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Impact of neutrophils to lymphocytes ratio on major clinical outcomes in patients with acute coronary syndromes: A systematic review and meta-analysis of the literature

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ABSTRACT

Background: Inflammatory markers are significantly associated with cardiovascular disease. The ratio between neutrophils and lymphocytes (NLR) is a potential new biomarker, which can single out individuals at risk for future cardiovascular events. Among total white blood cell count (WBC) and its subtypes, NLR seems to have the greatest predictive value for death and major adverse cardiovascular events (MACE) in patients with acute coronary syndrome (ACS). We conducted a meta-analysis of the literature to assess the relation between NLR and cardiovascular outcomes in STEMI/NSTEMI patients.

Methods: MEDLINE and EMBASE databases were searched. Two reviewers selected studies and extracted data. Pooled results were reported as odds ratios (ORs) and were presented with the corresponding 95% confidence intervals (CI).

Results: Twenty-three studies for a total of >16,000 patients were included. Compared to those with low NLR, high NLR on-admission was associated with a higher overall mortality both in patients with STEMI (OR: 4.60, 95% CI: 2.84–7.45; $P < 0.00001$) and in patients with NSTEMI (OR: 6.41, 95% CI: 2.65–15.50; $P < 0.00001$). An increased MACE risk was found in STEMI patients with high NLR (OR: 3.71, 95% CI: 2.67–5.17; $P < 0.00001$). Post-PCI mortality risk was significantly increased in patients with high NLR (OR: 3.76, 95% CI: 2.64–5.34; $P < 0.00001$).

Conclusions: In this large meta-analysis on prognostic significance of NLR in ACS we found that on-admission high NLR in patients with STEMI/NSTEMI appeared to affect clinically important outcomes including both in-hospital and long-term mortality and MACE.

1. Introduction

Increasing evidence indicates that inflammation plays an important role in the pathogenesis and the progression of atherosclerosis, participating to a number of events such as endothelial lesion, plaque formation and its disruption [1,2]. In particular, it has been demonstrated that inflammatory markers such as white blood cell count (WBC), erythrocyte sedimentation rate, C-reactive protein (CRP) and interleukin-6 are significantly associated with cardiovascular disease [3,4]. Above all, the ratio between the absolute number of neutrophils and the number of lymphocytes (NLR) has recently emerged as a potential new biomarker [5], which can single out individuals at risk for future cardiovascular events. Among total white blood cell count (WBC) and its subtypes, neutrophils to lymphocytes ratio (NLR) appeared to have the greatest predictive power for death [6,7] and major adverse cardiovascular events (MACE) [5] in patients with acute coronary syndrome (ACS) [8]. Our previous systematic review highlighted the potential application of this inexpensive and readily available inflammatory marker for risk stratification in patients with ACS and/or cardiac revascularization [9].

In addition, it has been suggested that NLR could be useful in predicting short- and long-term mortality after ST-segment elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention (PCI) [9,10]. Therefore, we conducted a meta-analysis of the literature with the aim of identifying all the available evidence to clarify the role of NLR as a prognostic risk factor in patients with ACS with or without PCI.

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2. Methods

A protocol was developed, detailing the specific objectives, criteria for study selection, and approach to assess study quality, outcomes, and statistical methods. Our primary endpoint was to evaluate the association between mortality rate and NLR in patients with STEMI/NSTEMI. As a secondary endpoint, the association between MACE and NLR was evaluated.

2.1. Study identification

We tried to identify all published studies that evaluated the role of neutrophils as a risk factor for clinical outcomes using MEDLINE (1999 to 2017, week 7) and EMBASE (1999 to 2017, week 7) electronic databases. The search strategy was developed without any language restriction. We used the medical subject headings and text words as reported in appendix. We decided not to include studies published before 1999, since patients included in older studies may not be representative of currently treated patients with ACS or undergoing cardiac PCI in our clinics due to the difference in cardiovascular therapies and surgical techniques. We supplemented our search by manually reviewing the reference lists of all retrieved articles for additional published or unpublished trials. The research of the literature was performed independently by two investigators (ON, FZ).

2.2. Data extraction

Two investigators (ON, MG) independently extracted data on study (year of publication, design, study centre) and patients' characteristics (number of subjects studied, mean age, variation in age, gender and race) as well as on clinical outcomes (death, development of a new episode or a recurrence of MI, UA or development or worsening of HF, re-hospitalization, stroke).

2.3. Study selection

Studies were included if they met the following criteria: 1) patients had a diagnosis of objectively confirmed ACS; 2) information on neutrophils was provided (including NLR); 3) at least one of the following clinical outcomes was evaluated during the acute phase or after a follow-up: death or development of major adverse cardiovascular events (MACE) (a new episode or a recurrence of MI, UA, ACS, development or worsening of heart failure (HF), re-hospitalization or stroke); 4) patients were 18 years or older. Only studies written in English language were included. We excluded all the studies in which cardiovascular disease was diagnosed on the basis of clinical symptoms only and not confirmed by objective data. Diagnosis of acute MI with ST elevation was defined as >30 min of continuous typical chest pain and ST-segment elevation ≥2 mm in 2 contiguous electrocardiography leads within 12 h of the symptom onset or within up to 18 h if there was evidence of continuing ischemia or hemodynamic instability. UA/NSTEMI was defined as electrocardiographic (ECG) prominent T-wave inversion or ST-segment depression and/or positive biomarkers of necrosis (e.g., troponin, creatine kinase-MB [CK-MB]) in the absence of ST-segment elevation and in an appropriate clinical setting (anginal equivalent or chest discomfort). Detailed information on all patients was also collected, including medical history as well as results from physical examination and laboratory examination (i.e. routine blood test, routine urine test, biochemical series, ECG, transthoracic echocardiography).

To assess the agreement between reviewers for study selection, we used the *k* statistic, which measures agreement beyond chance [11,12].

2.4. Study validity assessment

Two unmasked investigators (ON, FD) independently completed the assessment of study validity.

Given the characteristics of the included studies, the methodological quality of each study was also evaluated with the Newcastle-Ottawa Scale (NOS), a scale specifically developed to assess the quality of non-randomized observational studies [13]. The scoring system encompasses the following eight items: clear definition of study sample, selection, interventions, outcomes, adequate assessment of the outcome, analyses for comparability, adequate length of follow-up, and appropriate interpretation of results. If an item was adequately addressed, 2 points were awarded for analyses for comparability and 1 point each for the other seven specific items. This results in a quality score between 0 and 9. A total of at least 8 points defined high-quality studies; otherwise the studies were defined as low-quality.

2.5. Statistical analysis

Statistical analysis was carried out using Review Manager [Version 5.2, The Cochrane Collaboration, Copenhagen, Denmark] provided by The Cochrane Collaboration.

Associations between NLR and overall mortality (long-term and in-hospital), and between NLR and MACE in patients with ACS were evaluated.

Pooled results were reported as odds ratio (OR) and were presented with 95% confidence interval (CI) and with two-sided probability values. A P value of 0.05 or less was considered statistically significant. Weighted mean incidence (WMI) of the outcomes in patients with different NLR values was presented with the corresponding 95% CI.

Statistical heterogeneity among studies was assessed with Chi-square Cochran's Q test and with I^2 statistic, which measured the inconsistency across study results and described the proportion of total variation in study estimates due to heterogeneity rather than sampling error. In detail, I^2 values of 0% indicate no heterogeneity, 25% low, 25–50% moderate, and 50% high heterogeneity [10]. Heterogeneity was considered statistically significant when $P < 0.10$. Finally, funnel plots of effect size against standard error were completed, whenever possible, to assess the presence of publication bias. Visual inspection of funnel plot asymmetry was performed to address possible small-study effect, and Egger's test was used to assess publication bias, over and above any subjective evaluation. A $P < 0.10$ was considered statistically significant [14,15].

We repeated the analyses stratifying studies according to the NOS and including only high quality studies.

Finally, we provided separate results for the association between NLR and overall mortality/major cardiovascular outcomes in STEMI patients treated with PCI.

3. Results

3.1. Study identification and selection

We identified 1318 potentially relevant studies from EMBASE and MEDLINE databases. We excluded 1191 studies after title and abstract screening using predefined inclusion and exclusion criteria; the remaining 103 studies were retrieved in full for detailed evaluation. Of the 103 retrieved studies, 80 were excluded for the following reasons: some of them did not match inclusion criteria, others were editorial or narrative review. Twenty-three studies were therefore included in this meta-analysis. Inter observer agreement for study selection was good ($K = 0.81$).

The study identification and the selection progression are detailed in Fig. 1.

3.2. Study characteristics and clinical outcomes

Of the 23 included studies, 9 were prospective and 14 retrospective. Studies' size ranged from 204 to 2833 patients, for a total of >16,000 patients. The association between clinical outcomes and neutrophils was reported as NLR. For the purpose of this meta-analysis high NLR was defined as the highest tertile, quartile, quintile or half of the whole sample of NLR values in 12, 2, 1 and 7 studies respectively.

Thirteen out of 23 studies had mortality rate as endpoint and ten reported data on NLR and MACE (Table 1). Follow up duration, definition of MACE and prevalence of potential risk factors for a bad outcome (diabetes and cardiogenic shock at the time of the presentation) were summarized in Table 2.

3.3. Study quality

Results of the study quality assessment according to the NOS are reported in Table 1. Fourteen studies obtained at least 8 points and were considered as high quality.

3.4. NLR and mortality rate

Fourteen studies evaluated the association between NLR and overall mortality (4072 patients with high NLR and 2771 patients with low NLR) in patients with STEMI. High NLR value resulted significantly associated with a higher mortality risk (OR: 4.60, 95% CI: 2.84–7.45; $P < 0.00001$). Heterogeneity among the studies was substantial ($I^2 = 74\%$; $P < 0.00001$) (Fig. 2). In this group of patients in-hospital mortality was evaluated in eight studies (2337 patients with high NLR and 3205 patients with low NLR). High NLR value resulted significantly associated with a higher in-hospital mortality (OR: 3.80, 95% CI: 2.06–6.99; $P < 0.00001$) with a significant heterogeneity among the studies ($I^2 = 64\%$; $P = 0.006$). Nine studies evaluated the association between NLR and long-term mortality in patients with STEMI (1885 patients with high NLR and 3121 patients with low NLR). Included studies had a median follow up of 53.82 months [interquartile range 6.0–60.2 months]. High NLR value was significantly associated with a higher long-term mortality (OR: 4.62, 95% CI: 2.64–8.06; $P < 0.00001$, $I^2 = 66\%$; $P = 0.0001$). Heterogeneity among the studies was substantial ($I^2 = 80\%$; $P < 0.00001$).