Received: 24 January 2021 | Accepted: 1 July 2021

DOI: 10.1111/ijcp.14596

META-ANALYSIS

INFECTIOUS DISEASES

THE INTERNATIONAL JOURNAL OF CLINICAL PRACTICE WILEY

# Prognostic value of neutrophil-to-lymphocyte ratio in COVID-19 patients: A systematic review and meta-analysis

Juan R. Ulloque-Badaracco[1] | W. Ivan Salas-Tello[1] | Ali Al-kassab-Córdova[1] | Esteban A. Alarcón-Braga[1] | Vicente A. Benites-Zapata[2] | Jorge L. Maguiña[1,3] | Adrian V. Hernandez[4,5]

[1]Escuela de Medicina, Universidad Peruana de Ciencias Aplicadas, Lima, Peru

[2]Vicerrectorado de Investigación Unidad de Investigación para la Generación y Síntesis de Evidencias en Salud, Vicerrectorado de Investigación, Universidad San Ignacio de Loyola, Lima, Peru

[3]Instituto de Evaluación de Tecnologías en Salud e Investigación — IETSI, EsSalud, Lima, Peru

[4]Unidad de Revisiones Sistemáticas y Meta-análisis, Guías de Práctica Clínica y Evaluaciones de Tecnología Sanitaria, Vicerrectorado de Investigación, Universidad San Ignacio de Loyola, Lima, Peru

[5]Health Outcomes, Policy, and Evidence Synthesis (HOPES) Group, University of Connecticut School of Pharmacy, Mansfield, CT, USA

**Correspondence**
Jorge L. Maguiña, Escuela de Medicina, Universidad Peruana de Ciencias Aplicadas, Avenue Alameda San Marcos, Distrito de Chorrillos 15067, Lima, Peru.
Email: jorge.luis.maguina@gmail.com

## Abstract

**Background:** Neutrophil-to-lymphocyte ratio (NLR) is an accessible and widely used biomarker. NLR may be used as an early marker of poor prognosis in patients with COVID-19.

**Objective:** To evaluate the prognostic value of the NLR in patients diagnosed with COVID-19.

**Methods:** We conducted a systematic review and meta-analysis. Observational studies that reported the association between baseline NLR values (ie, at hospital admission) and severity or all-cause mortality in COVID-19 patients were included. The quality of the studies was assessed using the Newcastle-Ottawa Scale (NOS). Random effects models and inverse variance method were used for meta-analyses. The effects were expressed as odds ratios (ORs) and their 95% confidence intervals (CIs). Small study effects were assessed with the Egger's test.

**Results:** We analysed 61 studies (n = 15 522 patients), 58 cohorts, and 3 case-control studies. An increase of one unit of NLR was associated with higher odds of severity (OR 6.22; 95%CI 4.93 to 7.84; $P < .001$) and higher odds of all-cause mortality (OR 12.6; 95%CI 6.88 to 23.06; $P < .001$). In our sensitivity analysis, we found that 41 studies with low risk of bias and moderate heterogeneity ($I^2$ = 53% and 58%) maintained strong association between NLR values and both outcomes (severity: OR 5.36; 95% CI 4.45 to 6.45; $P < .001$; mortality: OR 10.42 95% CI 7.73 to 14.06; $P = .005$).

**Conclusions:** Higher values of NLR were associated with severity and all-cause mortality in hospitalised COVID-19 patients.

## 1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an acute respiratory infection caused by SARS-CoV-2.[1-3] On 30 January 2020, the World Health Organization (WHO) declared the epidemic as a public health emergency of international interest.[4] After more than 20 000 cases and 1000 deaths in the European Region, the WHO classified the disease as a pandemic.[5] To date (14 May 2021), more than 162 million cases and 3.37 million deaths have already been reported across the world.[6] According to recent studies, the basic reproduction number (R0) is 3.38, suggesting high transmissibility.[7] Besides the significant human losses, the quarantine and social distancing have had a great impact on the global economy.[8] However, despite the implementation of these strategies, the incidence of cases has been increasing in some countries, and nowadays, some nations are experiencing a second wave.

Sociodemographic and clinical factors, such as older age, male sex, hypertension and diabetes mellitus, increase the mortality rate

  

of COVID-19.[9,10] However, these factors have different distributions between countries.[11] In June 2020, a meta-analysis reported that the global mortality rate was 2.72% (95% CI 2.19-4.76).[12] Additionally, a current meta-analysis reported a 46% (95% CI 18.48-73.6) prevalence of asymptomatic patients, which has made it difficult to control the pandemic.[12] On the other hand, in symptomatic patients, the most common manifestations are fever, cough, dyspnea, muscle fatigue or muscular pain and chest distress. Moreover, 29.3% of those infected require admission to the intensive care unit (ICU).[12] Regarding the patients admitted to the ICU, reports do not suggest high mortality in them.[13]

The neutrophil-to-lymphocyte ratio (NLR) is an accessible, reproducible and widely used biomarker for evaluating the prognosis of many health-related problems such as cardiovascular diseases, various types of cancer, ocular diseases and infectious diseases, among others.[14-20] The biological basis of this biomarker is related to the response of the innate immune system against systemic inflammation, injury and stress. This is characterised by lymphocytopaenia and neutrophilia.[21] Although there is no consensus on normal cutoff values, two studies reported a cutoff value of 1.65 and 1.70.[22,23] Recently, a study showed that NLR is elevated in patients with severe COVID-19, and the authors suggest that its performance in the prognosis of severe disease should be further evaluated.[24] A brief meta-analysis, with several limitations, reported that the NLR was a good tool to assess the prognosis of severity in patients with COVID-19.[25] NLR evaluation can help physicians in initiating treatment and monitoring patient, thereby improving the prognosis and outcomes.

Several studies have evaluated the performance of the NLR in the prognosis of patients with COVID-19, so it is necessary to synthesise these results to give a more reliable tool for physicians. The objective of this study was to evaluate the prognostic value of the NLR in patients diagnosed with COVID-19.

**Review criteria**

Our systematic review and meta-analysis included a search strategy from different databases such as EMBASE, SCOPUS, Web of Science, OVID MEDLINE and preprints platforms. Four reviewers independently analysed the titles and abstracts of manuscripts to choose potentially relevant articles. The selected articles were grouped, and duplicates were eliminated with the Rayyan QCRI software. All discrepancies were resolved by group consensus, and finally, the analysis was conducted in RevMan 5.0.

**Message for the clinic**

The NLR is a biomarker accessible, reproducible and easy to use in COVID-19 patients. In our study, NLR was strongly associated with a higher odds of severity and all-cause mortality; NLR could help health professionals to quickly identify high-risk COVID-19 patients and adopt low-cost and timely intervention to prevent complications. This is relevant, especially now, that several countries continue to have a high transmission rate of SARS-CoV-2.

## 2 | METHODS

We used the Preferred Reporting Items for Systematic Reviews and Meta-analysis[26] statement to report our systematic review. A short version of our protocol has been registered in the International Prospective Register of Systematic Review [CRD42020190508].

### 2.1 | Data sources and searches

We searched on 23 December 2020 for studies assessing the association between NLR and clinical outcomes in patients diagnosed with COVID-19 in the following databases: OVID Medline, OVID Embase, PubMed, Web of Science, Scielo, Scopus, LILACS, Cochrane Library and WHO COVID-19 Global Research Database. Additionally, a manual search was performed in ScienceDirect, Springer Link, CNKI databases and preprints platforms, such as medRxiv and Scielo Preprints (see Supporting Information Appendix 1). The search strategy was done using the Peer Review of Electronic Search Strategies Checklist.[27] Our team co-built the search strategy in PubMed, and it was adapted to the other bibliographic databases. We did not apply language restrictions.

### 2.2 | Study selection and data extraction

We included studies that complied the following criteria: (1) prospective or retrospective observational studies (cross-sectional, case-control and cohort studies), (2) adult patients (aged > 18 years old) who were diagnosed with COVID-19, (3) NLR values reported at hospital admission and (4) the association between NLR values and disease severity or other clinical outcomes in COVID-19 patients was reported. We did not expect to find randomised controlled trials of NLR, as NLR cannot be randomised as interventions. Moreover, we excluded studies that were (1) conducted in animals, (2) duplicated, (3) conference abstracts, (4) case reports, (5) systematic reviews, (6) scoping reviews and (7) editorials or commentaries. Our primary outcome was disease severity, which was defined as meeting at least one of the following criteria: ICU admission, shortness of breath, respiration rate ≥30 times per minute, blood oxygen saturation at rest ≤ 93% and $PaO_2/FiO_2$ ≤ 300 mm Hg (ratio of partial pressure of oxygen to fraction of inspired oxygen). However, definitions of severity vary among studies. Mortality was also considered as a secondary outcome.

Four reviewers (IST, JRU, EAB-B and AAC) independently analysed the titles and abstracts of the selected articles to choose

potentially relevant articles. Once the potential literature to be included in our study was found, four authors (IST, JRU, EAB-B and AAC) independently read the full text of each article selected. If an article did not meet with one or more selection criteria, it was excluded from our study. Discrepancies were resolved by consensus among the team of researchers in each stage. We used Rayyan QCRI software (Qatar Computing Research Institute, Doha, Qatar) to conduct the process of screening and selection of studies.[28] Finally, two authors (IS and JRU) extracted the data from studies through a standardised data extraction sheet made in Microsoft Excel. We extracted the following information: title of the study, first author, year of publication, study design, country and name of the hospital where the study was performed, number of participants, sex, age, comorbidities, stratified sample data, mean or median NLR of the whole sample and according to sample stratification, crude and adjusted association measures, type of outcome and its definition.

## 2.3 | Evaluation of study quality and publication bias

The quality of the studies was assessed with the NOS[29] by two authors. This tool evaluates the quality of published nonrandomised studies and is based on three items: selection, comparability and outcome/exposure. Each item has subitems, on which a star-based score was assigned. Studies with scores ≥ 6 were considered as having a low risk of bias (high quality), scores of 4-5 as having a moderate risk of bias, and scores < 4 as having a high risk of bias. Furthermore, funnel plots and Egger's test were carried out to assess publication bias; *P* values >.1 were considered as indicative of no publication bias.

## 2.4 | Data synthesis and analysis

Statistical analyses were performed using Review Manager 5.3 (RevMan 5.3) (The Cochrane Collaboration, Copenhagen, Denmark). Measures of association such as hazard ratio (HR) and relative risk (RR) were converted into odds ratio (OR), which was the only association measure used.[30,31] OR, HR and RR adjusted were included in the analysis as they were reported. In order to analyze continuous NLR values, we used the Chinn's method.[32] This method allowed us to transform standardised mean differences to their equivalent OR per study. Then we calculated the natural logarithm of the OR (*logOR*) and its standard error (*SE[logOR]*) for each one of the studies. The variables reported as medians and interquartile ranges (IQRs) were converted into means and standard deviations (SD), respectively. The mean was estimated by the formula $x = (a + 2m + b)/4$ using the values of the median (m), P25 and P75 (a and b, respectively). Likewise, the SD was estimated using the following formula: SD = IQR/1.35.[33,34]

The heterogeneity of the studies in the measure of the effects was evaluated using the $I^2$ statistics. Values greater than 60% were

**FIGURE 1** PRISMA 2009 flow diagram

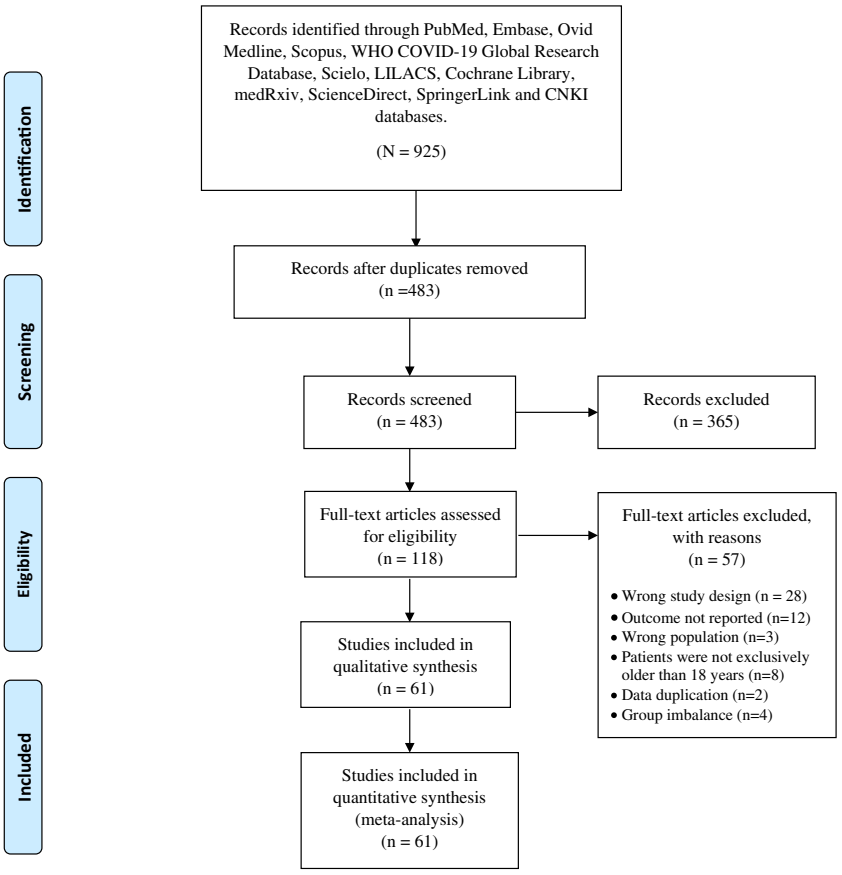

**TABLE 1** Characteristics of studies evaluating the association of NLR and severity

| Author | Year | Participants (male) | Median/mean age (IQR/SD) | NLR description | Type of outcome | NLR mean (SD) in severe patients | NLR mean (SD) in nonsevere patients | SD mean difference between severe and nonsevere patients | OR (adjusted) | HR (adjusted) |
|---|---|---|---|---|---|---|---|---|---|---|
| Chuan Qin et al | 2020 | 452 (235) | 57.5 (14.81) | Quantitative | Severity | 6.1 (4.96) | 3.27 (2.3) | 0.67 [0.48, 0.87] | NR | NR |
| Xiurong Ding et al | 2020 | 72 (33) | 49 0.75 (20) | Quantitative | Severity | 4.8 (5.33) | 2 (1.18) | 1.06 [0.47, 1.66] | NR | NR |
| Yafei Zhang e al. | 2020 | 115 (49) | 49.52 (17.06) | Quantitative | Severity | 758 (7.04) | 2.28 (1.29) | 1.39 [0.94, 1.74] | NR | NR |
| Fengjun Liu et al | 2020 | 134 (63) | 51.25 (20.74) | Quantitative | Severity | 3.85 (2.22) | 2.72 (1.41) | 0.73 [0.23, 1.22] | NR | NR |
| Xiaomin Luo et al | 2020 | 298 (150) | 55.75 (21.48) | Quantitative | Severity<br>Mortality | 6.28 (4.17) | 2.68 (1.32) | 1.47 [1.02, 1.93] | NR | NR |
| Ruchong Chen et al | 2020 | 548 (313) | 56 (14.5) | Quantitative | Severity<br>Mortality | 9.89 (9.2) | 3.86 (3.4) | 1.03 [0.83, 1.23] | NR | NR |
| Hou Keke et al | 2020 | 56 (29) | 48 (13.5) | Quantitative | Severity | 6.13 (6.08) | 4.01 (5.62) | 0.36 [−0.31, 1.04] | NR | NR |
| Changzheng Wang et al | 2020 | 45 (23) | 39 (34.07) | Quantitative | Severity | 29.9 (18.7) | 7.93 (8.36) | 1.90 [1.09, 2.72] | NR | NR |
| Jianhong Fu et al | 2020 | 75 (45) | 46.6 (14) | Quantitative | Severity | 6.29 (3.72) | 2.3 (1.22) | 1.97 [1.33, 2.61] | NR | NR |
| Song CY et al | 2020 | 79 (49) | 54 (45-63) | Quantitative | Severity | 9.87 (11.3) | 3.35 (2.6) | 0.72 [0.25, 1.19] | NR | NR |
| Lian J. et al | 2020 | 203 (90) | 66 (62-71) | Quantitative | Severity | 4.18 (2.82) | 2.59 (1.35) | 0.82 [0.51, 1.13] | NR | NR |
| Gormez S et al | 2020 | 247 (154) | 51.3 (14.2) | Quantitative | Severity | 8.13 (5.82) | 3.18 (2.33) | 1.50 [1.15, 1.84] | NR | NR |
| Feng Z et al | 2020 | 141 (72) | 44 (34-55) | Quantitative | Severity | 4.45 (1.48) | 2.55 (1.18) | 1.56 [0.99, 2.12] | NR | NR |
| Bennouar S et al | 2020 | 330 (206) | 66.6 (8.9) | Quantitative | Severity | 12.7 (10.9) | 5.1 (4.4) | 0.96 [0.73, 1.19] | NR | NR |
| Qun S et al | 2020 | 225 (96) | 59.8 (14) | Quantitative | Severity | 2.96 (2.47) | 2.41 (1.39) | 0.34 [−0.02, 0.70] | NR | NR |
| Xue G et al | 2020 | 114 (64) | 62 (51-70) | Quantitative | Severity | 6.58 (4.91) | 3.075 (1.86) | 0.93 [0.54, 1.32] | NR | NR |
| Zhichao F et al | 2020 | 141 (72) | 44 (34-45) | Quantitative | Severity | 5.1 (2.81) | 3.15 (1.48) | 1.17 [0.61, 1.72] | NR | NR |
| Chen et al | 2020 | 132 (76) | 63.4 (56-71) | Quantitative | Severity<br>Mortality | 7.63 (6.97) | 4.475 (3.9) | 0.69 [0.23, 1.14] | NR | NR |
| Ok F et al | 2020 | 139 (62) | 55.5 (18.5) | Quantitative | Severity | 6.1 (5.1) | 2.46 (2.3) | 0.99 [0.63, 1.35] | NR | NR |
| Basbus L et al | 2020 | 131 (71) | 52 (36-77) | Qualitative | Severity | NR | NR | NR | 8.73 (2.73-27.85)[a] | NR |
| Cheng B et al | 2020 | 456 (211) | 54.97 (18.59) | Quantitative | Severity | 3.615 (2.6) | 2.16 (1.35) | 0.68 [0.49, 0.87] | NR | NR |
| Shi S et al | 2020 | 87 (49) | 60 (22-88) | Quantitative | Severity | 7.3 (5.97) | 2.2 (0.97) | 1.30 [0.83, 1.77] | NR | NR |
| Asan A et al | 2020 | 695 (331) | NR | Quantitative | Severity | 6.6 (7.8) | 2.4 (2) | 1.69 [1.30, 2.09] | NR | NR |
| Lei Liu et al | 2020 | 294 (162) | 56.0 (39-67) | Quantitative | Severity | 12.33 (10.45) | 2.85 (2.07) | 1.55 [1.28, 1.83] | NR | NR |
| Hu Haifeng et al | 2020 | 40 (24) | 51.0 (42.0-66.8) | Quatitative | Severity | 10.59 (12.33) | 3.13 (2.4) | 0.80 [0.16, 1.45] | NR | NR |

(Continues)

**TABLE 1** (Continued)

| Author | Year | Participants (male) | Median/mean age (IQR/SD) | NLR description | Type of outcome | NLR mean (SD) in severe patients | NLR mean (SD) in nonsevere patients | SD mean difference between severe and nonsevere patients | OR (adjusted) | HR (adjusted) |
|---|---|---|---|---|---|---|---|---|---|---|
| Güner R et al | 2020 | 222 (132) | 50.6 (16.5) | Quantitative | Severity | 12.7 (27) | 8.35 (20.4) | 0.20 [−0.12, 0.51] | NR | NR |
| Gong J et al | 2020 | 189 (88) | 49 (35-63) | Quantitative | Severity | 4.03 (3.48) | 2.03 (1.11) | 1.19 [0.77, 1.61] | NR | NR |
| Liao D et al | 2020 | 294 (145) | NR | Quantitative | Severity | 4.96 (3.82) | 2.78 (1.78) | 0.73 [0.50, 0.97] | NR | NR |
| Ai-ping Yang et al | 2020 | 93 (56) | 46.4 (17.6) | NLR < 3<br>NLR ≥ 3 | Severity | 20.7 (24.1) | 4.8 (3.5) | 1.26 [0.76, 1.76] | NR | NR |
| Weifeng Shang et al | 2020 | 443 (220) | 55.475 (17.4) | NLR ≥ 4.283<br>NLR < 4.283 | Severity | 5.36 (5.11) | 2.51 (1.59) | 0.9 [0.69, 1.11] | NR | NR |
| Chen Xi et al | 2020 | 139 (76) | 45.5 (13.3) | NLR < 4.5<br>NLR ≥ 4.5 | Severity | 4.47 (2.99) | 3.31 (1.92) | 0.52 [0.12, 0.93] | NR | NR |
| Xintian Xia et al | 2020 | 63 (33) | NR | NLR < 4.795<br>NLR > 4.795 | Severity | 12.1 (14.32) | 5.77 (10.2) | 0.50 [0.00, 1.01] | NR | NR |
| Li Long et al | 2020 | 301 (150) | 50.25 (20) | NLR < 2.973<br>NLR ≥ 2.973 | Severity | NR | NR | NR | NR | 2.641 (1.421-4.908) $P = 0.002$* |
| Yue-Ping Liu et al | 2020 | 84 (47) | 54.25 (52.59) | NLR < 4.87<br>NLR ≥ 4.87 | Severity | 19.75 (48.96) | 4.3 (7.88) | 0.58 [0.10, 1.07] | NR | NR |
| Suyu Sun et al | 2020 | 116 (60) | 49.5 (11.85) | NLR < 4.5<br>NLR ≥ 4.5 | Severity | 8.9 (7.9) | 2.5 (1.28) | 1.61 [1.14, 2.09] | NR | NR |
| Chen Xing et al | 2020 | 296 (137) | NR | NR | Severity | 3.86 (3.28) | 1.88 (1.03) | 1.39 [1.00, 1.78] | NR | NR |

Abbreviations: HR, hazard ratio; IQR, interquartile range; NR, not reported NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio; SD, standard deviation.

[a]Adjusted to age and hypertension.

*Adjusted to sex, age, comorbidities, eosinophil count and C-reactive protein level.

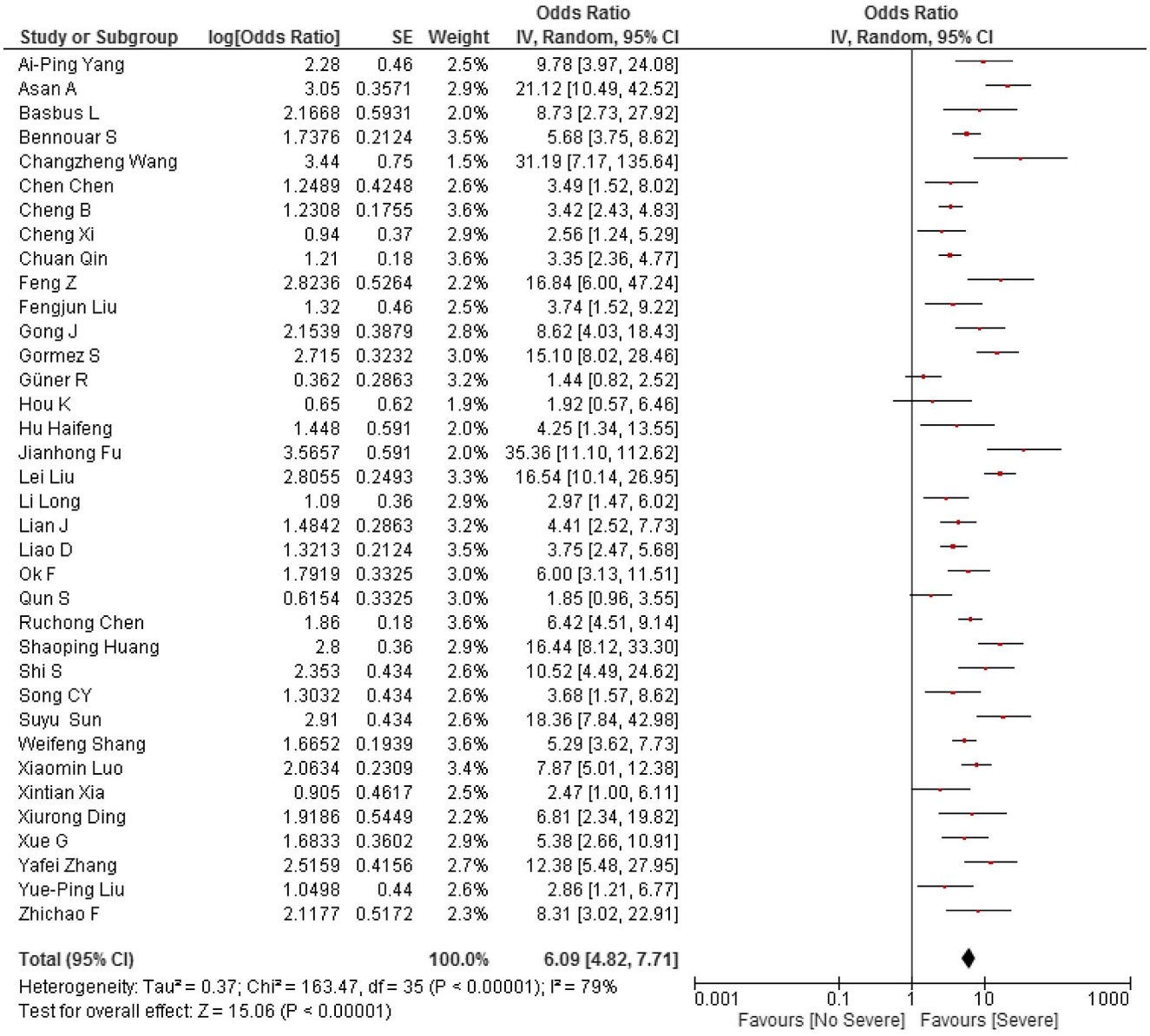


**FIGURE 2** (A) Association of NLR and COVID-19 severity. (B) Subgroup analysis according to study design of the association between NLR and severity in COVID-19 patients. (C) Subgroup analysis according to the origin country of the association between NLR and severity in COVID-19 patients. (D) Sensitivity analysis according to risk of bias of the association between NLR and severity in COVID-19 patients

considered as severe heterogeneity, 40%-60% as moderate heterogeneity and less than 40% as mild heterogeneity. The Cochran Q test was also reported. A *P* value of <.05 was considered statistically significant. We conducted a random effects meta-analyses as we anticipated that there was heterogeneity among studies. We performed subgroup analyses by location of the study (Chinese vs non-Chinese studies) and study design (cohorts, case-control studies) and reported the interaction test *P* value per subgroup analysis. Finally, sensitivity analyses were performed only using the low risk of bias studies.

## 3 | RESULTS

### 3.1 | Study selection

The flow diagram summarising the process of study retrieval is shown in Figure 1. In the initial electronic search, a total of 925 records were found. After excluding duplicate studies, 483 studies were preserved. Subsequently, during the evaluation of titles and abstracts, 365 more records were excluded. Finally, during the full-text assessment, 57 articles were excluded as a result of group

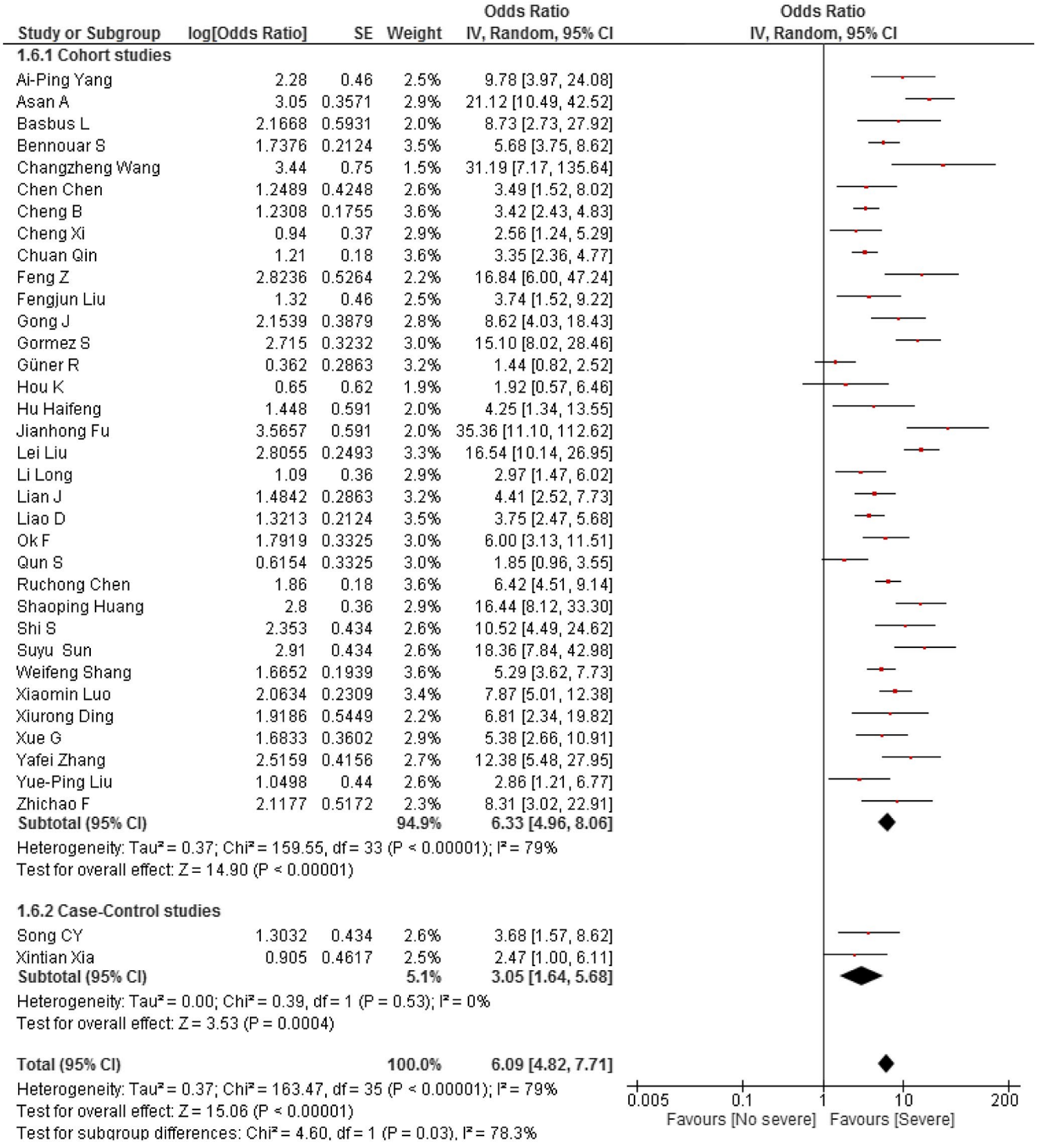


**FIGURE 2**

imbalance, outcome not reported, wrong population, or the patients were not older than 18 years. Finally, 61 studies were selected for the qualitative and quantitative syntheses.

## 3.2 | Study characteristics

The characteristics of the studies are presented in Table 1[35-68] and in Supporting InformationTable S1.[69-95] For this systematic review, 58 cohort studies and three case-control studies were included, most of them conducted in China and 20 studies in other countries. On the other hand, our primary outcome (severity) was present in 36 studies,[35-50] the secondary outcome (mortality) was present in 28 studies,[69-95] and three studies analysed both outcomes.[62,71,72]

There was a total of 15 522 patients within the studies, 53.74% were men and age ranged from 22 to 81 years. Seven studies did not present information about age. In 11 studies, the days elapsed

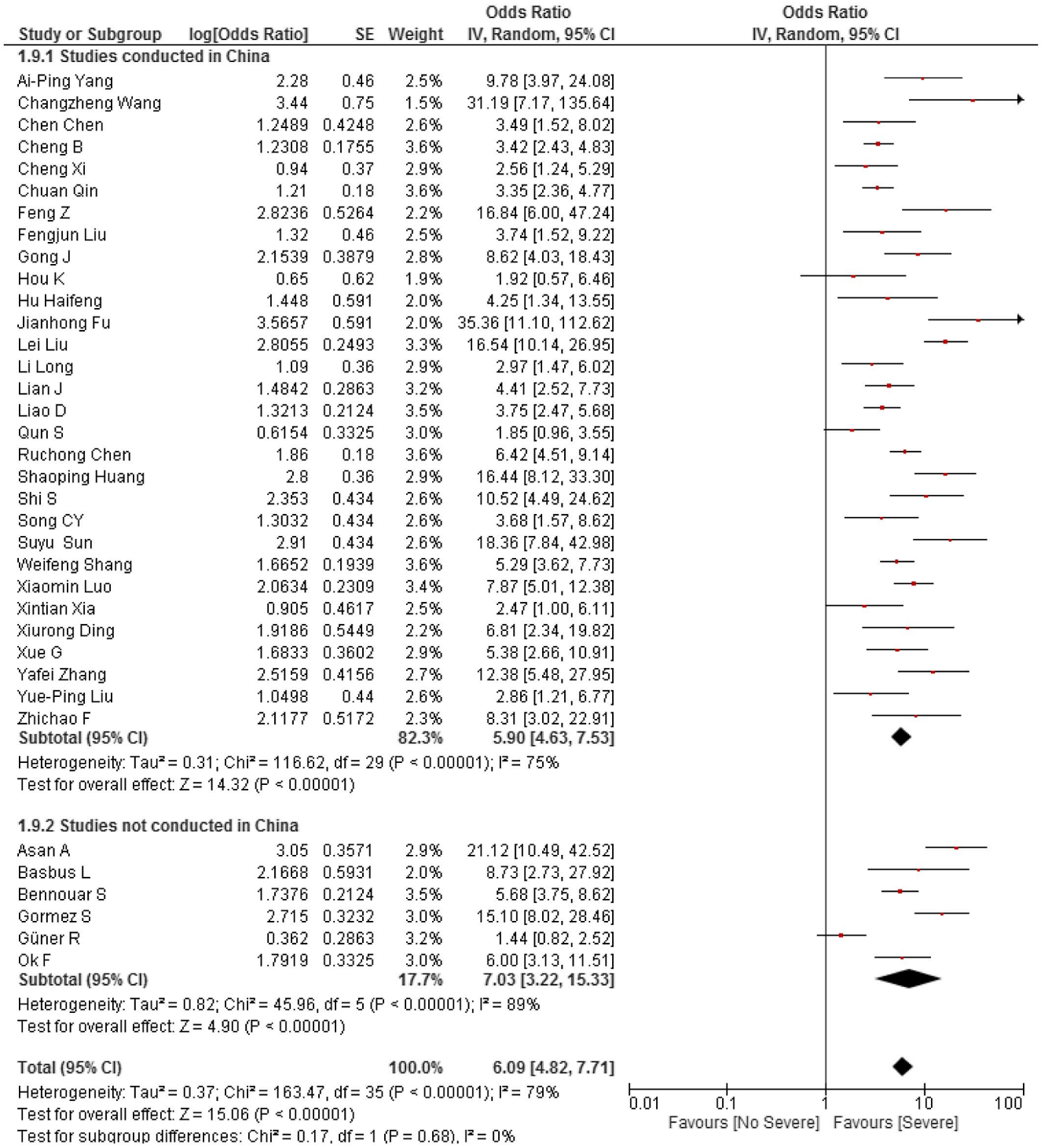
Study or Subgroup
log[Odds Ratio]
SE
Weight
Odds Ratio IV, Random, 95% CI
Odds Ratio IV, Random, 95% CI
1.9.1 Studies conducted in China
Ai-Ping Yang 2.28 0.46 2.5% 9.78 [3.97, 24.08]
Changzheng Wang 3.44 0.75 1.5% 31.19 [7.17, 135.64]
Chen Chen 1.2489 0.4248 2.6% 3.49 [1.52, 8.02]
Cheng B 1.2308 0.1755 3.6% 3.42 [2.43, 4.83]
Cheng Xi 0.94 0.37 2.9% 2.56 [1.24, 5.29]
Chuan Qin 1.21 0.18 3.6% 3.35 [2.36, 4.77]
Feng Z 2.8236 0.5264 2.2% 16.84 [6.00, 47.24]
Fengjun Liu 1.32 0.46 2.5% 3.74 [1.52, 9.22]
Gong J 2.1539 0.3879 2.8% 8.62 [4.03, 18.43]
Hou K 0.65 0.62 1.9% 1.92 [0.57, 6.46]
Hu Haifeng 1.448 0.591 2.0% 4.25 [1.34, 13.55]
Jianhong Fu 3.5657 0.591 2.0% 35.36 [11.10, 112.62]
Lei Liu 2.8055 0.2493 3.3% 16.54 [10.14, 26.95]
Li Long 1.09 0.36 2.9% 2.97 [1.47, 6.02]
Lian J 1.4842 0.2863 3.2% 4.41 [2.52, 7.73]
Liao D 1.3213 0.2124 3.5% 3.75 [2.47, 5.68]
Qun S 0.6154 0.3325 3.0% 1.85 [0.96, 3.55]
Ruchong Chen 1.86 0.18 3.6% 6.42 [4.51, 9.14]
Shaoping Huang 2.8 0.36 2.9% 16.44 [8.12, 33.30]
Shi S 2.353 0.434 2.6% 10.52 [4.49, 24.62]
Song CY 1.3032 0.434 2.6% 3.68 [1.57, 8.62]
Suyu Sun 2.91 0.434 2.6% 18.36 [7.84, 42.98]
Weifeng Shang 1.6652 0.1939 3.6% 5.29 [3.62, 7.73]
Xiaomin Luo 2.0634 0.2309 3.4% 7.87 [5.01, 12.38]
Xintian Xia 0.905 0.4617 2.5% 2.47 [1.00, 6.11]
Xiurong Ding 1.9186 0.5449 2.2% 6.81 [2.34, 19.82]
Xue G 1.6833 0.3602 2.9% 5.38 [2.66, 10.91]
Yafei Zhang 2.5159 0.4156 2.7% 12.38 [5.48, 27.95]
Yue-Ping Liu 1.0498 0.44 2.6% 2.86 [1.21, 6.77]
Zhichao F 2.1177 0.5172 2.3% 8.31 [3.02, 22.91]
Subtotal (95% CI) 82.3% 5.90 [4.63, 7.53]
Heterogeneity: Tau² = 0.31; Chi² = 116.62, df = 29 (P < 0.00001); I² = 75%
Test for overall effect: Z = 14.32 (P < 0.00001)
1.9.2 Studies not conducted in China
Asan A 3.05 0.3571 2.9% 21.12 [10.49, 42.52]
Basbus L 2.1668 0.5931 2.0% 8.73 [2.73, 27.92]
Bennouar S 1.7376 0.2124 3.5% 5.68 [3.75, 8.62]
Gormez S 2.715 0.3232 3.0% 15.10 [8.02, 28.46]
Güner R 0.362 0.2863 3.2% 1.44 [0.82, 2.52]
Ok F 1.7919 0.3325 3.0% 6.00 [3.13, 11.51]
Subtotal (95% CI) 17.7% 7.03 [3.22, 15.33]
Heterogeneity: Tau² = 0.82; Chi² = 45.96, df = 5 (P < 0.00001); I² = 89%
Test for overall effect: Z = 4.90 (P < 0.00001)
Total (95% CI) 100.0% 6.09 [4.82, 7.71]
Heterogeneity: Tau² = 0.37; Chi² = 163.47, df = 35 (P < 0.00001); I² = 79%
Test for overall effect: Z = 15.06 (P < 0.00001)
Test for subgroup differences: Chi² = 0.17, df = 1 (P = 0.68), I² = 0%
0.01
0.1
1
10
100
Favours [No Severe]
Favours [Severe]

FIGURE 2

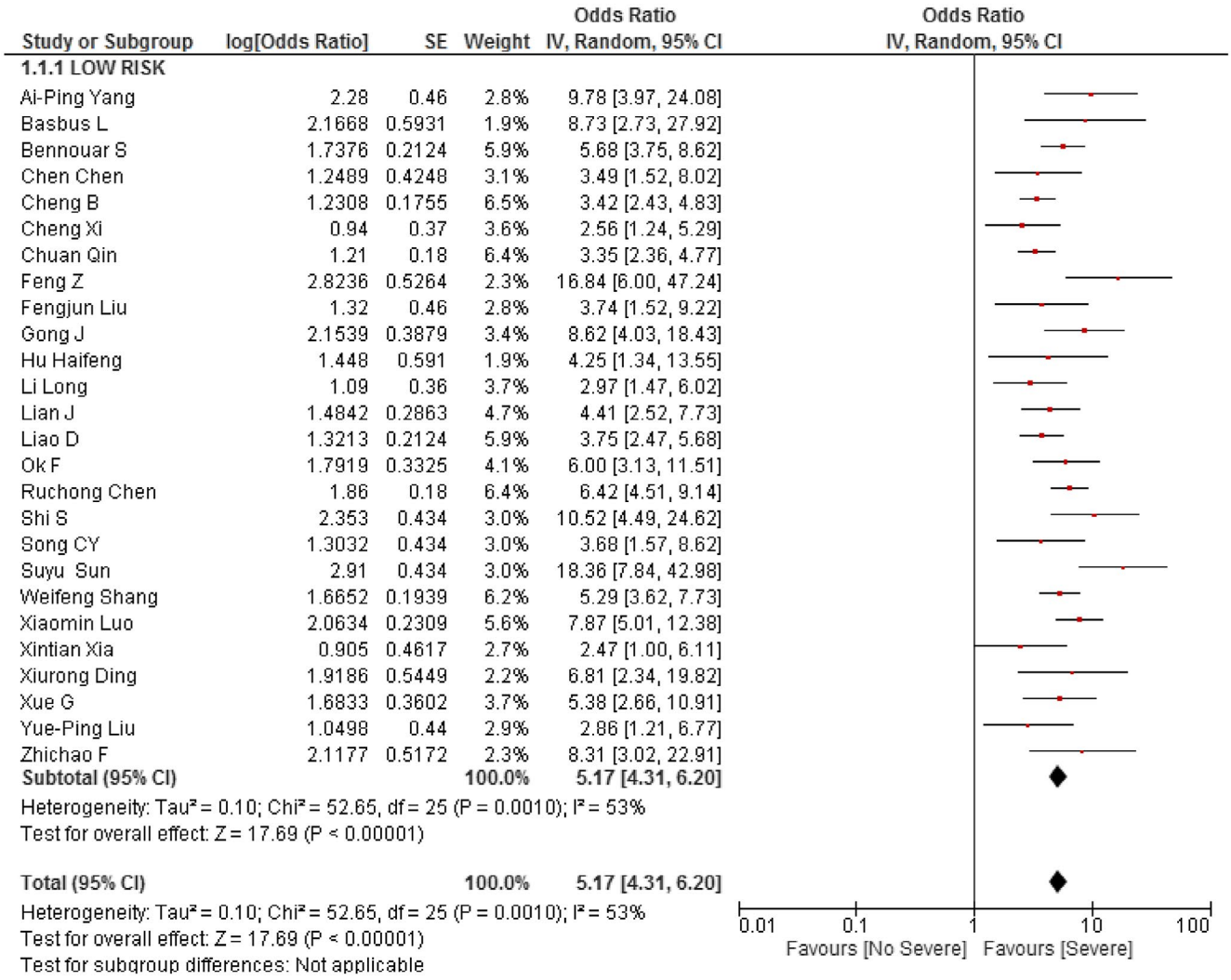


**FIGURE 2**

for the development of severity, from the day of admission, were reported, whose average was 5.64 days and ranged from 4 to 14 days.

The NOS was used for the quality assessment of the studies (see Supporting Information Table S2). It was identified that 2 studies had a high risk of bias, 21 studies had a moderate risk of bias and only 38 had a low risk of bias.

### 3.3 | Association of NLR with disease severity in hospitalised COVID-19 patients

This association was evaluated in 36 studies (n = 7489). As shown in Figure 2A, we found that higher NLR levels were associated with higher odds of severity in patients with hospitalised COVID-19 diagnosis (OR 6.09; 95% CI 4.82 to 7.71; $P < .001$). Because of severe heterogeneity ($I^2 = 79\%$, $P < .001$), subgroup analysis by study design (Figure 2B) did not change the main effects (cohorts: OR 6.33; 95% CI 4.96 to 8.06; $P < .001$ vs case-control studies: OR 3.05; 95% CI 1.64 to 5.68; $P = .53$; interaction test $P = .03$). Likewise, the subgroup analysis by country of origin (Figure 2C) showed differences between Chinese (OR 5.9; 95% CI 4.63 to 7.53; $P < .001$) and non-Chinese studies (OR 7.03; 95% CI 3.22 to 15.33; $P < .001$, interaction test $P < .68$). In sensitivity analysis, which included only studies at low risk of bias, the association between NLR values and severity was still present (OR 5.17; 95% CI 4.31 to 6.2; $P < .001$) with moderate heterogeneity ($I^2 = 53\%$, $P < .001$) (Figure 2D).

### 3.4 | Association of NLR with all-cause mortality in hospitalised COVID-19 patients

This association was evaluated in 28 studies (n = 8033). As presented in Figure 3A, we found that higher values of NLR were associated with higher odds of all-cause mortality in hospitalised COVID-19 patients (OR 12.6; 95% CI 6.88 to 23.06; $P < .001$) with high heterogeneity of effects ($I^2 = 98\%$). The subgroup analysis by country of origin (Figure 3B) showed that the strength of the association between NLR and mortality was even higher in Chinese studies (OR 26.94; 95% CI 14.57 to 49.81; $P < .001$) with high heterogeneity ($I^2 = 92\%$); whereas the association in the non-Chinese

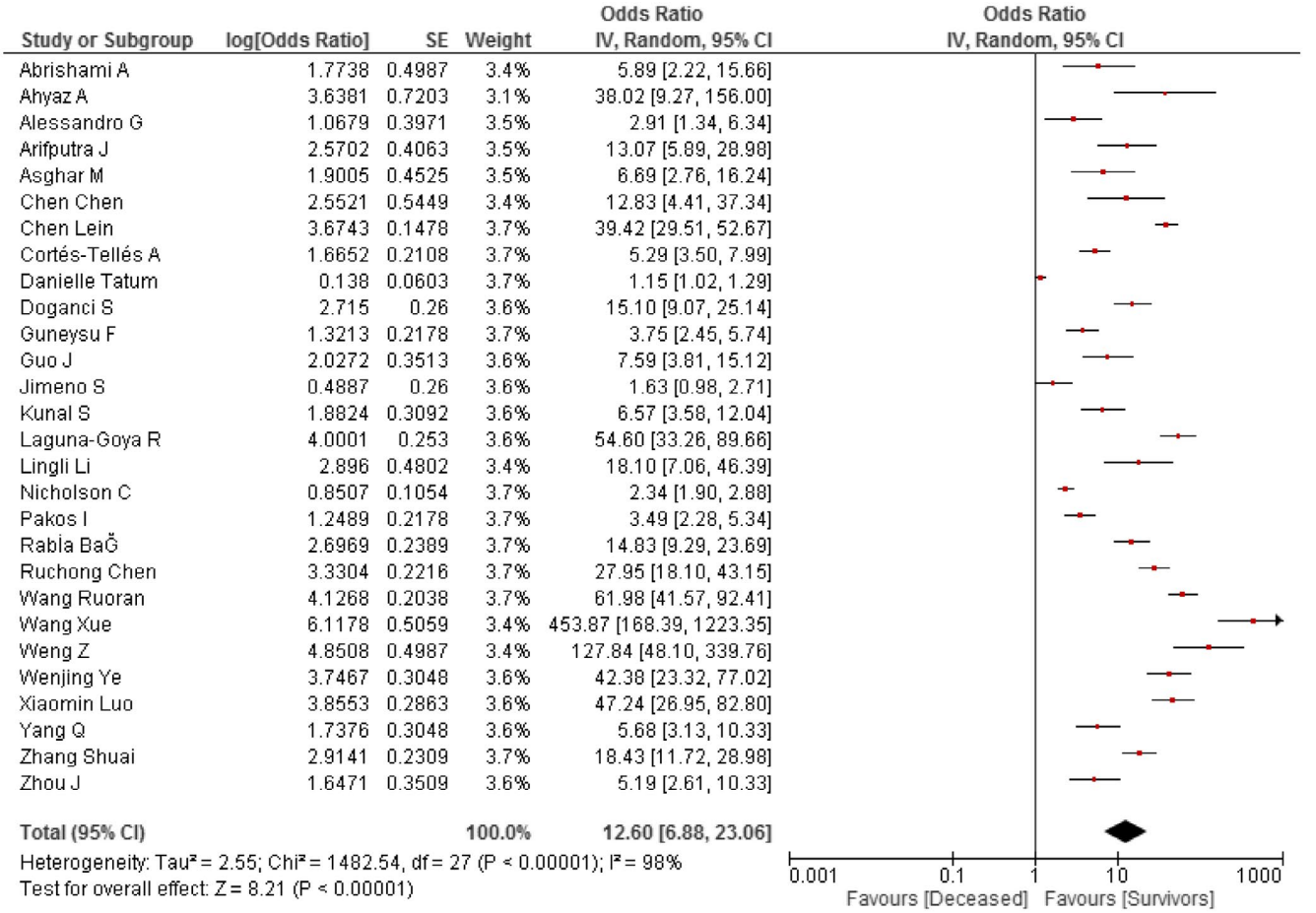


**FIGURE 3** (A) Association between NLR and mortality in COVID-19 patients. (B) Subgroup analysis according to the origin country of the association between NLR and mortality in COVID-19 patients. (C) Subgroup analysis according to study design of the association between NLR and mortality in COVID-19 patients. (D) Sensitivity analysis according to risk of bias of the association between NLR and mortality in COVID-19 patients

studies was very different compared with the main mortality analysis (OR 5.89 95% CI 3.18 to 10.9; $P < .001$). There were differences between effects according to country of origin (interaction test $P < .001$). Regarding the subgroup analysis by study design (Figure 3C), both cohort (OR 12.51 95% CI 6.73 to 23.27; $P < .001$) and case-control (OR 15.1 95% CI 9.07 to 25.14; $P < .001$) studies revealed higher odds of mortality (interaction test $P = .65$). In the sensitivity analysis of low risk of bias studies, there was moderate heterogeneity (OR 10.42 95% CI 7.73 to 14.06; $P = .005$; $I^2 = 58\%$, $\chi^2$ $P = .005$) (Figure 3D).

### 3.5 | Publication bias

There was no indication that there were small study effects for the severity of disease (Egger's test $P = .112$) (see Supporting Information Figures S4.A and S4.B).

## 4 | DISCUSSION

In the current context of the COVID-19 pandemic, an efficient, fast and cheap method is required to determine the prognosis of patients with COVID-19. Given the growing number of studies that established NLR as a possible prognostic biomarker of severity and mortality in patients diagnosed with COVID-19, we decided to carry out a systematic review and a meta-analysis to consolidate the information regarding this topic. The present meta-analysis incorporated a total of 61 studies and found that high NLR values on admission day were associated with progression towards severity and mortality.

The prognostic value of NLR has been studied and correlated to multiple chronic, inflammatory and infectious diseases,[14-20] such as community-acquired pneumonia (CAP), where NLR had a more significant prognostic performance towards severity than other markers such as white blood cell count, C-reactive protein, and neutrophil count.[96] Likewise, NLR has also been proven to predict

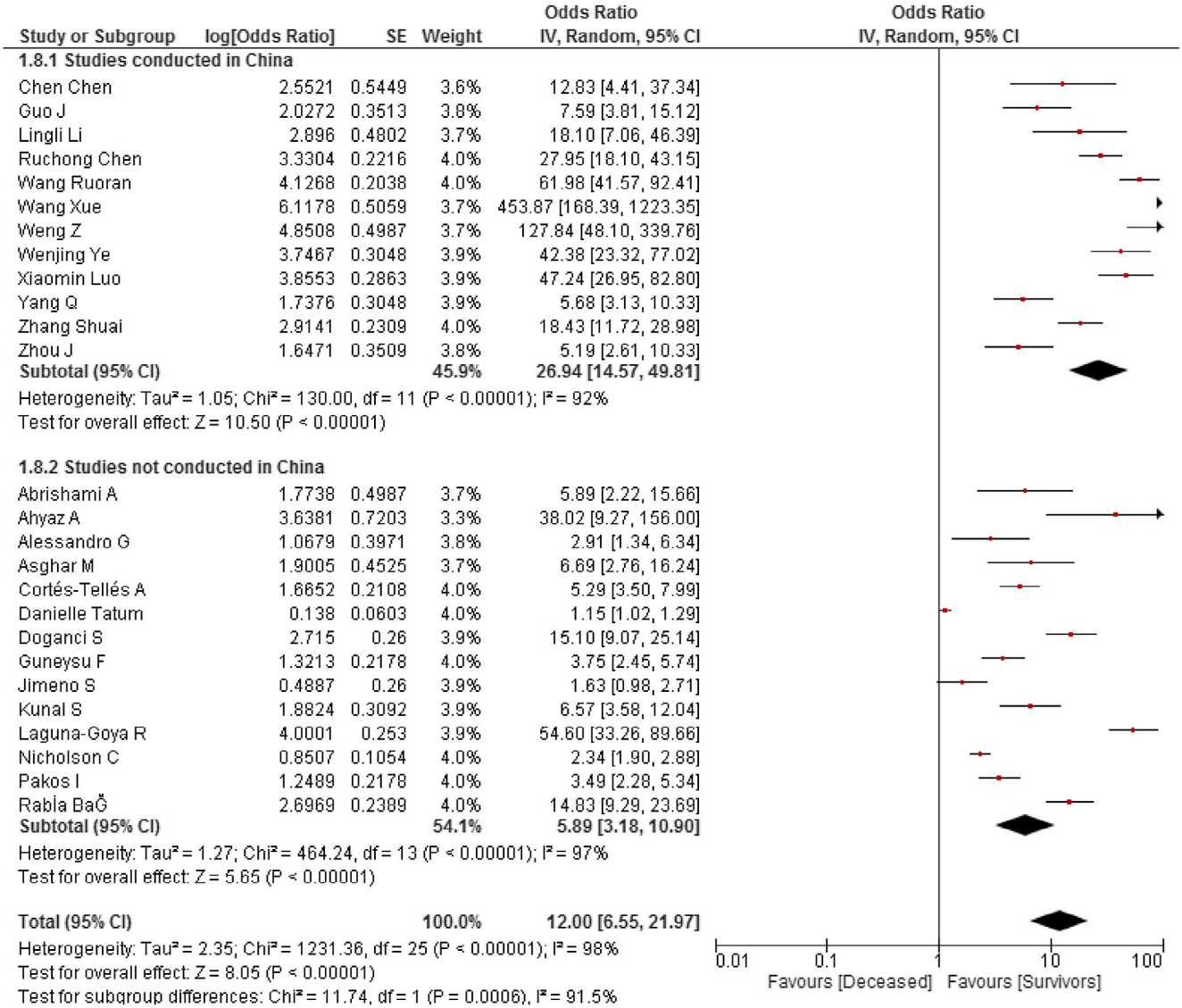


**FIGURE 3**

30-day mortality in CAP with a positive predictive value of 100% and a negative predictive value of 78%.[97]

The hemogram is usually altered in COVID-19 patients, being higher in patients with severe illness compared with mild illness.[98] This could be reflected in the cohort study conducted by Wang S. et al in COVID-19 patients where it was found that an increase on NLR values was associated with severity (OR 8.56, 95% CI, 1.39-52.61, $P$ = .021) as we found in our study.[99] The biological mechanism by which these variations arise in the neutrophil and lymphocyte counts has not been elucidated so far; however, several possible explanations have been proposed. The first one is based on the physiological relationship that exists between systemic inflammation and stress with the appearance of neutrophilia and lymphocytopaenia. The second possible explanation is based on the depletion of the number of lymphocytes, especially CD4 + and CD8 + T cells. These two agents have, as one of their functions, the regulation of the immune system response against viral infections. A low circulating number of these two lymphocytes could cause a generalised dysregulation of the immune system, especially of neutrophils. On the other hand, lymphocytopaenia has been linked to lymphocyte exhaustion and to the ability of SARS-CoV-2 to infect lymphocytes. Lymphocyte exhaustion occurs in chronic inflammatory processes where there is a continuous and excessive stimulation of T lymphocytes that causes their exhaustion and therefore impairing their functions.[100-103] All in all, several of the latest prediction scores include NLR as part of their prognostic variables.[104]

Two meta-analyses have previously been published where the prognostic value of NLR was analysed in patients diagnosed with COVID-19, the first one by Lagunas-Rangel[105] and the second one by Xudong Feng et al.[25] Despite the existence of these studies, it was necessary to carry out a systematic review exclusively about the neutrophil-lymphocyte ratio because the previous studies presented an exceedingly small number of studies incorporated in the meta-analysis (only five and six studies, respectively). Moreover, they used few databases for the literature search, and they did not perform

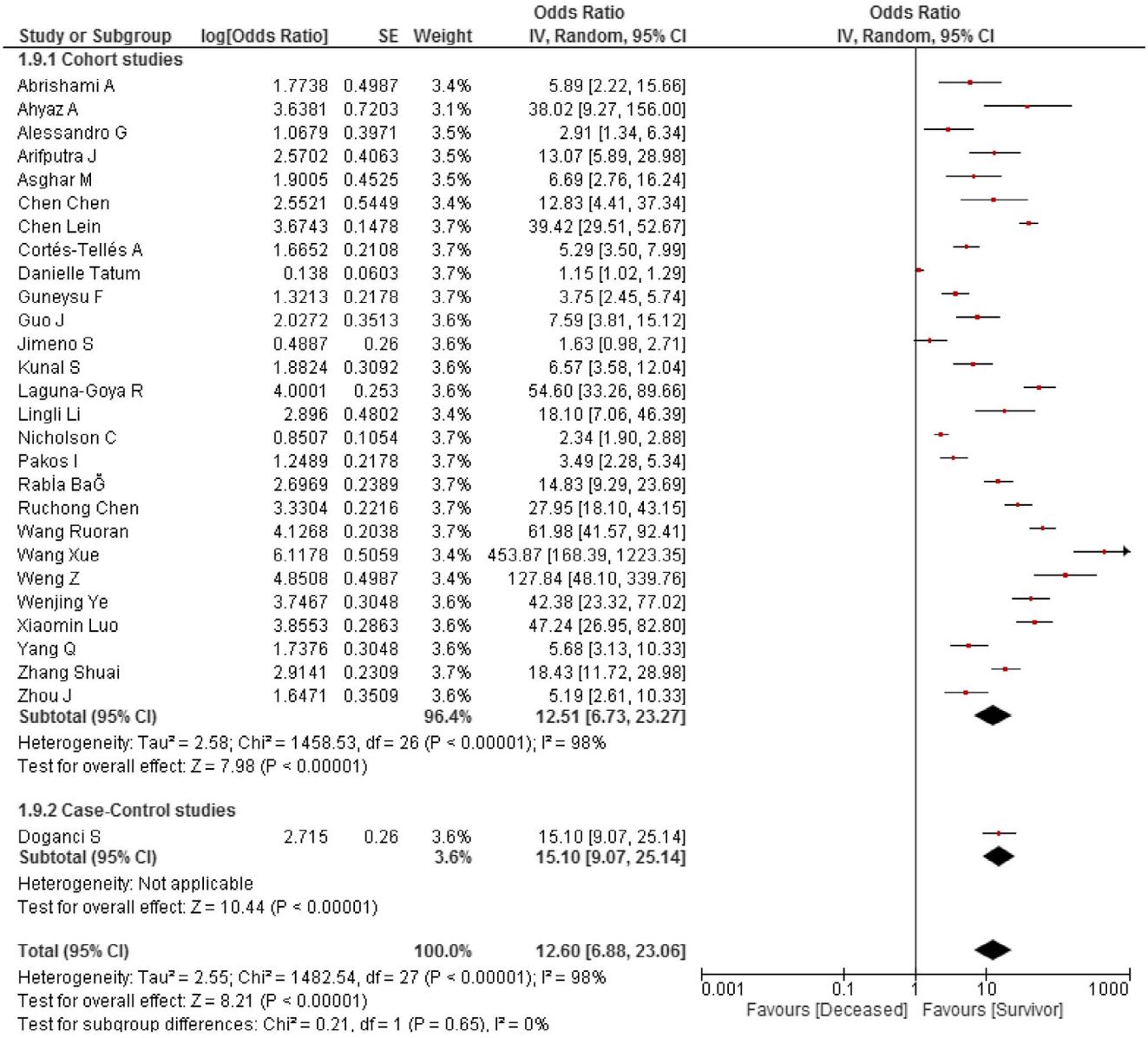


**FIGURE 3**

the sensitivity analysis, which allows identifying possible sources of heterogeneity. Specifically, in the article done by Lagunas-Rangel, a heterogeneity of 96, 45% was reported, and despite this, it was concluded that there was an association between the NLR and the progression to severity. This is an error since high variability suggests that studies should not be combined in a meta-analysis.

Our meta-analysis contribution was to perform a conversion from the mean difference to a more reliable measure of effect, such as OR through Chinn's method.[32] This conversion allowed us to include those studies that have no continuous values for NLR. In our sensibility analysis, the moderate/high risk of bias studies was possibly the primary source of heterogeneity. It is important to emphasise this last point because the desire to produce scientific knowledge that helps guide therapeutic decisions during the pandemic has caused studies to be carried out in an expeditious manner, often by personnel with little methodological knowledge and without adequate advice.[106] This has resulted in a low-quality scientific production that has been reflected in the present study since 23 of the 61 studies analysed have a moderate to high risk of bias.

## 4.1 | Limitations

Our study has several limitations. First, our meta-analysis reported high OR values and broad CI for both outcomes. This could be because of some small sample sizes and clinical diversity. When we did the conversion, the values of the standardised mean differences, which we use for the OR conversion, were very high, so that also influences the high OR values. The broad CI could be explained by some small sample sizes, so the effect is detected but has low precision. Second, all the incorporated studies in this systemic review,

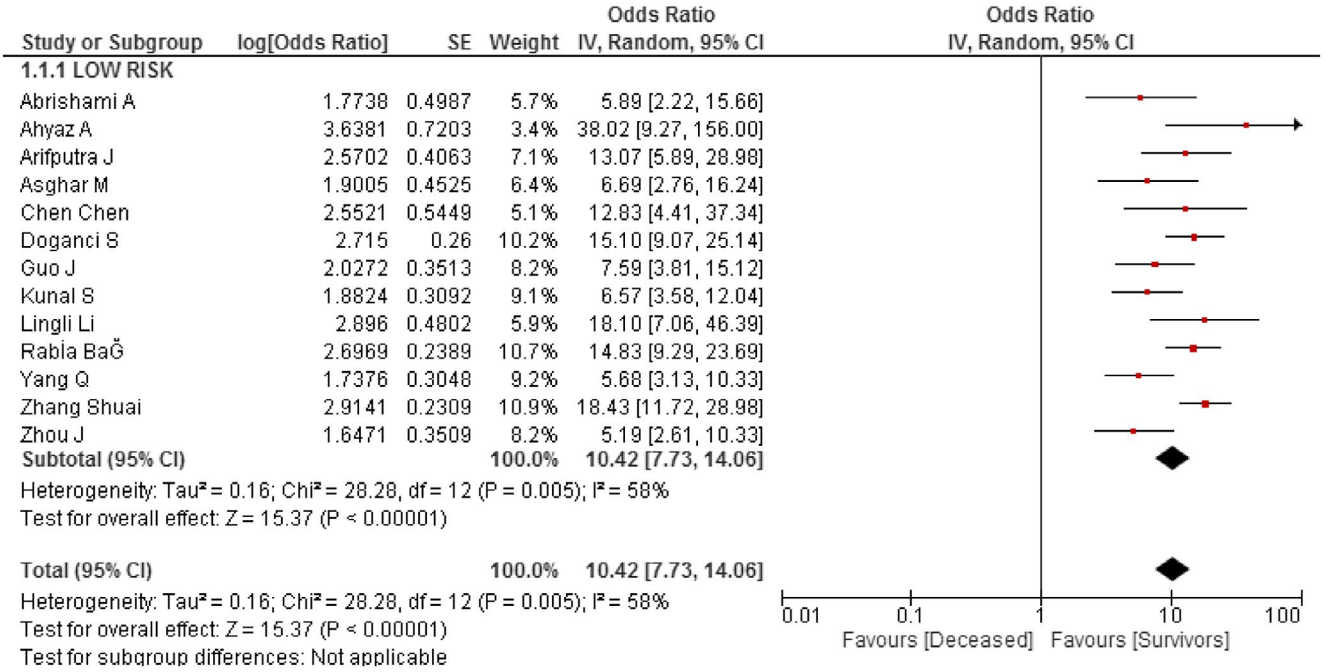


**FIGURE 3**

except for one, were developed in China, which do not allow a fair ethnic comparison in COVID-19 patients. Third, we found high heterogeneity between the included studies, which was traced back to the bad quality found in some publications. Finally, there was no consensus among the articles analysed regarding the cutoff to define elevated NLR and the severity definition differed between some studies that could lead to bias.

## 5 | CONCLUSIONS

In the presented systematic review and meta-analysis, the elevated NLR values were clearly associated with the development of severity and mortality in patients diagnosed with COVID-19. Therefore, an elevated NLR could be used as an early and easy prognostic parameter for severity and mortality in COVID-19 patients.

### DISCLOSURES

Authors declare no conflict of interest.

### AUTHOR CONTRIBUTIONS

Study design and concept: IST, JRUB, JLM, AVH and VB-Z. Acquisition of data: AAC, EA-B, JRUB, IST, AVH, VB-Z and JLM. Drafting of the manuscript: JRUB, IST, AAC and EA-B. Critical revision of the manuscript: AVH, VB-ZM and JLM. Statistical analysis: VB-ZM, JRUB, IST and AVH. Study supervision: AVH, JLM and VB-Z.

### DATA AVAILABILITY STATEMENT

Data available on request from the authors—The data that support the findings of this study are available from the corresponding author upon reasonable request.

### ORCID

*Juan R. Ulloque-Badaracco* https://orcid.org/0000-0002-1093-4937
*W. Ivan Salas-Tello* https://orcid.org/0000-0001-5105-4082
*Ali Al-kassab-Córdova* https://orcid.org/0000-0003-3718-5857
*Esteban A. Alarcón-Braga* https://orcid.org/0000-0003-3125-5949
*Vicente A. Benites-Zapata* https://orcid.org/0000-0002-9158-1108
*Jorge L. Maguiña* https://orcid.org/0000-0002-4136-7795
*Adrian V. Hernandez* https://orcid.org/0000-0002-9999-4003

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## SUPPORTING INFORMATION

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

**How to cite this article:** Ulloque-Badaracco JR, Ivan Salas-Tello W, Al-kassab-Córdova A, et al. Prognostic value of neutrophil-to-lymphocyte ratio in COVID-19 patients: A systematic review and meta-analysis. *Int J Clin Pract*. 2021;00:e14596. https://doi.org/10.1111/ijcp.14596