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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Neutrophil-to-lymphocyte ratio on admission to predict the severity and mortality of COVID-19 patients: A meta-analysis

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ABSTRACT

Background: The neutrophil-to-lymphocyte ratio (NLR), an inflammatory marker, was suggested to be predictive of severity and mortality in COVID-19 patients. Here, we investigated whether NLR levels on admission could predict the severity and mortality of COVID-19 patients.

Methods: A literature search was conducted on 23 July 2020 to retrieve all published articles, including grey literature and preprints, investigating the association between on-admission NLR values and severity or mortality in COVID-19 patients. A meta-analysis was performed to determine the overall standardized mean difference (SMD) in NLR values and the pooled risk ratio (RR) for severity and mortality with the 95% Confidence Interval (95%CI).

Results: A total of 38 articles, including 5699 patients with severity outcomes and 6033 patients with mortality outcomes, were included. The meta-analysis showed that severe and non-survivors of COVID-19 had higher on-admission NLR levels than non-severe and survivors (SMD 0.88; 95%CI 0.72–1.04; $I^2 = 75.52\%$ and 1.87; 95%CI 1.25–2.49; $I^2 = 97.81\%$, respectively). Regardless of the different NLR cut-off values, the pooled mortality RR in patients with elevated vs. normal NLR levels was 2.74 (95%CI 0.98–7.66).

Conclusion: High NLR levels on admission were associated with severe COVID-19 and mortality. Further studies need to focus on determining the optimal cut-off value for NLR before clinical use.

1. Introduction

As of 11 March 2020, over 120,000 Coronavirus disease 2019 (COVID-19) cases were confirmed globally, resulting in its declaration as a pandemic [1]. By the first week of December 2020, there were 65 million COVID-19 confirmed cases with more than 1.5 million deaths worldwide [2]. COVID-19 is caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), a novel virus in the same cluster as the SARS-CoV-1 and MERS-CoV, that previously caused outbreaks in 2003 and 2012 [3,4]. The clinical manifestations of COVID-19 patients range from asymptomatic to severe symptoms. A minority (30%) progresses into severe manifestations such as acute respiratory distress syndrome (ARDS), severe pneumonia, septic shock, coagulopathy, and death [5]. This rapid progression to severe conditions is caused by an overwhelming inflammation, known as the cytokine storm.

Biomarkers allowing prediction of disease severity in COVID-19 are urgently needed to address the problem of resource scarcity in this pandemic [6]. Early risk stratification for COVID-19 patients upon hospital admission is the key to providing optimal interventions and to carefully allocate the ongoing scarce human and technical resources [7]. This would ensure that the limited available resources are given to the right patients. The neutrophil-to-lymphocyte ratio (NLR) is an inflammatory marker derived from combining the absolute blood neutrophil and lymphocyte counts, two routinely performed parameters in clinical settings. Recently, studies have reported that NLR levels were higher in more severe patients and were suggested to confer a prognostic value in COVID-19 patients [8,9]. The underlying pathophysiology that justifies for the clinical use of this biomarker is that severe COVID-19 patients were more likely to present with higher levels of inflammation upon hospital admission. Therefore, obtaining NLR levels on hospital admission could allow early risk stratification, identifying patients who should be prioritized for scarce resources.

We performed a systematic review and meta-analysis to investigate whether clinical outcomes of severity and mortality in COVID-19 patients can be predicted with on-admission NLR values.

2. Methods

This systematic review and meta-analysis is reported according to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) Checklist (Table S1). Before writing this review, a detailed protocol was created and registered on the International

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Prospective Register of Systematic Reviews (PROSPERO) on 1 June 2020 (CRD42020189218).

2.1. Eligibility criteria

We included all research papers investigating adult patients (older than 18 years old) with COVID-19 (diagnosed with RT-PCR) that contain information on the NLR value at the time of hospital admission and clinical grouping of outcomes with a clinically validated definition of COVID-19 severity or death. The following articles were excluded from this review: non-research letters, correspondences, case reports, review articles, and original articles with samples below 20. Due to the limited resources, we only included articles published in English.

2.2. Search strategy

We searched for all published articles, including preprints and grey literature, from electronic databases on 23 July 2020. Peer-reviewed papers were sought from four databases (Ovid MEDLINE, Ovid EMBASE, SCOPUS, and the Cochrane Library); preprints were searched from three databases (MedRxiv, BioRxiv, and SSRN); and grey literature was searched from two databases (WHO COVID-19 Global Research Database, and the Centers for Disease Control and Prevention COVID-19 Research Article Database). The search strategies used were developed from the following key concepts: "COVID-19", "Neutrophil-to-lymphocyte ratio", "Severity", and "Mortality" (Table S2). Manual hand-searching and forward and backward tracing of citations from relevant articles were also done to identify additional studies.

2.3. Study selection

All articles retrieved from the systematic searches of electronic databases were exported to EndNote X9 bibliographic and reference manager. Following deduplication, the titles and abstracts were screened independently by three reviewers (DMS, ADW, NAAI), and the remaining articles were screened for its full text against the eligibility criteria. Any disagreements were resolved through discussion until a common consensus was reached.

2.4. Quality assessment

The studies were critically appraised using the Newcastle Ottawa Scale (NOS) by three independent reviewers (DMS, ADW, NAAI), and when there was a discrepancy in the assessment score, discussions were done to reach an agreement.

2.5. Data extraction and synthesis

Prior to the data extraction, a customized, standardized data extraction form was developed. The data extracted included: first author, year of study, publication type, study location, study design, baseline population characteristics (including age, gender, and underlying diseases such as diabetes mellitus, hypertension, and cardiovascular diseases), exposures, and outcomes. The exposure was defined as the NLR value on admission to the hospital, presented as either continuous or dichotomized NLR values. The outcomes of interest were severe COVID-19 and mortality. Severe COVID-19 was defined as patients who met any of the following features: (1) respiratory rate > 30 breaths per minute; (2) oxygen saturation < 93% (ambient air); (3) ratio of the

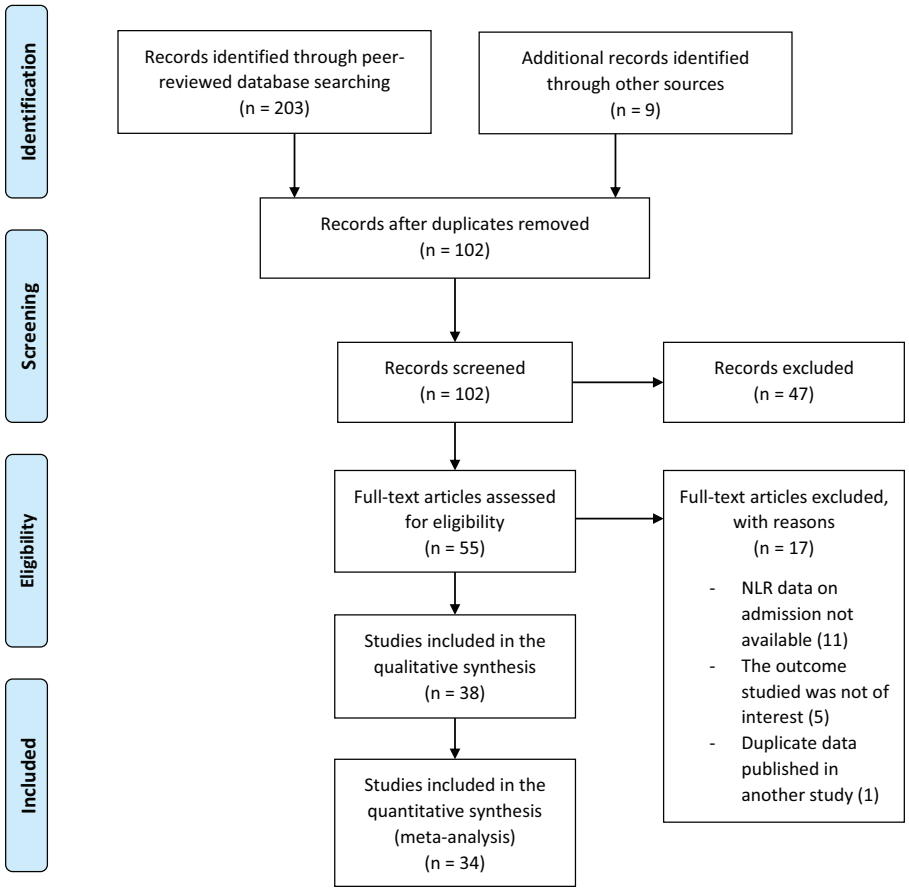


Fig. 1. Prisma diagram for study selection. A systematic literature search was done on 23 July 2020 to identify peer-reviewed papers, preprints, and grey literature.

partial pressure of arterial blood oxygen (PaO_2)/oxygen concentration (FiO_2) ≤300 mmHg [10]. Due to different severity grouping criteria among studies, non-severe COVID-19 included patients with either mild, moderate, common, ordinary, or any combination. Meanwhile, severe COVID-19 included patients in severe, critical, or a combination of the two. Additionally, for studies that performed and reported receiver operating characteristic (ROC) analysis on either severity or mortality, we extracted the optimal NLR cut-off values, the area under the curve (AUC), sensitivity, and specificity.

2.6. Statistical analysis

The quantitative data were exported to Stata version 16, and a meta-analysis of studies was performed. For non-normal data, we extrapolated the mean and standard deviation from the available median and interquartile range (IQR) using the method by Hozo et al. [11]. For studies that reported the means of NLR among groups, pooled standardized mean difference (SMD) and the 95% Confidence Interval (95%CI) were obtained using the inverse variance method. For NLR values reported as

Table 1
Baseline characteristics of included studies comparing severe and non-severe COVID-19 patients

First Author	Study Location	Groups	Sample (N)	Male %	Age (years) Mean ± SD / Median (IQR)	DM N (%)	HT N (%)	CVD N (%)	NLR Value Mean ± SD / Median (IQR)	NOS Score
Qin C et al	China	Severe	286	54	61 (51–69)	53 (19)	105 (37)	24 (8)	5.5 (3.3–10.0)	5
		Non-severe	166	48	53 (41–62)	22 (13)	30 (18)	3 (2)	3.2 (1.8–4.9)	
Zhang Y et al	China	Severe	31	65	65 ± 13	NR	NR	NR	7.58 ± 7.04	7
		Mild	84	35	44 ± 15	NR	NR	NR	2.28 ± 1.29	
Yang AP et al	China	Severe	24	75	58 ± 12	13 (54)	16 (67)	9 (38)	20.7 ± 24.1	7
		Non-severe	69	55	42 ± 19	8 (12)	7 (10)	4 (6)	4.8 ± 3.5	
Gong J et al	China	Severe	28	57	64 (55–72)	NR	NR	NR	3.7 (2.0–6.7)	7
		Non-severe	161	45	45 (33–62)	NR	NR	NR	1.9 (1.4–2.9)	
Zhu Z et al	China	Severe	16	56	58 ± 12	0 (0)	8 (50)	2 (13)	4.24 (3.00–10.87)	7
		Non-severe	111	66	50 ± 16	10 (9)	23 (21)	4 (4)	2.75 (1.90–3.95)	
Sun S et al	China	Severe	27	67	62 (53–71)	NR	NR	NR	8.71 (3.77–14.4)	5
		Common	89	47	47 (37–55)	NR	NR	NR	2.41 (1.73–3.47)	
Liu F et al	China	Severe	19	79	63 (40–66)	3 (16)	6 (32)	1 (5)	3.4 (2.8–5.8)	8
		Non-severe	115	42	50 (36–64)	7 (6)	21 (18)	4 (4)	2.7 (1.8–3.7)	
Fu J et al	China	Severe	16	63	52 ± 13	4 (5)	7 (9)	NR	6.29 ± 3.72	6
		Mild/moderate	59	59	45 ± 14				2.33 ± 1.22	
Ding X et al	China	Severe	15	60	67 (55–76)	5 (7)	9 (13)	6 (8)	3.6 (2.4–9.6)	7
		Non-severe	57	42	46 (35–60)				1.9 (1.3–2.9)	
Chen R et al	China	Critical	48	79	61 ± 14	5 (10)	23 (48)	7 (15)	16.06 (11.26–26.35)	9
		Severe	155	60	61 ± 14	23 (15)	52 (34)	14 (9)	8.96 (4.62–17.04)	
		Mild/moderate	345	53	67 ± 12	33 (10)	73 (21)	14 (4)	3.37 (2.05–6.65)	
Shang W et al	China	Severe	139	59	64 (54–73)	20 (14)	45 (32)	25 (18)	4.75 (2.51–9.42)	7
		Non-severe	304	45	58 (47–67)	43 (14)	86 (28)	19 (6)	2.38 (1.57–3.72)	
Xie G et al	China	Severe	12	83	52 (35–66)	2 (17)	4 (33)	2 (17)	3.0 (1.56–6.55)	5
		Non-severe	85	51	45 (32–60)	3 (4)	16 (19)	5 (6)	2.74 (2.03–3.96)	
Xie L et al	China	Severe	51	57	NR	8 (16)	12 (24)	6 (12)	7.90 ± 10.20	5
		Non-severe	322	52	NR	21 (7)	59 (18)	12 (4)	2.93 ± 1.80	
Zhou Y et al	China	Moderate	140	39	56 ± 14	NR	NR	NR	3.1 ± 2.41	5
		Severe	123	47	64 ± 14	NR	NR	NR	11.66 ± 27.66	
		Critically severe	41	61	65 ± 13	NR	NR	NR		
Wu S et al	China	Severe or critical	67	67	66 (54–73)	8 (12)	22 (33)	6 (9)	5.8 (3.3–13.0)	7
		Moderate	203	42	61 (50–68)	27 (13)	59 (29)	5 (3)	2.2 (1.5–3.4)	
Kong M et al	China	Severe	87	52	68 ± 12	18 (21)	47 (54)	11 (13)	6.6 (2.1–11.1)	7
		Mild	123	48	53 ± 16	9 (7)	32 (26)	9 (7)	3.3 (1.0–3.4)	
Wang F et al	China	Severe	70	64	60 (49–64)	NR	NR	NR	2.72 (1.87–4.37)	8
		Non-severe	253	43	41 (32–56)	NR	NR	NR	1.72 (1.19–2.53)	
Liao D et al	China	Critical	86	71	68 (61–78)	17 (20)	28 (33)	8 (9)	16.02 (6.49–24.79)	7
		Severe	145	52	67 (58–76)	30 (21)	49 (34)	8 (6)	4.71 (2.62–7.78)	
		Moderate	149	46	56 (42–68)	14 (9)	37 (25)	4 (3)	2.67 (1.69–4.08)	
Ok F et al	Turkey	Severe	54	44	68 ± 15	3 (13)	10 (44)	6 (26)	6.1 (5.1)	7
		Non-severe	85	45	47 ± 16	4 (7)	6 (10)	2 (3)	2.46 (2.3)	
Guner R et al	Turkey	SARI/Critical	50	66	62 ± 12	10 (20)	16 (32)	20 (40)	5.6 (1.5–38)#	6
		Mild/pneumonia	172	58	48 ± 16	20 (12)	36 (21)	36 (21)	2.5 (0.4–28)#	
Song CY et al	China	Severe	42	71	56 (48–64)	4 (10)	22 (52)	4 (10)	8.2 (3.9–19.2)	6
		Non-severe	31	52	48 (37–59)	2 (7)	4 (13)	1 (3)	3.0 (1.9–5.5)	
Liu J et al	China	Severe	79	58	65 (54–71)	13 (17)	37 (47)	2 (3)	8.83 (4.20–15.53)	7
		Common	43	61	55 (38–66)	2 (5)	13 (30)	0 (0)	3.11 (1.96–5.00)	
Ma Y et al	China	Severe	63	46	53 ± 13	6 (10)	15 (24)	NR	9.38 ± 10.52	6
		Ordinary (Moderate)	486	54	45 ± 15	23 (5)	75 (15)	NR	3.58 ± 3.07	
		Mild	86	43	39 ± 18	6 (7)	15 (17)	NR	2.73 ± 2.28	
Chen C et al	China	Critical	23	65	68 (63–79)	9 (39)	19 (83)	7 (30)	7.08 (3.48–12.89)	8
		Mild	109	56	62 (53–70)	36 (27)	71 (65)	24 (22)	4.10 (2.19–7.51)	
Wang J et al	China	Severe	8	49	45 (25–61)	5 (9)	13 (24)	1 (2)	2.4 (1.4–16.2)	5
		Moderate	25						2.3 (1.7–2.9)	
		Mild	22						1.8 (0.9–2.8)	

CVD = Cardiovascular Disease; DM = Diabetes Mellitus; HT = Hypertension; IQR = Interquartile Range; NLR = Neutrophil-to-lymphocyte ratio; NOS = Newcastle-Ottawa Scale; NR = Not Reported; SD = Standard Deviation; # = min and max data.

dichotomized variables, the pooled risk ratio (RR) with the 95%CI was obtained using the Mantel-Haenszel method. Statistical heterogeneity was determined using the Cochrane chi-square and I^2 with cut-off values for I^2 of greater than 50% to be considered significantly heterogeneous. In this study, we used the DerSimonian-Laird random-effects model if I^2 was greater than 50%, and the fixed-effects model if I^2 was less than or equal to 50%. Sensitivity analysis was done by omitting one study at a time to identify any source of heterogeneity and restricting the studies to only peer-reviewed papers and only studies with low risk of bias. Publication bias was assessed qualitatively using the funnel plot by comparing the SMD and the standard error of the natural log of SMD [SE(SMD)], and quantitatively using Egger's linear regression test to evaluate the presence of small-study effects. A random-effects meta-regression was performed for the following potential confounders: age, gender, diabetes mellitus, hypertension, and cardiovascular disease. A statistically significant difference was considered if a two-tailed $p < 0.05$.

3. Results

3.1. Search selection

A total of 203 papers were identified from the peer-reviewed databases, and an additional nine papers were retrieved from manual hand-searching, preprint, and grey literature databases. After removing duplicates, 102 unique articles were reviewed for its titles and abstracts, leaving a total of 55 articles eligible for full-text review. After a thorough evaluation, according to the eligibility criteria, 38 papers met the inclusion criteria (Fig. 1).

3.2. Characteristics of studies

This systematic review included 38 articles incorporating 5699 patients with severity outcomes and 6033 patients with mortality outcomes. Thirty-two articles were peer-reviewed [9,12-42], and six were preprints [43-48]; 23 articles compared NLR values on admission in severe vs. non-severe COVID-19 patients, 13 articles compared NLR values on admission in survivors vs. non-survivors of COVID-19, and only two articles compared the NLR values on admission in regard to both the severity and mortality of COVID-19 patients [21,47]. All the studies were retrospective observational studies, except for one which was prospective [33]. Most of the studies were conducted in China, with only four studies (11%) performed outside of China, among which two studies were in Turkey [40,41], and two were in the United States of America [33,34] (Table 1, Table 2, Table S3–4). Studies with severity as the outcome measure had a median risk of bias score of 7 (IQR 5.5–8.5; range 5–9). On the other hand, studies comparing the NLR value on admission in survivors and non-survivors of COVID-19 had a median risk of bias score of 8 (IQR 7–9; range 6–9) (Table S5).

3.3. Neutrophil-to-lymphocyte ratio (NLR) and severity of COVID-19

There was a total of 5699 patients from a total of 25 included articles comparing on-admission NLR levels in COVID-19 patients with different severity levels. Overall, 1805 patients (32%) had severe COVID-19, and seven studies reported significantly higher proportions of males in the severe COVID-19 group. Compared to the non-severe group, patients with severe COVID-19 were generally older and had more comorbidities, such as diabetes mellitus, hypertension, and cardiovascular diseases. All

Table 2
Baseline characteristics of included studies comparing survivors and non-survivors of COVID-19 patients

First Author	Study Location	Groups	Sample (N)	Male %	Age (years) Mean ± SD / Median (IQR)	DM N (%)	HT N (%)	CVD N (%)	NLR value Mean ± SD / Median (IQR)	NOS Score
Liu Y et al	China	NLR Tertile 1 (0.54–2.21)	82	29	48 ± 16	5 (6)	11 (13)	5 (6)	NR	8
		NLR Tertile 2 (2.21–4.82)	81	49	53 ± 17	6 (7)	14 (17)	3 (4)	NR	
		NLR Tertile 3 (4.85–88.09)	82	61	61 ± 15	12 (15)	27 (33)	10 (12)	NR	
Chen R et al	China	Survivor	445	55	54 ± 14	41 (9)	103 (23)	24 (5)	3.71 (2.27–7.54)	9
		Non-survivor	103	67	67 ± 12	20 (19)	45 (44)	11 (11)	13.45 (9.33–23.60)	
Huang J et al	China	Survivor	283	53	53 ± 17	31 (11)	63 (22)	14 (5)	3.3 ± 4.3	8
		Non-survivor	16	69	69 ± 10	4 (25)	11 (69)	4 (25)	13.3 ± 14.3	
Zhang N et al	China	Survivor	50	72	63 ± 11	5 (10)	18 (36)	11 (22)	8.4 ± 7.5	6
		Non-survivor	10	70	71 ± 9	4 (40)	4 (40)	3 (30)	18.7 ± 16.6	
Li L et al	China	Survivor	68	38	44 ± 13	6 (9)	0 (0)	0 (0)	2.3 (1.6–3.8)	7
		Non-survivor	25	60	69 ± 11	5 (20)	5 (20)	4 (16)	3.8 (2.8–6.6)	
Luo X et al	China	Survivor	214	46	51 (37–63)	27 (13)	37 (17)	13 (6)	2.96 (2.13–4.61)	8
		Non-survivor	84	61	71 (64–80)	18 (21)	49 (58)	13 (16)	8.17 (6.15–10.90)	
Yan X et al	China	Survivor	964	48	62 (50–70)	97 (11)	215 (22)	65 (7)	4.11 (2.44–8.12)	8
		Non-survivor	40	68	68 (58–79)	10 (25)	20 (50)	10 (25)	49.06 (25.71–69.70)	
Chen L et al	China	Survivor	1651	47	57 (43–66)	203 (12)	475 (29)	205 (12)[$]	3 (2–4)	9
		Non-survivor	208	74	70 (63–78)	59 (28)	104 (50)	62 (30)[$]	11 (6–20)	
Tatum D et al	USA	NLR ≤ 4.94	62	43	56.1 ± 15.2	NR	NR	NR	NR	6
		NLR > 4.94	57	47	62.1 ± 14.1	NR	NR	NR	NR	
Ullah W et al	USA	NLR < 10	141	47	63.6	49 (35)	93 (66)	27 (19)	NR	8
		NLR > 11	26	62	61.6	10 (39)	14 (54)	2 (8)	NR	
Ye W et al	China	Survivor	297	46	60 (50–67)	41 (14)	73 (25)	5 (2)	2.88 (1.79–6.74)	8
		Non-survivor	52	69	69 (63–76)	16 (31)	30 (58)	11 (21)	14.96 (8.52–26.58)	
Yang Q et al	China	Survivor	176	47	50 ± 15	28 (16)	47 (27)	6 (3)	2.98 (1.70–5.51)	8
		Non-survivor	50	62	68 ± 16	17 (34)	37 (74)	7 (14)	6.18 (3.58–12.78)	
Zhang S et al	China	Survivor	420	51	59 (48–67)	60 (14)	107 (26)	53 (13)	3.91 (2.07–6.79)	7
		Non-survivor	96	75	67 (61–74)	16 (17)	31 (32)	14 (15)	10.99 (7.68–20.97)	
Cheng B et al	China	Survivor	67	33	71 ± 7	11 (16)	39 (58)	11 (16)	4.1 ± 2.9	8
		Non-survivor	51	61	73 ± 7	16 (31)	25 (49)	12 (24)	13.3 ± 14.9	
Chen C et al	China	Survivor	119	56	NR	42 (35)	80 (68)	24 (20)	4.19 (2.30–7.39)	8
		Non-survivor	13	69	NR	3 (23)	10 (77)	7 (54)	12.21 (3.66–14.98)	

CVD = Cardiovascular Disease; DM = Diabetes Mellitus; HT = Hypertension; IQR = Interquartile Range; NLR = Neutrophil-to-lymphocyte ratio; NOS = Newcastle-Ottawa Scale; NR = Not Reported; SD = Standard Deviation; USA = United States of America; $ = included cerebrovascular disease.

studies reported higher NLR values on admission in severe COVID-19 patients than non-severe COVID-19 patients (Table 1, Table S3). Four out of 25 studies (16%) performed a ROC analysis to determine the optimal cut-off value for NLR value to predict severity [14,17,43,46]. The optimal cut-off value, the area under the curve (AUC), sensitivity, and specificity from the four studies are presented in Table 3.

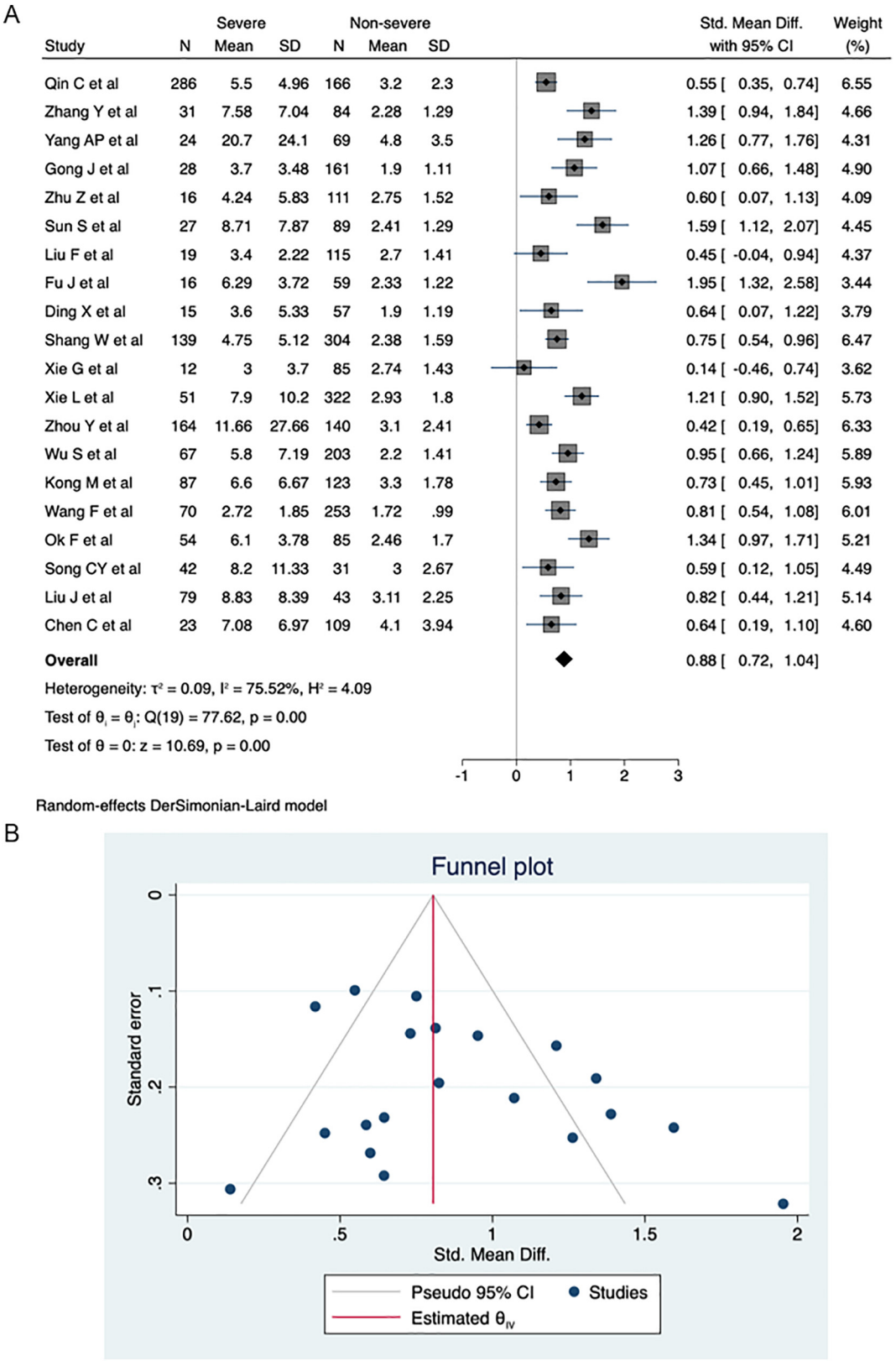


Fig. 2. Neutrophil-to-lymphocyte ratio (NLR) value on admission in severe vs. non-severe COVID-19 patients. A) Forest Plot for all included studies using the DerSimonian-Laird random-effect models showing elevated NLR values on admission in severe compared to non-severe COVID-19. B) Publication bias analysis of all included studies using the Funnel Plot indicating a potential publication bias.

We performed a meta-analysis from 20 eligible articles comparing on-admission NLR levels in COVID-19 patients with different severity groups. From a total of 3859 patients, 1250 patients (32%) experienced severe COVID-19. The pooled analysis showed that severe COVID-19 patients had higher NLR on admission than non-severe patients, with an SMD of 0.88 (95%CI 0.72–1.04) (Fig. 2A). However, the included studies were significantly heterogeneous ($I^2 = 75.52\%$). The funnel plot indicated there was an asymmetry with studies lying outside of the 95%CI, however, Egger's test showed a low risk of publication bias ($p = 0.218$) (Fig. 2B). Sensitivity analysis resulted in no significant changes to the outcome of the analysis (Table S6). Furthermore, restricting the analysis to only peer-reviewed studies and studies with low risks of bias showed similar pooled results (SMD 0.91; 95%CI 0.73–1.10; $I^2 = 79.01\%$ and 0.87; 95%CI 0.77–0.96; $I^2 = 47.23\%$, respectively) (Fig. S1, S2). Meta-regression analysis showed that the association between NLR values on admission and severity in COVID-19 patients was not influenced by age ($p = 0.236$), gender ($p = 0.895$), cardiovascular diseases ($p = 0.886$), diabetes mellitus ($p = 0.880$), or hypertension ($p = 0.222$) (Fig. 3A, Fig. S3A–D).

3.4. Neutrophil-to-lymphocyte ratio (NLR) and mortality in COVID-19 patients

From a total of 15 studies incorporating 6033 patients with NLR levels on admission in survivor and non-survivor of COVID-19 patients, 822 (14%) died in the hospital. Three of the studies (20%) reported the all-cause mortality of COVID-19 patients in dichotomized NLR values with varying cut-off values (Table 2). Generally, those with COVID-19 who died were mostly males, significantly older and had higher proportions of diabetes mellitus, hypertension, and cardiovascular diseases. All studies reported an elevated NLR level on admission in non-survivors compared to survivors.

Two studies performed a ROC analysis to determine the optimal cut-off value of 11.75 with an AUC value of 0.945 (95%CI 0.917–0.973), a sensitivity of 97.5%, and a specificity of 78.1% [27]; and a cut-off value of 7.945 with an AUC value of 0.827 (95%CI not reported), a sensitivity of 65.3%, and a specificity of 90.6% [45] (Table 3). The multivariable regression comparing patients with low (<11.75) and high (>11.75) NLR levels in Yan X et al. resulted in an adjusted odds ratio (AOR) of 44.351 (95%CI 4.627–425.088) [27].

A meta-analysis was done on 12 eligible studies. From a total of 5502 patients, 748 (14%) were non-survivors. The meta-analysis showed that non-survivors had higher NLR on admission than survivors, with a pooled SMD of 1.87 (95%CI 1.25–2.49). Significant heterogeneity was found among the studies ($I^2 = 97.81\%$) (Fig. 4A). The funnel plot was visually asymmetric with studies lying outside the 95%CI, however, the calculated Egger's test showed a low risk of publication bias ($p = 0.797$) (Fig. 4B). Sensitivity analysis by removing one study at a time did not significantly alter the conclusion of the results (Table S7). Restricting the analysis to only peer-reviewed studies and studies with low risks of bias also showed similar pooled SMD of 1.97 (95%CI 1.27–2.66; $I^2 = 98.11\%$) and 1.93 (95%CI 1.28–2.58; $I^2 = 97.99\%$) (Fig. S4, S5). Furthermore, the association between NLR and mortality in COVID-19 was also unaffected by age ($p = 0.595$), gender ($p = 0.644$), cardiovascular diseases ($p = 0.477$), diabetes mellitus ($p = 0.239$), hypertension ($p = 0.545$) (Fig. 3B, Fig. S6A–D).

For the three studies with dichotomized NLR values on admission, a meta-analysis showed that patients with elevated NLR had a higher risk of mortality than those with normal NLR (RR 2.74; 95%CI 0.98–7.66), regardless of the NLR cut-off values used. Significant heterogeneity between the studies was found ($I^2 = 77.09\%$) (Fig. 4C).

4. Discussion

With an increasing number of COVID-19 cases and the limited healthcare capacity, early prediction of COVID-19 severity and mortality is crucial in the patient triage process. Scoring systems such as the Acute Physiology and Chronic Health Evaluation (APACHE) II score was suggested to be a useful clinical tool to predict in-hospital mortality in COVID-19 patients [49]. Other clinical risk scores, such as the COVID-GRAM, are being developed to precisely predict disease progression [50]. However, both scoring systems cannot be implemented in resource-limited healthcare settings, especially in the acute phase, as they heavily rely on advanced laboratory examinations such as serum electrolytes and arterial pH in the APACHE II and lactate dehydrogenase in the COVID-GRAM. Therefore, simpler tools for predicting the severity and mortality of COVID-19 patients in the early stages are urgently needed.

In this study, we performed a systematic review of 38 studies to evaluate the role of NLR levels on admission in predicting the severity and mortality of COVID-19. Our meta-analysis showed that higher NLR values on admission were associated with higher risks of severity and mortality in COVID-19 patients, suggesting that this readily available biomarker can be used to predict the prognosis of COVID-19 patients. However, the differences in NLR values on admission between the survivor and non-survivor patients were greater than those between severe and non-severe patients. Those with high NLR levels on admission had roughly two times the risk of death compared to those with normal NLR levels. Both relationships were shown to be independent of age, gender, diabetes mellitus, hypertension, and cardiovascular diseases.

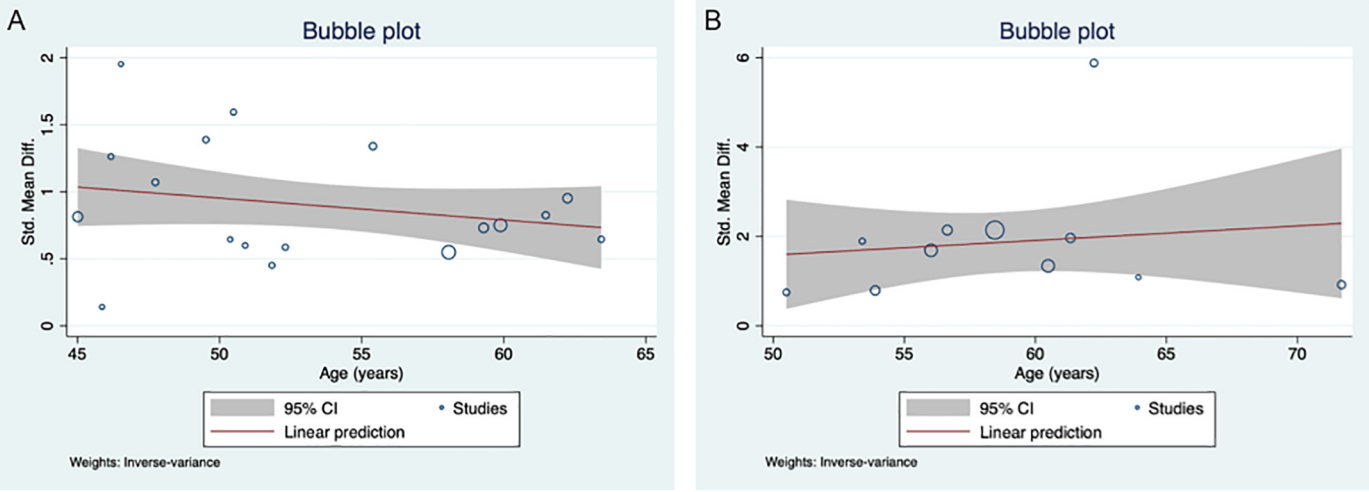
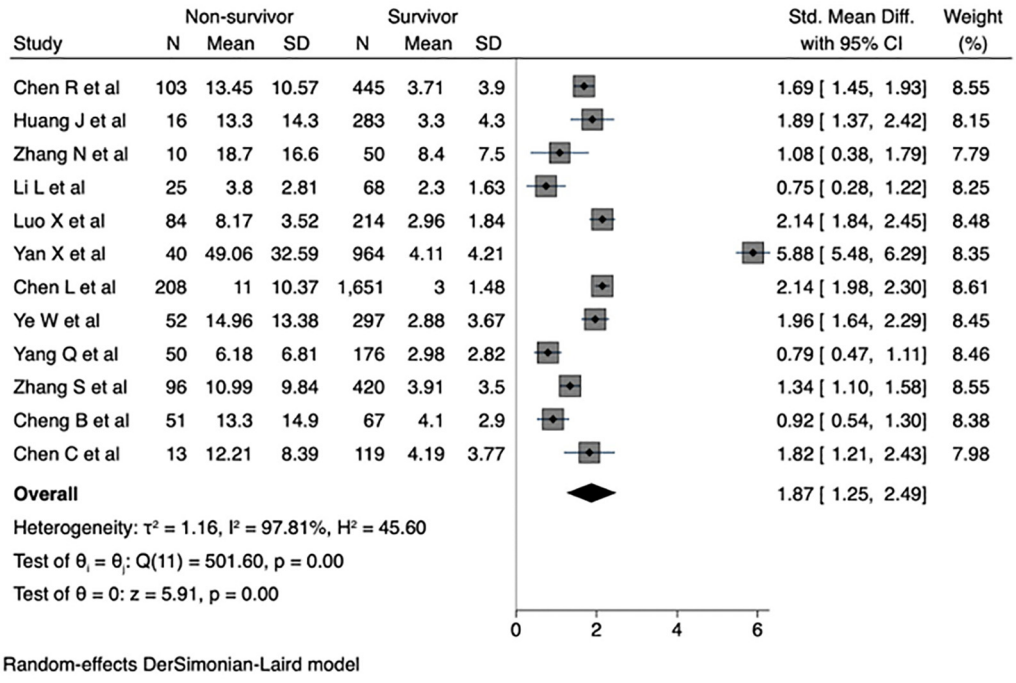
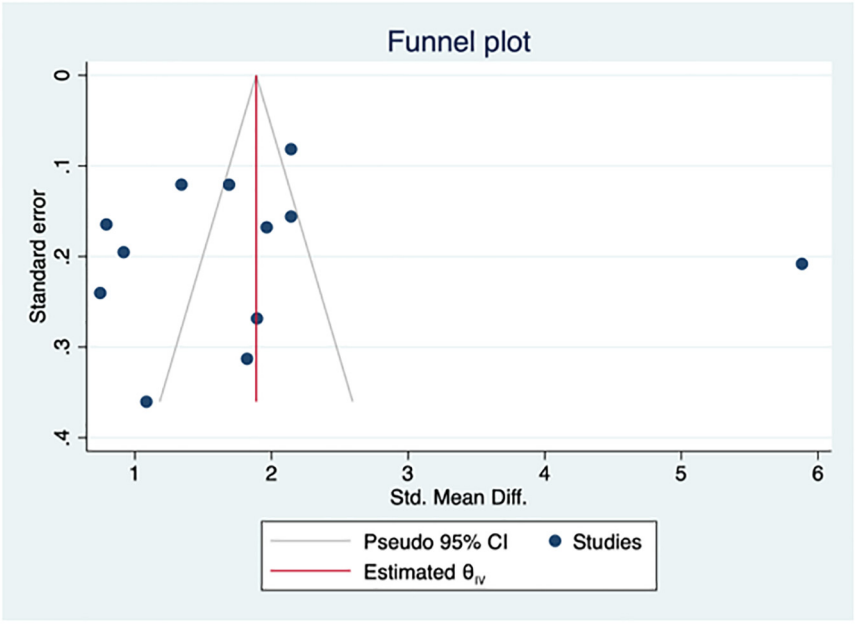


Fig. 3. Bubble plot for meta-regression. The association between NLR values on admission and severity of COVID-19 (A) and COVID-19 mortality (B) was not affected by age ($p = 0.236$; $p = 0.595$, respectively).

A



B



C

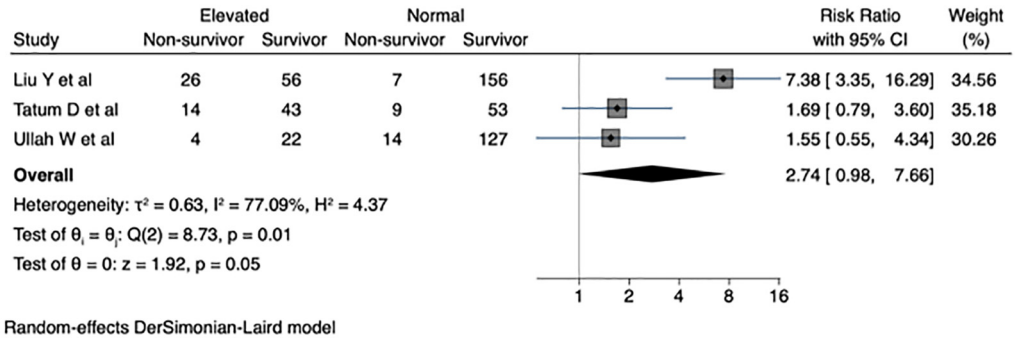


Fig. 4. Neutrophil-to-lymphocyte ratio (NLR) value on admission in non-survivor vs. survivor of COVID-19 patients. A) Forest Plot for all included studies using the DerSimonian-Laird random-effects model showing elevated NLR values on admission in non-survivors compared to survivors of COVID-19. B) Publication bias analysis of all included studies using the Funnel Plot indicating a potential publication bias. C) Forest Plot using the DerSimonian-Laird random-effects model showing the association between NLR value on admission and all-cause mortality risk.

Table 3
Studies performing Receiver Operating Curve (ROC) analysis

First Author	Outcome	Optimal NLR Cut-off Value	Area under the curve (AUC)	Sensitivity (%)	Specificity (%)
Yang AP et al	Severity	3.3	0.841	88	63.6
Sun S et al	Severity	4.5	NR	74.07	89.89
Song CY et al	Severity	5.87	0.72	64	81
Ma Y et al	Severity	4.06	0.727	61.9	76.2
Yan X et al	Mortality	11.75	0.945	97.5	78.1
Cheng B et al	Mortality	7.945	0.827	65.3	90.6

NR = Not Reported.

COVID-19 severity is primarily affected by the innate inflammatory response of the body, where more severe cases were attributed to cytokine storm, a condition when there is an excessive immune response [51]. NLR is a known indicator of systemic inflammation that has been widely used for many conditions, such as predicting in-hospital mortality in sepsis patients, outcomes in cardiovascular diseases, and poor prognosis and higher ICU admissions in acute pancreatitis [52-55]. The biological mechanism underlying this association is that high NLR indicates an imbalance in the inflammatory response, which resulted from increased neutrophil and decreased lymphocyte counts. Inflammatory factors related to viral infection, such as interleukin-6, interleukin-8, and granulocyte colony-stimulating factor, could stimulate neutrophil production [14]. In contrast, systemic inflammation accelerates lymphocyte apoptosis, depresses cellular immunity, decreases CD4+, and increases CD8+ suppressor T-lymphocytes [56,57].

Compared with other laboratory parameters that predict the prognosis of COVID-19, such as interleukin-6, D-dimer levels, C-reactive protein, and erythrocyte sedimentation rate; NLR is more practical for clinical application as it is easily obtained in routine blood tests [58,59]. Due to the low cost and no need for specific assay equipment, NLR remains a simple, accessible, near real-time, and cost-effective biomarker, especially for healthcare facilities with limited medical resources [60].

However, to date, no NLR consensus cut-off value has been established to determine normal and elevated NLR values, especially for COVID-19. In determining the optimal cut-off value of NLR, four studies used various NLR values ranging from 3.3 to 5.9 to predict severity [14,17,43,46], whereas two studies used 7.9 and 11.8 to predict mortality [27,45]. This wide variation indicates that absolute NLR values measured in different populations are hardly comparable and that optimal cut-off values may vary from one population to another.

NLR values were previously reported to vary with age and sex; thus, NLR must be interpreted carefully [61]. Studies have also reported NLR to be race-specific, where different average NLR values were found in different populations [62,63]. In a Chinese population, the reference range of NLR in normal males and females, from a total of 5000 people, was 0.43–2.75 and 0.37–2.87, respectively [61]. The included studies in this meta-analysis generally showed significant differences in age and gender between groups; thus, they could theoretically explain the NLR differences between groups. However, the meta-regression analysis showed that the associations between NLR and COVID-19 severity and mortality were independent of age, gender, and underlying diseases. Therefore, determining the cut-off value is essential for NLR to be used in clinical settings, allowing early risk stratification upon hospital admission.

Our meta-analysis showed significant heterogeneity among the studies. The sensitivity analysis could not determine the source of heterogeneity except for the association between on-admission NLR and severity, when restricting studies to only those with low risks of bias eliminated the heterogeneity. However, in overall, the pooled estimate results were not significantly altered even after performing the sensitivity analysis. The identification of heterogeneity among studies with mortality outcomes was not possible due to the possibility of higher variability in treatment protocols among studies with mortality outcomes compared to severity.

To date, our study is the first meta-analysis to describe the predictive values of NLR on admission for the severity and mortality of COVID-19 patients. Additionally, our results showed definitive results that can be directly applied to clinical practice. Moreover, our analysis has emphasized that the association between NLR levels on admission and poor outcomes for COVID-19 was independent of predictors, such as age, hypertension, diabetes mellitus, and cardiovascular diseases.

There are some limitations to this meta-analysis. First, we acknowledge that most of the included studies were primarily conducted in China. Thus, our data might have less clinical relevance in other countries, especially in countries with higher cases and death rates, such as in the United States of America and Europe. Second, we included preprints in the meta-analysis. However, the preprints included had low risks of bias, and further sensitivity analysis to only peer-reviewed studies showed similar results to when preprints were included. Lastly, the studies included in our meta-analysis were all retrospective, except for one, which was a prospective cohort study.

5. Conclusion

Our meta-analysis demonstrated that NLR on admission is predictive of the severity and mortality in COVID-19 patients, where higher NLR levels are associated with poor outcomes. To date, no optimal cut-off value has been validated across different populations. Therefore, prior to clinical use, further studies should be developed to obtain an exact consensus cut-off value with the optimal sensitivity and specificity. However, our findings support the use of NLR levels to perform early risk stratification in clinical settings, thus allowing patients with higher NLR to be prioritized for healthcare resource allocation.

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Authors' contributions

DMS: Idea formulation, article draft writing, data collection and analysis, interpretation of the data, and critical review of the writing; JC: data collection and analysis, interpretation of the data, and critical review of the writing; ADW: article draft writing, data collection and analysis, and critical review of the writing; NAAI: article draft writing, data collection and analysis, and critical review of the writing. All authors have substantially contributed to the formulation of this manuscript. We declare no conflicts of interest.

Credit authorship contribution statement

Daniel Martin Simadibrata: Conceptualization, Data curation, Formal analysis, Writing - original draft, Writing - review & editing, Supervision. **Julius Calvin**: Data curation, Formal analysis, Writing - review & editing. **Alya Darin Wijaya:** Data curation, Writing - original draft, Writing - review & editing. **Naufal Arkan Abiyyu Ibrahim:** Data curation, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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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.2021.01.006.

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