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Review

Prognostic role of the neutrophil-to-lymphocyte ratio in pancreatic cancer: A meta-analysis containing 8252 patients

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ABSTRACT

Several studies were carried out to explore the prognostic role of neutrophil-to-lymphocyte ratio (NLR) in pancreatic cancer, however, with contradictory results. The objectives of this study were to summarize the prognostic value of NLR in pancreatic cancer. Embase, PubMed and Cochrane Library were comprehensively retrieved. All the cohort studies focusing on the prognostic value of NLR in pancreatic cancer were eligible. 37 papers containing 43 cohort studies with pancreatic cancer were finally included into this study. The results presented that patients with low NLR might have longer OS when compared to the patients with high NLR (HR = 1.81, 95%CI = 1.59–2.05, P < 0.00001; I^2 = 82%). Similar results were detected in the subgroup analyses of OS, which was based on the analysis model, ethnicity, treatment, sample size and cut-off value. In additions, low NLR was significantly associated with longer DFS when compared to high NLR in pancreatic cancer (HR = 1.66, 95%CI = 1.17–2.35, P = 0.005; I^2 = 67%). Moreover, patients with low NLR had significantly smaller tumor size (P = 0.0007), better differentiation (P = 0.003), earlier stage (P = 0.02) and low CA-199 level (P = 0.007). In conclusion, it was revealed that low NLR was a favorable predictor of OS and DFS in patients with pancreatic cancer, and NLR is a promising prognostic biomarker for pancreatic cancer.

1. Introduction

Pancreatic cancer is one of the most common digestive system neoplasms, which is the fourth leading cause of cancer deaths in the United States, and causes estimated 227,000 deaths a year around the world [1,2]. Risk factors of pancreatic cancer include age, tobacco smoking, and nutrition conditions. Some benign diseases such as chronic pancreatitis and diabetes mellitus, as well as some germline diseases including hereditary pancreatitis and Familial atypical mole–multiple melanoma (FAMMM) are also closely related to pancreatic cancer [3,4]. Although great developments have been made in the early diagnosis and treatment of pancreatic cancer, the prognostic outcomes of patients with pancreatic cancer remains disappointing. And it is reported that the 5-year overall survival (OS) is lower than 7% for patients with pancreatic cancer, even those receiving curative surgery have an OS no > 25% [4].

In view of the disappointing prognosis of patients with pancreatic cancer, more and more researchers turn their attentions to the biomarkers to predict the prognosis and optimize the treatment. And the interesting biomarkers includes carbohydrate antigen 19-9 (CA19-9), Eastern Cooperative Oncology Group system (ECOG), C-reactive protein (CRP) and so on [5,6]. However, there's still in lack of prognostic biomarkers with enough sensitivity and specificity.

Chronic pancreatitis, characterized by the persistent inflammation of the pancreas, is one of the leading risk factors of pancreatic cancer [7]. Pancreatic cancer itself, would in turn trigger inflammatory response by both actively secreting and passively releasing pro-inflammatory cytokines [8,9]. In additions, chemotherapies and radiotherapies could also affect the tumor microenvironment (TME), thus promoting the inflammatory response in pancreatic cancer [10]. And systemic inflammatory response (SIR) has been proved to be associated with prognosis of various tumors [11]. Recently, several studies have investigated the possibilities of using neutrophil-to-lymphocyte ratio (NLR), another inflammation biomarker, as a prognostic biomarker of pancreatic cancer [12–15]. NLR is the ratio of two immune cells and can be easily obtained by blood cell count. Previous studies presented that level of NLR might be significantly associated with the prognosis in several tumors, including colorectal cancer [13], lung cancer [16], urologic cancer [17], gastric cancer [18], esophageal cancer [19] and so on.

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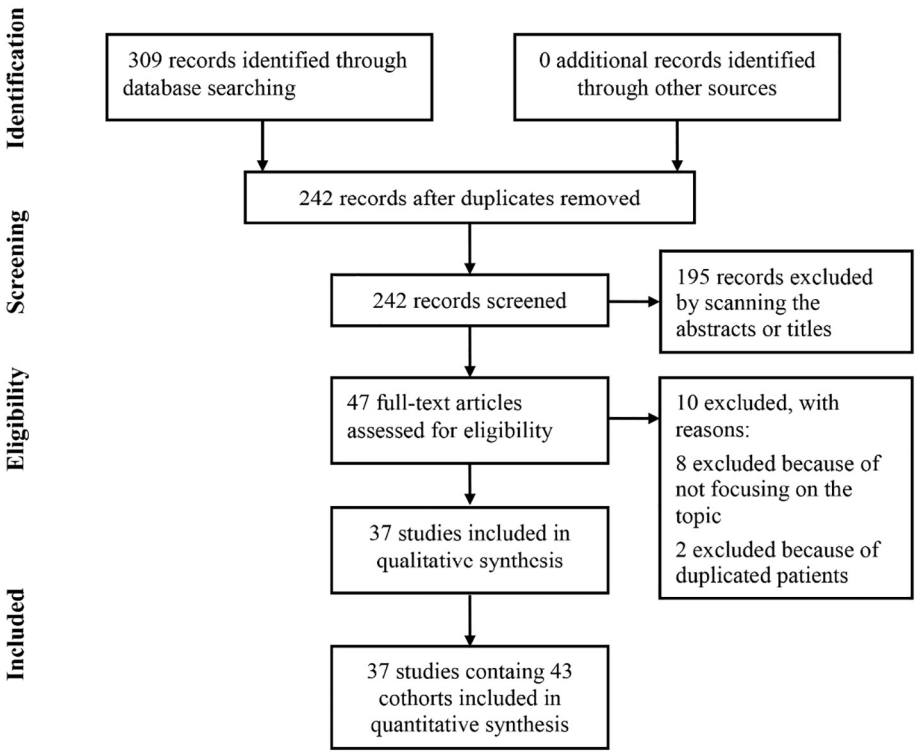

Fig. 1. Flow diagram of study selection process.

Currently, only two meta-analyses focused on the prognostic significance of NLR for pancreatic cancer, which only included 9 cohorts and 11 cohorts, respectively [20,21]. The limited included studies of these two meta-analyses heavily decreased the convening and applicability of the conclusion [20,21]. Besides, in Cheng et al. study, no subgroup analysis has been done to deal with the existing heterogeneity. Simply pooling the results of different studies with different baseline, demographic features and different cut-off values of NLR have rendered their study more susceptible to various risk of biases [20]. Meanwhile, more new studies focusing on the association between NLR and prognosis in pancreatic cancer have been conducted, still with controversial results [22–25]. Therefore, the current meta-analysis containing more studies was conducted to comprehensively explore the association between NLR and prognosis in pancreatic cancer.

2. Materials and methods

This study was performed in compliance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) for reporting systemic review and meta-analysis [26].

2.1. Search strategy

A search of three databases including PubMed, Embase and the Cochrane Library was performed up to the date of May 29, 2017. And the search strategy was "((((pancreatic cancer) OR pancreatic neoplasm)) AND ((((((neutrophil lymphocyte ratio) OR NLR)) OR neutrophilic leukocytosis)) OR neutrophil-lymphocyte ratio))". We also reviewed the references of the retrieved articles to avoid missing relative articles.

2.2. Inclusion and exclusion criteria

The inclusion criteria are as follows: (i) observational studies with cohorts (ii) focusing on the association between NLR of peripheral blood and prognosis in pancreatic cancer (iii) reporting OS, disease-free survival (DFS), progression-free survival (PFS), time to progression (TTP), local recurrence (LR), distant disease-free survival (DDFS) and time to treatment failure (TTF); (IV) full text is accessible. The exclusion criteria are as follows: duplicate publications, literature reviews, systematic reviews, case reports or case series, animal experiments or cell experiments, required data are not available even after correspondence with the authors.

2.3. Data extraction and quality assessment

With a data extraction template designed in advance, the following data were collected by two reviewers independently: the first author's name, publication year, country in which the study was carried out, treatment for patients, sample size, cut-off value of NLR, stages of the included patients, analysis model, endpoint measures as well as some clinical parameters and information needed to evaluate the quality of each study. Any discrepancies during study selection and data extraction were resolved by discussion and consultation with another reviewer. The HRs of OS, DFS, RFS, PFS and DDFS obtained directly or indirectly from published articles were integrated in the meta-analysis according to the study conducted by Tierney et al. [27]. Two reviewers evaluated all the included studies independently after reading the full text of each study. The Newcastle–Ottawa scale (NOS) was used to evaluate the quality of the included studies [28]. A value of Cohen's Kappa was calculated to evaluate the level of agreement between two reviewers.

2.4. Statistical analysis

All statistical analyses were conducted using Review Manager 5.3 (Cochrane Collaboration) and STATA 12.0 software (Stata Corp., College Station). For OS and disease-free survival (DFS) outcome, hazard ratios (HR) and corresponding 95% CI were used as the summary measure. While for clinical parameters, the odds ratios (OR) and corresponding 95%CI was used. Inter-study heterogeneity was assessed using Chi-square test and I^2 statistic. The $I^2 < 50\%$ indicates that the heterogeneity was not statistically significant, thus the fixed-effect model was used. If the I^2 no $< 50\%$, there is a significant heterogeneity