity	OR 1.117 (1.01, 1.236)	CD4+ T cell count, D-dimer, constant
Wang M	China	657	63 (49, 70)	347 (52.8)	R	Liver injury	OR 2.154 (1.486, 3.124)	Gender, metabolic disorder, viral hepatitis, body temperature, HsCRP
Xue G	China	114	62 (51, 70)	64 (56.1)	R	Severity	OR 0.999 (0.987, 1.011) OR 1.368 (1.144, 1.637)	Age, gender, PLR, LMR, HsCAR, PNI, SII, AFR, HsCPAR
Chinnadurai R	UK	215	74 (60, 82)	133 (61.9)	R	Death	OR 1.02 (0.98, 1.06)	Age, care home resident, frailty, smoking, BMI, CVD, respiratory diseases, CRP, eGFR, acute kidney injury

Note: The values of age are mean ± standard deviation (SD) or median (interquartile range, IQR); the values of male are n (%).

Abbreviations: A, ambispective study; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; AFR, albumin-to-fibrinogen ratio; ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AMC, absolute monocyte count; aPTT, activated partial thromboplastin time; ARDS, acute respiratory distress syndrome; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; BUN/Cr ratio, blood urea nitrogen/creatinine ratio; CI, confidence interval; CK, creatinine kinase; CKD, chronic kidney disease; CK-MB, creatine kinase isoenzyme-MB; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; CRPR, ratio of C-reactive protein (the ratio of CRP value/upper limit of the CRP value); CVD, cardiovascular disease; DM, diabetes mellitus; dNLR, derived neutrophil-lymphocyte ratio; eGFR, estimated glomerular filtration rate; ESR, erythrocyte sedimentation rate; FIB, fibrinogen content; GFR, glomerular filtration rate; GLU, fasting blood glucose; HF, heart failure; HR, hazard ratio; HsCAR, high-sensitivity C-reactive protein-albumin ratio; HsCPAR, high-sensitivity C-reactive protein-prealbumin ratio; HTN, hypertension; IL-6, interleukin-6; INR, international normalized ratio; LDH, lactate dehydrogenase; LMR, lymphocyte-to-monocyte ratio; LYM%, lymphocyte percentage; MLR, monocyte-to-lymphocyte ratio; NEU%, neutrophil percentage; NLR, neutrophil-to-lymphocyte ratio; NR, not reported; NT-proBNP, N-terminal pro-brain–type natriuretic peptide; OR, odds ratio; P, prospective study; PCT, procalcitonin; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutritional index; PT, prothrombin time; R, retrospective study; SaO_2, arterial oxygen saturation; Scr, serum creatinine; SII, systemic immune-inflammation index; SOFA, sequential organ failure assessment; T2DM, type 2 diabetes mellitus; TBIL, total bilirubin; WBC, white blood cell count.

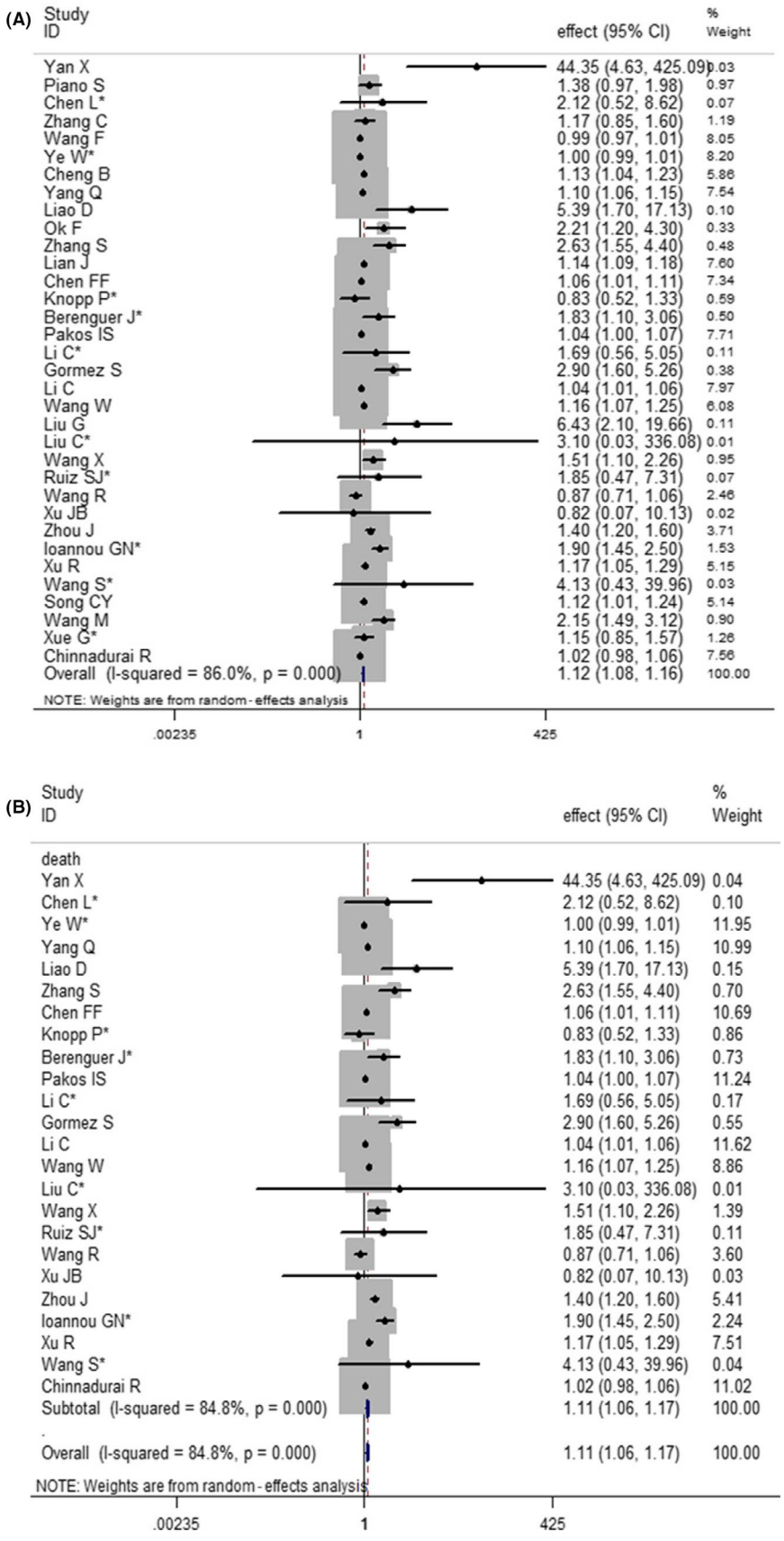

FIGURE 1 (A) Forest plot of the association between elevated NLR and an increased risk for COVID-19 severity; (B) forest plot of the association between NLR and death among COVID-19 patients when the disease outcomes were restricted to death. * indicates combined effects based on subgroups

association between NLR and COVID-19 severity was observed in retrospective studies (pooled effect = 1.13, 95% CI: 1.08-1.18), but not in ambispective studies (pooled effect = 1.64, 95% CI: 0.90-2.99) or prospective studies (pooled effect = 0.98, 95% CI: 0.78-1.24; Table S2 and Figure S6). Sensitivity analysis indicated that our results were reliable and robust (Figure S7). Publication bias was found in Egger's test ($P < .001$; Figure S8A), but not in Begg's test ($P = .906$; Figure S8B).

It is worth noting that our research finally included 34 articles, of which 25 were from China, 2 from Spain, 1 from Italy, 2 from the USA, 2 from Turkey, and 2 from the UK. In particular, the only one article originating from Italy presented that there was no significant association between NLR and COVID-19 severity. In addition, two articles originating from the USA presented statistically significant results, but the final results were not statistically significant, which may be due to high heterogeneity. Thus, our results should be verified by further meta-analyses based on a large number of sample sizes from different countries.

However, there are still some limitations in our study. First, the main disadvantage was that the adjustment factors were different in the selected studies. Second, publication bias likely existed in our current study as the *P* value was less than .001 in Egger's test, although we tried to screen out eligible studies as possible as we can. Third, different study designs have their own characteristics. Prospective study can be used to verify the cause of diseases, but it may take a long time to explore diseases' pathogenesis. In such situations, a retrospective approach may be more fruitful, at least in the interim. However, a main limitation of the retrospective approach is the general frailty of information collected about the past, especially the remote past. Most included studies are retrospective; thus, our results should be verified by further meta-analyses based on a large number of prospective studies. Fourth, the data on clinical treatment for COVID-19 patients in the included studies were not available; thus, we could not address the effects of clinical treatment on the association between NLR and COVID-19 severity.

In summary, our findings demonstrated that elevated NLR was an independent risk factor associated with COVID-19 severity. Therefore, patients with elevated NLR should be given more attention to prevent further deterioration of the disease or even death.

KEYWORDS

COVID-19, death, meta-analysis, NLR, severity

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CONFLICT OF INTEREST

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

AUTHOR CONTRIBUTIONS

Haiyan Yang conceptualized the study. Yang Li and Hongjie Hou performed literature search and extracted the data. Yang Li, Hongjie Hou, and Jie Diao analyzed the data. Yang Li and Yadong Wang wrote and reviewed the manuscript. All the authors approved the final version of this manuscript.

DATA AVAILABILITY STATEMENT

All data relevant to this study are included in this article or uploaded as supplementary information.

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DATA AVAILABILITY STATEMENT

All data relevant to this study are included in this article or uploaded as supplementary information.

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SUPPORTING INFORMATION

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