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Usefulness of Neutrophil/Lymphocyte Ratio as a Predictor of Atrial Fibrillation: A Meta-analysis

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Background and Aims. Current evidence suggests that a high neutrophil/lymphocyte ratio (NLR) may increase the risk of atrial fibrillation (AF), but this association is still uncertain. The aim of the comprehensive meta-analysis was to evaluate the potential association between NLR and the risk of AF.

Methods. We conducted a systematic literature search using electronic databases (PubMed, Ovid, Embase, Cochrane Database and Web of Science) to identify the studies reporting the association between NLR and risk of AF. We searched the literature published January 2015 or earlier. We used both fixed-effects and random-effects models to calculate the overall effect estimate. An $I^2 > 50\%$ indicates at least moderate statistical heterogeneity. A sensitivity analysis and subgroup analysis were performed to find the origin of heterogeneity.

Results. We retrieved 11 studies involving a total of 2,766 participants. The combined odds ratio (OR) of incident AF for baseline NLR level was 1.25 (95% confidence interval [CI] 1.16–1.35) with significant heterogeneity across studies ($I^2 = 82.7\%$, $p < 0.01$) and for the post-NLR level (following CABG, RFCA and cardioversion) was 1.518 (95% CI 1.076–2.142) with significant heterogeneity across studies ($I^2 = 93.7\%$, $p = 0.017$). We also showed an association between AF recurrence following CABG, RFCA and cardioversion and baseline NLR level (OR 1.517, 95% CI 1.108–2.079) with significant heterogeneity across studies ($I^2 = 86.8\%$, $p < 0.01$).

Conclusions. Our comprehensive meta-analysis suggests that the high level of NLR, whether baseline or postsurgery/procedure, is associated with the increased risk of AF recurrence/occurrence.

Key Words: Neutrophil/lymphocyte ratio, Atrial fibrillation, Inflammation, Marker, Meta-analysis.

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and increases the risk of stroke and death. The role of inflammation in the development of AF is well demonstrated. The relationship between various inflammatory biomarkers and AF has been established in the past few years and several anti-inflammatory therapies are related to AF risk reduction. Elevation of inflammatory biomarkers such as high-sensitive C-reactive protein (hs-CRP) has been associated with increased risk of AF recurrence following successful electrical cardioversion (1,2) and catheter ablation (3). Neutrophil/lymphocyte ratio (NLR) has emerged as a novel systemic inflammatory marker and a prognostic indicator of adverse cardiovascular diseases (4,5). Neutrophils represent activated non-specific inflammation and lymphopenia is a marker of poor general heath and physiological stress. NLR reflects the balance between the neutrophil and lymphocyte levels and integrates these two important and opposite immune pathways, which

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has served as a measure of both systemic inflammation and stress response. Recently, some studies (6–12) have evaluated the potential association between NLR and development of AF. However, others (13–16) showed that this association does not exist, which yielded conflicting results. In this comprehensive meta-analysis, we aimed to further investigate the potential association between NLR and risk of AF.

Methods

Search Strategies

Two reviewers (QS and KC) systematically and independently searched the online databases of PubMed, Ovid, Embase, Cochrane Database and Web of Science to identify relevant studies. We used the following keywords: 'Neutrophil/lymphocyte ratio' or 'NLR' and 'atrial fibrillation'. Titles and abstracts as well as the reference lists of all of the identified reports were examined independently in duplicate by two reviewers (QS and KC) to include potentially relevant studies published before January 2015. Additionally, a manual search was conducted on the scientific sessions of the American College of Cardiology, the American Heart Association, and the European Society of Cardiology during the past 5 years. Finally, we contacted relevant experts and pharmacological companies to obtain unpublished data.

Inclusion Criteria

Studies were included if they met the following criteria: a) the study design was a prospective cohort study, retrospective cohort study and case–control studies. Individual case reports, editorials, and review articles were excluded; b) measured NLR at baseline or after surgery, cardioversion and documented clinical outcome during follow-up; c) the hazard ratio (HR) or odds ratio (OR) and the corresponding 95% confidence interval (CI) for NLR and the occurrence of AF were reported; d) only studies where diagnosis of AF is clearly defined and in accordance with current guideline based definitions were selected. We included published and unpublished studies without language restriction.

Study Selection

Two independent reviewers (Q.S. and K.C.) screened the abstracts or titles of the studies from the electronic search to identify all potential eligible studies. Potentially relevant reports were then retrieved as complete manuscripts and assessed for compliance with the inclusion criteria. Any uncertainties or discrepancies between the reviewers were resolved through consensus after rechecking the source data and consultation with the third reviewer (TL).

Data Extraction

Two blinded reviewers (QS and KC) independently performed data extraction using a standard data extraction form to determine eligibility for inclusion. We extracted and analyzed all the multivariate adjusted HR/OR and the corresponding 95% CI to evaluate NLR in predicting the risk of AF occurrence. The extracted data elements of this study included first author's last name, publication year, study design, study population, sample size, participants' age and sex, duration of follow-up, methods of AF detection and rates of AF recurrence.

Quality Assessment

To limit the heterogeneity secondary to differences among study designs, the quality of each study was evaluated according to the guidelines developed by the United States Preventive Task Force (17) and the Evidence-Based Medicine Working Group (18). A point score system was applied according to the quality of the study. The following characteristics were assessed: a) clear inclusion and exclusion criteria; b) study sample representative for the mentioned population; c) explanation of sample selection; d) full specification of clinical and demographic variables; e) follow-up at least 3 months; f) reporting loss of follow-up; g) clear definition of AF; h) clear definition of outcomes and outcome assessment; i) adjustment of potential confounders in multivariate analysis. Studies were graded as poor quality if they met <5 criteria, fair if they met 5–7 criteria, and good if they met ≥ 8 criteria.

Statistical Analysis

Pooled effect sizes were presented as the OR with 95% CI. HR value in each primary study was directly considered as OR. To evaluate the heterogeneity across studies, we used I^2 derived from the χ^2 test, which describes the percentage of the variability in effect estimates resulting from heterogeneity rather than sampling error. An $I^2 > 50\%$ indicates at least moderate statistical heterogeneity. When pooled analysis resulted in significant heterogeneity, the random effects model was used. We conducted fixed effects meta-analysis using the inverse variance method for pooling effect sizes, and random effects meta-analysis using the inverse variance heterogeneity method. Sensitivity analysis was also done in a random predefined manner. We also performed subgroup analysis on the study design (cohort study or case–control study), duration of follow-up (≥ 3 months or <3 months) and sample size (≥ 300 or <300), AF occurrence after coronary artery bypass grafting (CABG) or radiofrequency catheter ablation (RFCA) or cardioversion (CV). Publication bias was evaluated using the funnel plot. Statistical significance was defined as a two-tailed p value of 0.05. All statistical analyses were performed using STATA 11 (Stata Corp LP, College Station, TX).