



Original Article

Can preoperative neutrophil-to-lymphocyte ratio predict in-hospital mortality in postoperative patients with Stanford type A aortic dissection? Evidence-based appraisal by meta-analysis and GRADE

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ABSTRACT

Objectives: In-hospital mortality in postoperative patients with type A aortic dissection (AAD) is high. Neutrophil-to-lymphocyte ratio (NLR) is a novel predictor of adverse outcomes in many cardiovascular diseases. We examine NLR as a predictive tool in AAD in this meta-analysis. **Materials and Methods:** We systematically searched in four databanks. Risk of bias was appraised using the Quality Assessment of Diagnostic Accuracy Studies 2 tool. The midas and metandi commands in Stata 15 were used for the meta-analysis. The certainty of evidence was assessed by the Grading of Recommendations, Assessment, Development, and Evaluation methodology (GRADE). **Results:** Four studies with 502 cases in total were included. Pooled sensitivity and specificity were 0.71 (95% confidence interval [CI] = 0.52–0.79) and 0.64 (95% CI = 0.55–0.71), respectively. Area under the hierarchical summary receiver operating characteristic curve yielded 0.73 (95% CI = 0.68–0.76). The diagnostic odds ratio was 4.42 (95% CI = 2.56–7.62). Pooled positive and negative likelihood ratios yielded 1.98 (95% CI = 1.53–2.55) and 0.45 (95% CI = 0.32–0.62), respectively. When the pretest probabilities were 25%, 50%, and 75%, the positive posttest probabilities were 40%, 66%, and 86%, and the negative posttest probabilities were 13%, 31%, and 57%, respectively, according to the Fagan's nomogram plot. The overall certainty of evidence in GRADE was low and very low in sensitivity and specificity, respectively. **Conclusion:** The pooled diagnostic values of preoperative NLR, an inexpensive and routine laboratory examination, provide a practicable help for predicting in-hospital mortality for patients with postoperative AAD in our meta-analysis.

KEYWORDS: *In-hospital mortality, Neutrophil-to-lymphocyte ratio, Type A aortic dissection*

INTRODUCTION

Aortic dissection is a life-threatening emergency disease defined as the separation of aortic wall layers because of intimal tear [1]. In the Stanford classification of aortic dissection, the involvement of ascending aorta is classified as type A and the involvement of descending aorta as type B [2]. The involvement of ascending aorta can also be classified into modified DeBakey types I and II [3]. Type I involves the ascending and descending aorta, whereas type II is located entirely in the ascending aorta. In the absence of treatment, mortality in patients with type A aortic

dissection (AAD) increases by 1%–2% every hour after the onset of symptoms [4]. The case fatality rates of AAD under medical treatment are 30%–68% and 49%–73% within 2 days and the first 2 weeks, respectively [4]. Surgical repair is the recommended standard procedure for managing AAD by

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practice guideline, but postoperative in-hospital mortality in AAD patients is still a critical issue [5]. A few decades ago, postoperative mortality yielded as high as 60.7% [6]. An 8% of in-hospital mortality rate in a recent report, although it is a much more improved number, remains high among major surgeries [7]. Therefore, predictive tools for identifying patients with AAD who are at an increased risk of death after surgery enable physicians to exploit clinical progress and make good decisions.

Recent clinical and basic studies have demonstrated the inflammatory signaling in the pathophysiology of aortic dissection [8,9]. Neutrophil-mediated adventitial inflammation may play important roles in the progression of aortic dissection [10]. Subsequent chemokine-dependent signaling after the formation of aortic dissection may elicit neutrophilia and massive neutrophil accumulation in the injured site, thereby leading to aortic enlargement and rupture [10]. Meanwhile, relative lymphocytopenia is a presentation of cortisol-induced stress response [11]. According to recent evidence, neutrophil-to-lymphocyte ratio (NLR) is a novel predictor of adverse outcomes in many cardiovascular diseases [12]. Most studies investigating NLR as a predictor of in-hospital mortality for patients with AAD were restricted to a small number of patients at a single center. Therefore, we performed a diagnostic meta-analysis to evaluate the accuracy and applicability of NLR in predicting in-hospital mortality in patients with postoperative AAD.

MATERIALS AND METHODS

Search strategy and study eligibility

We registered our protocol of systematic review at the Center for Open Science (DOI 10.17605/OSF.IO/YXPQF). The guideline of “Preferred Reporting Items for Systematic Reviews and Meta-Analysis” (PRISMA)[13] and the methodology of “Cochrane Handbook for Systematic Reviews”[14] were followed. BR Chung AND YT Huang independently searched PubMed, Embase, Cochrane Library, and Airiti Library for clinical studies published before August 31, 2020. Keywords with free texts and medical subject heading terms of neutrophil to lymphocyte ratio and type A aortic dissection were used. No language limitation was applied. After the removal of duplication with EndNote X9 (Clarivate Analytics, Philadelphia, PA, USA), both authors screened articles according to title and abstract first. If possible, the full texts of the articles were read. Related articles in some narrative reviews and studies investigating patients with AAD who received surgery were also read to check if suitable studies were quoted as references. We excluded studies with unavailable study data. In the selected studies, preoperative NLR should be recorded with cutoff values for the prediction of in-hospital mortality. True-positive (TP), false-positive (FP), false-negative (FN), and true-negative (TN) data, or sufficient information for deriving these parameters (sensitivity, specificity, negative predictive value [NPV], and positive predictive value [PPV]), should be obtained in the studies. The final list of the included studies was decided by discussion between BR Chung and YT Huang. The corresponding author (PC Lai) was consulted to resolve discrepancies among the enrolled studies.

Methodologic quality assessment

Methodologic quality was appraised by the tool of “Quality Assessment of Diagnostic Accuracy Studies 2” (QUADAS-2) [15]. Two reviewers (YT Huang and PC Lai) scored the four domains in risk of bias (patient selection, index test, reference standard, and flow and time) and three domains of applicability concerns (patient selection, index test, and reference standard) and resolved disagreements through face-to-face discussion.

Data extraction and statistical analysis

BR Chung AND YT Huang independently extracted data, which comprised the following items: (1) name of the first author, (2) year of publication, (3) country, (4) total number of patients, (5) gender distribution, (6) mean/median age, (7) in-hospital mortality rate, and (8) cutoff value of NLR. Disagreements were resolved by discussion. Pooled estimates for sensitivity, specificity, and positive and negative likelihood ratios (LRs) (LR [+], and LR [-]), as well as PPV and NPV with the corresponding 95% confidence interval (CI), were calculated using the midas command in Stata 15 (StataCorp LLC., College Station, TX, USA). Heterogeneity across studies was assessed, and Cochran Q-statistic was used in examining inconsistency through I^2 statistic. A hierarchical summary receiver operating characteristic (hsROC) curve was generated, and the area under the curve (AUC) was used in describing overall accuracy as a potential summary of the hsROC curve. The diagnostic odds ratio (DOR), calculated by the formula of “(TP × TN)/(FP × FN),” is also a measure of the effectiveness of a diagnostic test. DOR was calculated using the metandi command in Stata 15. Fagan’s Nomogram plot analysis was performed for posttest probability based on the pretest probability and LR(+)/LR(-). Publication bias was assessed by the Deeks’ linear regression test [16], and $P < 0.05$ was considered statistically significant.

Grading of the certainty of evidence

We assessed the certainty of evidence by using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology for diagnostic test [17]. The overall certainty of evidence in sensitivity and specificity was evaluated on the basis of five downgrading domains and three upgrading domains. Level of evidence was classified as high, moderate, low, or very low. GRADE was performed using the GRADEpro Guideline Development Tool (McMaster University, 2015 [developed by Evidence Prime, Inc.], available from gradepr.org). According to the pooled results, the number of TP/FP/TN/FN per 1000 patients tested was calculated and illustrated according to difference prevalence.

RESULTS

Characteristics of the enrolled studies

The flowchart for the selection process and explanation is illustrated in Figure 1. Nineteen articles met the initial search criteria. We removed six duplicates and further excluded eight references because the contents were not relevant to our subject. Finally, four studies were included for the meta-analysis [18-21]. Bedel and Selvi [18] reported a high percentage (89.6%) of patients with AAD who received

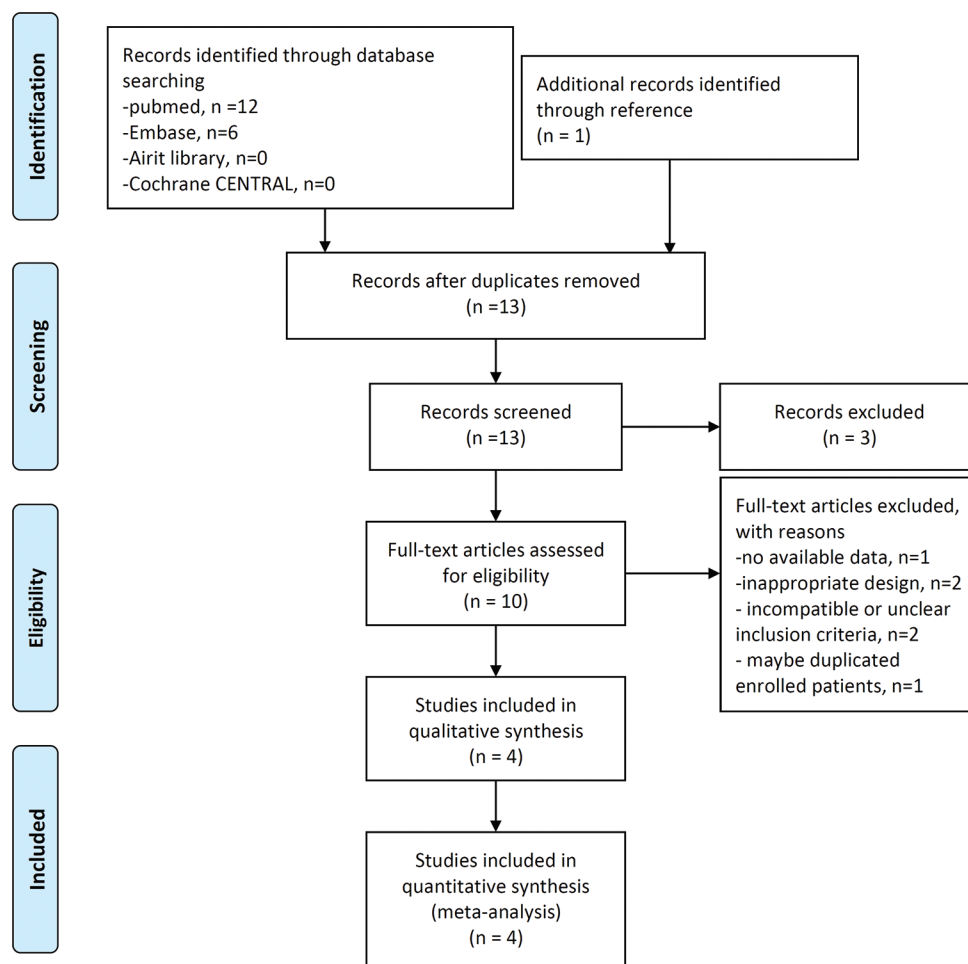


Figure 1: Flowchart of articles enrolled after searching databases and reasons for exclusions

surgery, so we still enrolled this study. Karakoyun *et al.*[22] did not mention whether AAD patients received surgery, and we finally decided to get rid of it because the 4.2 ± 2.2 days of mean time from hospital admission to death aroused our suspicion that AAD patients without surgery might be also included. Two studies were published in the same year (2017) from an overlapped hospital [20,23]. The time period for investigating postoperative AAD patients was not reported in the study by Oz *et al.* [23], so we did not adopt this study, too. All of these studies in our meta-analysis enrolled a total of 502 cases and were published from 2014 to 2020 in Turkey. The in-hospital mortality rate ranged from 17.7% to 37.7%. The cutoff values of NLR ranged from 6.5 to 9.74 [Table 1].

Quality of the enrolled studies

Figure 2 illustrates the methodological quality of the included studies assessed by the QUADAS-2 tool. The results reflected the risk of bias and concerns about applicability. In the first domain, “to avoid inappropriate exclusion” is considered one item for evaluation. Some studies did not appropriately mention exclusion criteria for patient selection, such as active or chronic inflammatory status, autoimmune disease, known malignancy, or other conditions, which may influence NLR. Bedel *et al.* excluded an unknown number of cases with missing laboratory data, which may elicit bias

potentially. Both index test (NLR detected by commercialized machine) and reference standard (in-hospital mortality) were a clear and unique detection. However, lots of factors may impact the outcome during the interval between perioperative NLR detection when admission and date of mortality. Therefore, a high risk of bias was rated in the domain of flow and timing of all the included studies.

Pooled estimates of sensitivity/specificity, hierarchical summary receiver operating characteristic, and diagnostic odds ratio

For the evaluation of the accuracy of NLR in predicting in-hospital mortality in patients with AAD who received surgery, pooled sensitivity and specificity were calculated. As shown in Figure 3, the pooled sensitivity and specificity were 0.71 (95% CI = 0.62–0.79; $I^2 = 0\%$) and 0.64 (95% CI = 0.55–0.71; $I^2 = 69.51\%$), respectively. After the mathematical manipulation of true and false positivity (1-specificity) of each study, linear regression was performed for the generation of the hsROC curve [24]. The AUC of hsROC was 0.79 [95% CI = 0.75–0.82; Figure 4]. In this study, DOR of preoperative NLR to predict in-hospital mortality in postoperative NLR was 4.42 (95% CI = 2.56–7.62).

Table 1: Basic characteristics of studies included in the meta-analysis

Study	Lafçi <i>et al.</i>	Kalkan <i>et al.</i>	Bedel <i>et al.</i>	Erdolu <i>et al.</i>
Year	2014	2017	2019	2020
Country	Turkey	Turkey	Turkey	Turkey
Study design	Retrospective	Retrospective	Retrospective	Retrospective
Case number (Male/female)	104 (79/25)	184 (134/50)	96 (78/18)	118 (89/29)
Age (years) mean±SD	55.2±14.0	53.1±11.4	63.7±13.6	57.0±11.7
In-hospital mortality rate	31.7%	20.7%	17.7%	20.3%
Cut-off value of NLR	8	6.5	9.74	8.8

NLR: Neutrophil-to-lymphocyte ratio, SD: Standard deviation

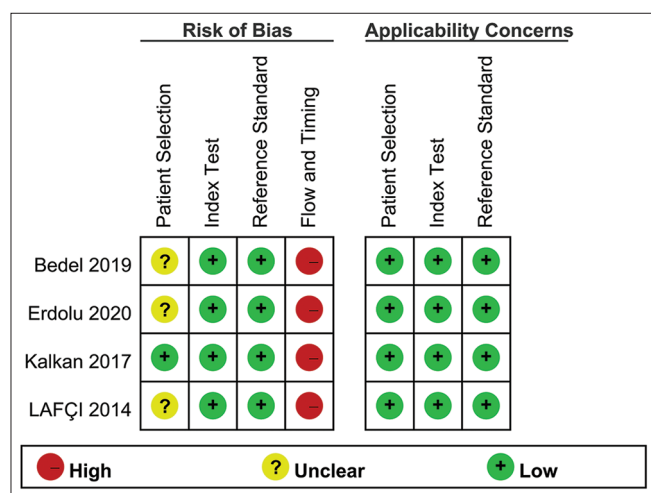


Figure 2: Evaluation of the quality of the included studies with Quality Assessment of Diagnostic Accuracy Studies 2

Fagan’s nomogram plot analysis

In our study, pooled LR (+) and LR (-) showed 1.98 (95% CI = 1.53–2.55) and 0.45 (95% CI = 0.32–0.62), respectively. The Fagan’s nomogram plot is a tool for estimating the degree of probability changes when this diagnostic tool is used. The posttest probability of a disease or outcome can be predicted using this tool after pretest probability is estimated prior to testing. Pretest probability may be related not only to the prevalence of a disease or outcome but also to an adjusted possibility in a patient according to clinical information. After a line connecting the pretest probability and the LR (+) or LR (-) is drawn until the extension of this line intersects with posttest probability, the point of intersection becomes the new estimate of probability (known as posttest probability) that a patient has a particular disease or outcome. In the Fagan plot in this study, the positive posttest probabilities were 40%, 66%, and 86% when the pretest probabilities were 25%, 50%, and 75%, respectively, and the corresponding negative posttest probabilities were 13%, 31%, and 57% [Figure 5].

Grading the certainty of evidence by Grading of Recommendations Assessment, Development, and Evaluation

Owing to the high risk of bias appraised in all the included studies, we downgraded two levels in the first domain of GRADE. High heterogeneity ($I^2 > 50%$) of pooled specificity was observed, and thus the certainty of specificity was downgraded by one level. The *P* value of Deeks’ linear regression

test was 0.39, and thus publication bias was not concerned. The overall certainty of evidence was low and very low in sensitivity and specificity, respectively [Table 2]. The number of TP/FP/TN/FN per 1000 patients tested based on 10%, 25%, and 40% of pretest probability is listed in Table 2.

DISCUSSION

In this diagnostic meta-analysis, NLR provided a practical help in predicting in-hospital mortality for patients with post-operative AAD. The differential counting of leukocytes is a routine laboratory examination method for patients with chest pain or with confirmed AAD, and thus the physician did not need to order additional tests. It might be the simplest method for predicting the risk of fatality in patients with postoperative AAD before surgery. The value of NLR may provide an extra confidence of approximately 10%–20% for calculating the probability of death. To predict the postoperatively in-hospital mortality in AAD patients with high NLR, as shown in Table 2, the probability of accuracy will be higher under the condition of higher prevalence of in-hospital mortality rate. In contrast, the probability of accuracy to rule out in-hospital mortality will be higher under the condition of lower prevalence of in-hospital mortality rate in AAD patients with low NLR.

A substantial amount of evidence is available regarding the prognosis of cancer with high NLR based on dysregulated immune system via inflammation [25-27]. Regarding the relationship between NLR and cardiovascular diseases, Angkananard *et al.* reported that high NLR is significantly associated with the risk of acute coronary syndrome, coronary artery disease, or stroke, in a systematic review and meta-analysis [28]. Regarding postoperative complications, Liu *et al.* conducted a systematic review and meta-analysis and showed that elevated preoperative NLR is significantly efficient in predicting the incidence of postoperative atrial fibrillation and obtained a pooled odds ratio of 1.42 (95% CI: 1.16–1.72) from 12 included studies [29]. The value of NLR in various clinical diseases or conditions may be based on the different causes of physiologic stress. Apart from cytokines, endogenous catecholamines have also been reported to increase neutrophil count while eliciting the apoptosis of lymphocytes [30,31]. Thus, preoperative NLR seems reasonable as a mortality predictor for patients with AAD receiving surgery based on the above pathophysiology.

The diagnostic value of NLR or mortality prediction in this study yielded a slightly lower utility in comparison to the diagnostic values for predicting outcomes in a meta-analysis

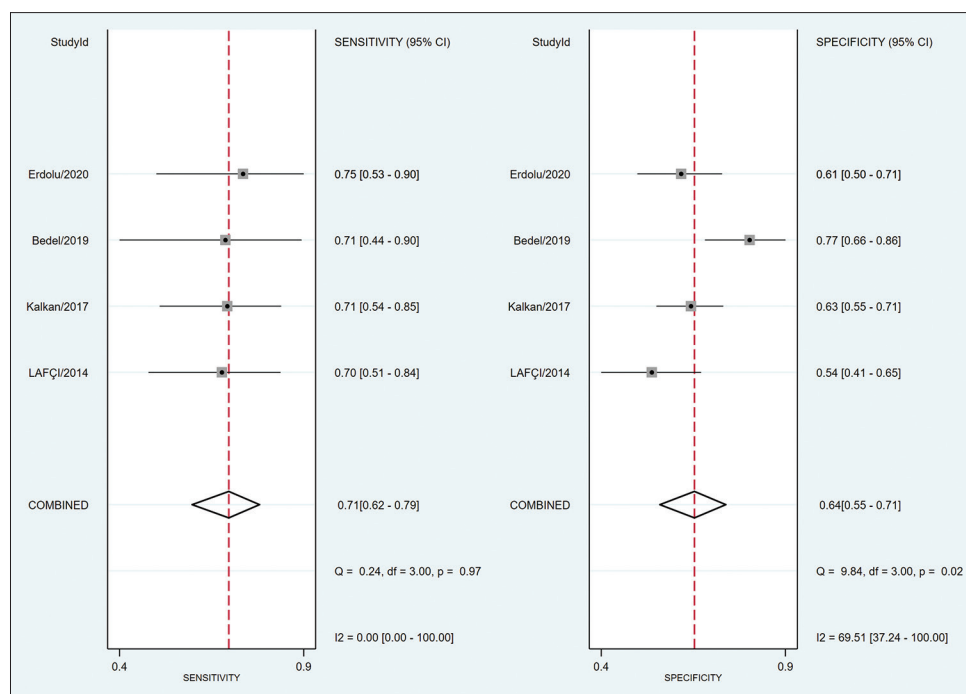


Figure 3: Forest plots of sensitivity and specificity for the included studies and pooled effects. Neutrophil-to-lymphocyte ratio was used in predicting in-hospital mortality in patients with postoperative type A aortic dissection

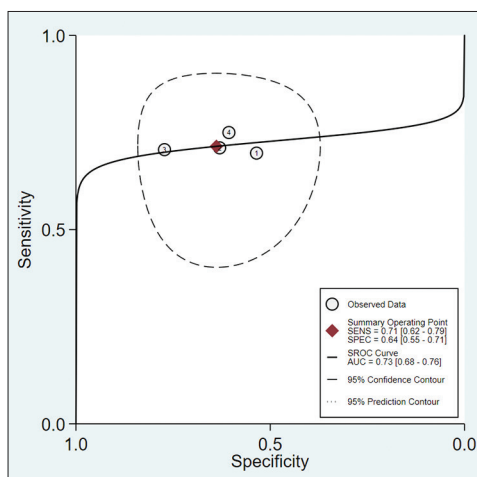


Figure 4: hsROC curves of NLR for the prediction of in-hospital mortality in patients with postoperative AAD. SENS: Sensitivity, SPEC: Specificity, SROC: Summary receiver operating characteristic, AUC: Area under the curve, hsROC: Hierarchical summary receiver operating characteristic, NLR: Neutrophil-to-lymphocyte ratio, AAD: Type A aortic dissection

of other inflammatory disease. The pooled NLR in the prediction of the severity of acute pancreatitis showed that sensitivity, specificity, AUC of ROC, LR (+), and LR (-) were 0.79 (95% CI = 0.73–0.84), 0.71 (95% CI = 0.59–0.80), 0.82 (95% CI = 0.78–0.85), 2.7 (95% CI = 1.8–4.0), and 0.30 (95% CI = 0.21–0.41), respectively [32]. The pooled NLR for predicting short-term mortality in the cases with acute pulmonary embolism yielded LR (+) and LR (-) values of 2.93 (95% CI = 2.41–3.55) and 0.32 (95% CI = 0.23–0.42), respectively [32]. Not unexpectedly, there are several limitations of the diagnostic values of pooled NLR in predicting in-hospital mortality in patients with AAD who received surgery. First,

comorbidities involving atherosclerosis [33], chronic inflammation [34], and even chronic diseases[35] elicited a high NLR and were confounding biases in our study. Moreover, the experiences of perioperative teams, the type of operation, the skills of surgeons, duration of cardiopulmonary bypass procedures, the abilities of postoperative care, and complications after surgeries may directly affect the in-hospital mortality of patients with AAD. Besides, the four enrolled studies were all from Turkey and the total number of participants was only 502. The number of available studies, experience from nation, and the number of cases would lead to limitation of this review and prevent the findings from being conclusive.

Recently, Xu *et al.* reported a meta-analysis of observational studies to determine the prognostic role of NLR in aortic disease [36]. They enrolled studies including patients with both aortic aneurysm (AA) and AAD/type B aortic dissection (BAD). They found that NLR was significantly higher in patients with aortic diseases, and NLR was also significantly higher in death cases with aortic diseases. They concluded that NLR may be a good prognostic parameter in aortic disease, which is similar with that of our findings. Although BAD shares the similar pathophysiology with AAD, the mortality rate is quite different. It is more likely to cause aortic regurgitation, cardiac tamponade, stroke, frank rupture, and myocardial infarction in AAD, leading to a potentially fatal condition [37]. Uncomplicated BAD could be treated by medication alone. For patients with uncomplicated BAD, controlling blood pressure aggressively by drug(s) is associated with a much lower mortality compared to that of emergent surgery [38]. Besides, studies including patients with and without surgeries were all pooled in this study. Thus, we do not think it is suitable to pool the results from both AAD and BAD. AA is a chronic disease,

Table 2: Certainty of evidence assessed by GRADE

Outcome	№ of studies (№ of patients)	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy Certainty of evidence
		Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pretest probability of 10%	pretest probability of 25%	pretest probability of 40%	
True positives (patients with mortality)	4 studies 112 patients	very serious ^a	not serious	not serious	not serious	none	71 (62-79)	178 (155-198)	284 (248-316)	⊕⊕○○ LOW
False negatives (patients incorrectly classified as not having mortality)							29 (21-38)	72 (52-95)	116 (84-152)	
True negatives (patients without mortality)	4 studies 390 patients	very serious ^a	not serious	serious ^b	not serious	none	576 (495-639)	480 (413-533)	384 (330-426)	⊕○○○ VERY LOW
False positives (patients incorrectly classified as having mortality)							324 (261-405)	270 (217-337)	216 (174-270)	

^aAll included studies are at high risk of bias, ^bI²>50%

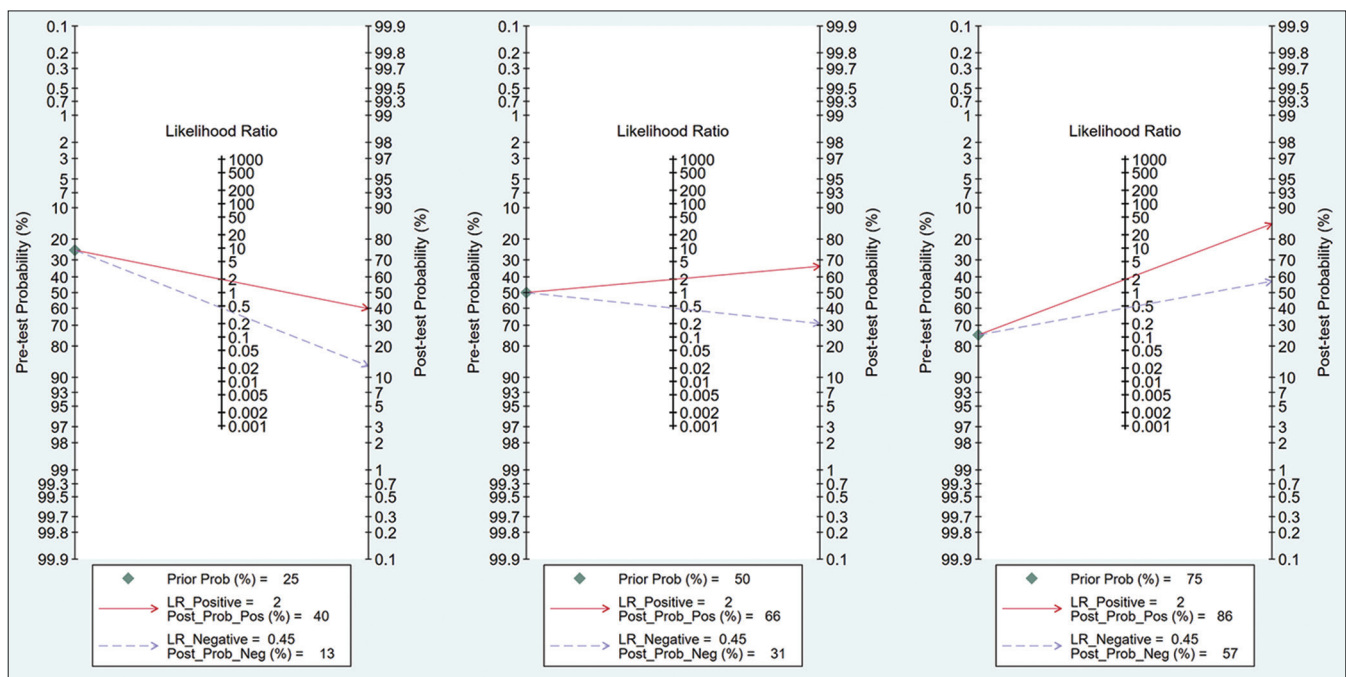


Figure 5: Evaluating the clinical utility of NLR for in-hospital mortality prediction in postoperative AAD patients by Fagan's nomogram plot. LR: Likelihood ratio, Prob: probability, Pos: Positive, Neg: Negative, NLR: Neutrophil-to-lymphocyte ratio, AAD: Type A aortic dissection

and it is not suitable to merge the mortality of AA and in-hospital mortality of AD because the duration from disease onset to death is quite diverse in these aortic diseases.

CONCLUSION

Complete blood count with differential count of leukocytes is an inexpensive and routine laboratory examination for AAD patients with admission or preoperative status. Although there were only few studies and they were not large, the pooled diagnostic values of NLR in this meta-analysis provide a practicable improvement in the probability prediction of in-hospital mortality for patients with postoperative AAD. Our objective findings suggest that NLR may be one of the parameters to develop a scoring system for predicting in-hospital mortality in patients with postoperative AAD. Besides, further studies

would be worthwhile to reduce the current level of uncertainty and ensure the effective use of NLR in the prediction of complications in postoperative AAD patients.

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Conflicts of interest

There are no conflicts of interest.

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