



# Neutrophil to lymphocyte ratio predict mortality and major adverse cardiac events in acute coronary syndrome: A systematic review and meta-analysis

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## ABSTRACT

**Objectives:** Neutrophil to lymphocyte ratio (NLR) might be associated with the mortality or major adverse cardiac events (MACEs) in acute coronary syndrome (ACS) patients. We performed a meta-analysis to evaluate the correlation between NLR and mortality/MACEs in ACS.

**Methods:** We assessed clinical trials through Pubmed, EMBASE, the Cochrane Library and Web of science in investigating the association between NLR and mortality/MACEs in ACS patients up to August 15, 2017. The primary outcome was mortality or recurrent MACEs.

**Results:** In total, 8 studies of 9406 patients were included in the systematic and meta-analysis. Our analysis indicated that elevated pretreatment NLR was a poor prognostic marker for patients with recent ACS in predicting medium to long-term mortality/MACEs (OR 1.26, 95%CI 1.13–1.41). And the analysis indicated that higher pretreatment NLR value was associated with higher in-hospital mortality in ACS patients (OR 6.39, 95%CI 1.49–27.38,  $p < 0.001$ ). The NLR value of 5.0 maybe a cut-off value for ACS risk.

**Conclusions:** In patients with a recent ACS, an elevated pretreatment NLR value is effective in predicting the risk of mortality/MACEs.

## 1. Introduction

Patients with acute coronary syndrome (ACS) are at a high risk of mortality and recurrent major cardiovascular events (MACEs). About 5.5%–18.2% ACS patients died in the hospital [1–3], with a high mortality of nearly 15% in a long-term follow up [4]. Therefore, higher age, low ejection fraction [5], HBP [6], SYNTAX scores et al. were reported associated with the prognosis of ACS [7]. Some laboratory index such as cTNI, NT-proBNP and neutrophil may also independently predict the mortality or MACEs of ACS [8–10].

Neutrophil to lymphocyte ratio (NLR) is one of the inflammation factor has been proven to be useful in many diseases. A decrease of the proportion of NLR is associated with more favorable outcomes in metastatic renal cell carcinoma and metastatic pancreatic cancer [11,12]. And it may be a useful prognostic marker for other neoplastic diseases [13]. NLR showed its efficiency in cerebrovascular diseases at the same time [14–16]. In cardiovascular diseases (CAD), NLR was an independent predictor of ventricular dysfunction [17,18], and was related to CAD severity and mortality.

Recent studies have declared the prognostic significance of NLR and acute coronary syndrome [19–21], we found that NLR values were

associated with ACS prognosis, the higher the NLR value, the worse the prognosis of ACS patients. However, the NLR values were diverse in different studies. In order to analysis the association and the NLR cut-off value that can predict the prognosis of ACS patients, we performed an updated systematic and meta-analysis of NLR for the mortality/MACEs in patients with ACS, to find an inexpensive and effective way predicting the prognosis of ACS patients.

## 2. Materials and methods

### 2.1. Search strategy

A systematic literature search was conducted through Pubmed, EMBASE, the Cochrane Library and Web of science. The search was updated to August 15, 2017. The following terms or keywords were used: “acute coronary syndrome”, “myocardial infarction”, “neutrophil to lymphocyte ratio”, “neutrophil/lymphocyte ratio”, “neutrophil-lymphocyte ratio”. Searches were all completed trials in human beings with abstracts or full texts publish in English. The last study was performed on May 8, 2017.

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## 2.2. Inclusion and exclusion criteria

Two researchers (CH D and ZM W) read the literature review independently of each other. Disagreements were solved by consensus. To insure the reliability of the researches, the following criteria were included: (1) Adults patients (> 18 years old) with ACS (STEMI, non-ST-segment elevation acute coronary syndrome (NSTEMI-ACS)). (2) pretreatment NLR were available (odds ratio with corresponding 95% confidence intervals) and were associated with mortality or MACEs. (3) NLR cut-off value were clearly. (4) Articles were published as full-text in any language. The study must meet all the four inclusion criteria. Studies were excluded if they met any of the following characteristics: (1) overlapping or duplicate reports; (2) nonhuman experiments; (3) absence of odds ratio (OR), their corresponding 95% confidence intervals (95% CIs) and cut-off values. (4) sample size < 200.

## 2.3. Data extraction and quality assessment

The following data were extracted: Publication characteristics, study regions, patient characteristics, sample size of patients, duration of follow up, type of ACS, cut-off value, ORs and 95% CIs, quality scores, and endpoints. The endpoints of the studies included mortality (in-hospital, or medium to long-term) or MACEs (including cardiovascular death, nonfatal MI, unstable angina, nonfatal ischemic stroke, acute left ventricular failure, cardiogenic shock and ventricular arrhythmia).

The quality of included studies was evaluated by the Newcastle-Ottawa scale (NOS). We considered studies as high quality if they met a score more than six.

## 2.4. Statistical analysis

All data were analyzed using STATA statistical software (version 14.0). For the analysis of the association between NLR values and clinical outcomes, odds ratio (OR) with corresponding 95% confidence intervals (CIs) was synthesized as the effective value. Between-study heterogeneity was explored by Cochrane's Q and  $I^2$  tests. A fixed effect model was used in the absence of significant heterogeneity ( $I^2 < 50\%$ ), or the random effect model was used. Publication bias of study with different samples size was assessed by Begg's funnel plots. We regarded two-sided probability values of < 0.05 as statistically significant.

## 3. Results

### 3.1. Literature search and include studies

A diagram of the study selection is shown in Fig. 1. Initially, a total of 151 references were included in the primary search in the major databases. By screening title and abstracts, 91 papers were excluded. And finally, 7 references including 8 studies published from 2010 to 2017 were selected for our meta-analysis according to the inclusion criteria [22–28]. A total of 9406 patients were included. The main characteristics of the included studies were listed in Table 1. These studies were all observation researches, and were conducted in Italy (2), USA (2), China (1), Turkey (2) and India (1). As the study by Zuin M including two subgroups (STEMI group and NSTEMI group), we tagged them as Zuin M (STEMI) and Zuin M (NSTEMI). And two researches by Soylu K reporting on different years for different groups were marked as Soylu K (2013) and Soylu K (2015). 5 studies reported the mortality [22,23,25,28], 1 reported MACEs [24], and two studies reported both [26,27]. The follow up ranges from 6 months to 60 months (except one study only reported in-hospital mortality). For all the studies, the mean age of the patients was 50s or 60s. Three studies were STEMI patients [23,24,28], while 3 studies were NSTEMI-ACS patients [22,25,28], 2 studies were mixed [26,27]. The odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) were all

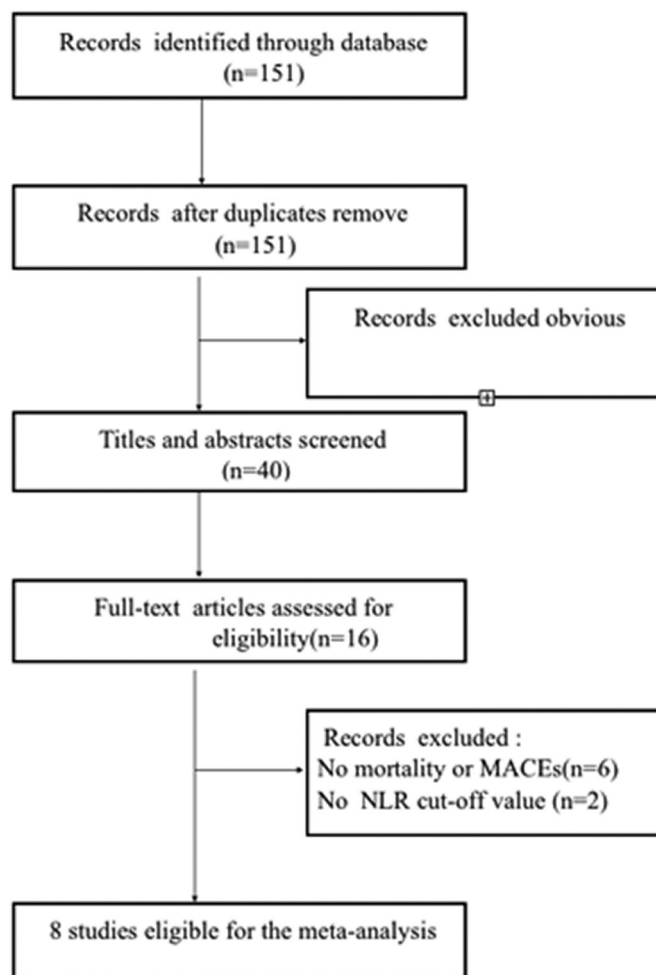


Fig. 1. Flow chart for selection of published eligible studies for the meta-analysis.

obtained by multivariate analysis. According to the Newcastle-Ottawa scale (NOS), all cohort studies were of high quality and had scores of seven or more.

### 3.2. NLR and medium to long-term mortality/MACEs

The combined analysis of 7 cohorts covering 9089 patients described the association between NLR and medium to long-term mortality/MACEs [22–24,26–28]. The pooled outcome for high NLR value group was found to be 1.26 (95%CI 1.13–1.41) when compared with low NLR value ( $p < 0.0001$ , random effects, Fig.2). Due to extreme heterogeneity between studies ( $I^2 = 87.2\%$ ,  $p < 0.000$ ), we conducted four subgroup analysis according to the study region (western countries and eastern countries), sample size (size  $\geq 500$  and size < 500), NLR cut-off value (value  $\geq 5.0$  and value < 5.0) and ACS subtype (STEMI, NSTEMI-ACS and Mixed). When grouped based on study region, pretreatment NLR predicted medium to long-term mortality/MACEs in Asian (OR 1.18, 95%CI 1.04–1.34,  $p < 0.001$ , random effects) and European countries (OR 2.11, 95%CI 1.07–4.18,  $p < 0.001$ , random effects). The prognostic role of pretreatment NLR in predicting mortality/MACEs was obvious in researches with large sample size (size  $\geq 500$ ) (OR 1.22, 95%CI 1.07–1.40,  $p = 0.003$ , random effects). However, analysis showed no significant differences in small sample size (size < 500) (OR 1.79, 95%CI 0.97–3.29,  $p = 0.061$ , random effects). In comparison with subtype of ACS patients, similar results were identified in STEMI group (OR 2.76, 95%CI 1.77–4.31,  $p < 0.001$ , fixed effects) and Mixed group (OR 1.17, 95%CI 1.04–1.31,  $p = 0.010$ , random effects), except that no significant differences in NSTEMI-ACS

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