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META-ANALYSIS

Prognostic significance of neutrophil to lymphocyte ratio in pancreatic cancer: A meta-analysis

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Abstract

AIM: To conduct a meta-analysis evaluating the association between the peripheral blood neutrophil to lymphocyte ratio (NLR) and the outcome of patients with pancreatic cancer.

METHODS: Studies evaluating the relationship between the peripheral blood NLR and outcome of patients with pancreatic cancer published up to May 2014 were searched using electronic databases, including PubMed, Web of Science, Embase and Ovid. A meta-analysis was performed to pool the hazard ratios (HRs) or odds ratios (ORs) and their 95% confidence intervals (CIs) using either a fixed-effects model or a random-effects model to quantitatively assess the prognostic value of NLR and its association with clinicopathological parameters.

RESULTS: Eleven studies containing a total of 1804 patients were eligible according to our selection criteria, and combined hazard ratios indicated that high NLR was a poor prognostic marker for pancreatic cancer patients because it had an unfavorable impact on the overall survival (OS) (HR = 2.61, 95%CI: 1.68-4.06, P = 0.000) and cancer specific survival (HR = 1.66, 95%CI: 1.08-2.57, P = 0.021). Subgroup analysis revealed that high NLR was associated with poor OS in patients with mixed treatment (HR = 4.36, 95%CI: 2.50-7.61, P = 0.000), chemotherapy (HR = 2.08, 95%CI: 1.49-2.9, P = 0.000), or surgical resection (HR = 1.2, 95%CI: 1.00-1.44, P = 0.048). Additionally, high NLR was significantly correlated with tumor metastasis (OR = 1.69, 95%CI: 1.10-2.59, P = 0.016), poor tumor differentiation (OR = 2.75, 95%CI: 1.19-6.36, P = 0.016), poor performance status (OR = 2.56, 95%CI: 1.63-4.03, P = 0.000), high cancer antigen 199 (OR = 2.62, 95%CI: 1.49-4.60, P = 0.000), high C-reactive protein (OR = 4.32, 95%CI: 2.71-6.87, P = 0.000), and low albumin (OR = 3.56, 95%CI: 1.37-9.27, P = 0.009).

CONCLUSION: High peripheral blood NLR suggested a poor prognosis for patients with pancreatic cancer,

and it could be a novel marker of survival evaluation and could help clinicians develop therapeutic strategies for pancreatic cancer patients.

Key words: Neutrophil to lymphocyte ratio; Pancreatic cancer; Overall survival; Cancer specific survival; Clinicopathological features; Meta-analysis

Core tip: We performed a meta-analysis to evaluate the relationship between the peripheral blood neutrophil to lymphocyte ratio (NLR) and outcome of patients with pancreatic cancer. The results showed that high NLR was a poor prognostic marker and high NLR was associated with poor overall survival in patients with mixed treatment, chemotherapy, or surgical resection. Furthermore, high NLR was significantly correlated with tumor metastasis, poor tumor differentiation, poor performance status, high carbohydrate antigen 199, high C-reactive protein, and low albumin. This is the first comprehensive and detailed analysis for evaluating the prognostic value of the NLR and its association with the clinicopathological features for pancreatic cancer patients. NLR might be a novel marker of the survival evaluation for pancreatic cancer patients.

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INTRODUCTION

As one of the most common cancers with a high degree of malignancy, pancreatic cancer is the fourth leading cause of cancer-related death worldwide[1]. Although therapeutic strategies have been improved in recent years, the prognosis of pancreatic cancer patients remains disappointing. Only 4% of pancreatic cancer patients live five years or longer after diagnosis, and 80%-85% of diagnosed patients lose the opportunity for radical surgery[2]. Currently, individual treatment for pancreatic cancer receives substantial attention[3,4]. To take appropriate measures for individual treatment in patients with pancreatic cancer, looking for biomarkers for evaluating the prognosis is especially urgent. On one hand, traditional prognostic markers for pancreatic cancers are clinicopathological parameters, most of which are determined after surgery, and these clinicopathological features are invalid for predicting pancreatic cancer prognosis before treatment. On the other hand, with the progress in molecular pathology, large cohorts of molecules have been suggested to predict pancreatic cancer prognosis[5-8]; however, these molecular markers are still not in widespread use because they are not applicable for external validation and are not routinely measured in the clinic. Therefore, seeking novel, convenient and practical biomarkers is necessary.

An increasing body of evidence shows that systemic inflammation activation exerted by cancer cells anticipates tumor progression *via* inducing cancer proliferation and metastasis or promoting angiogenesis and repairing DNA damage[9-11]. Several systemic inflammatory biomarkers have been investigated to predict the prognosis in various cancers, such as C-reactive protein (CRP)[12], neutrophil-to-lymphocyte ratio (NLR)[13], platelet-to-lymphocyte ratio, and modified Glasgow Prognostic Score[14]. Among these biomarkers, elevated NLR has been shown to be the most valuable for predicting the prognosis of various cancer types besides pancreatic cancer[15-17]. Several studies have evaluated the correlation between high NLR and the outcome of patients with pancreatic cancer, but the conclusions are not consistent, which may be due to the different sample size, NLR cutoff value, different treatments or genetic heterogeneity in these studies. Therefore, it is necessary to conduct a meta-analysis that combines these studies and to identify the prognostic value of NLR in patients with pancreatic cancer. In this research, we pooled the data from eligible studies that focus on the relationship between elevated NLR and the overall survival (OS) or cancer specific survival (CSS) in patients with pancreatic cancer; we also investigated the correlation between elevated NLR and clinicopathological parameters in pancreatic cancer.

MATERIALS AND METHODS

Study selection

We searched for relevant studies that focused on the relationship between NLR and the outcome of patients with pancreatic cancer using Pubmed, Embase, Ovid, and Web of Science databases in May 2014. The search strategy was conducted with the following terms: (neutrophil to lymphocyte ratio or NLR) AND (pancreatic cancer or pancreatic tumor), and only studies in English were reviewed. The references in the relevant studies were also searched. If there were doubts about the original articles, we asked the authors to supply additional information. Two investigators extracted all data from the original articles, and consensuses were reached by discussion if there were disagreements.

Inclusion and exclusion criteria

Studies meeting the following criteria were included: (1) the NLR was measured with a peripheral blood test before treatment; (2) the relationship between the NLR and outcome of patients with pancreatic cancer was provided; and (3) when the same authors reported the same patient populations in different articles, only the most comprehensive one was included. Studies with

the following were excluded: (1) reviews, meetings, abstracts, expert opinions, and case reports; (2) overlapping data; and (3) data were not extracted.

Outcomes and clinicopathological feature definitions

The NLR was defined as the pretreatment blood neutrophil count divided by the lymphocyte count. The mixed treatment group was defined as patients treated with combined therapies or different people with different therapies. The chemotherapy group was defined as those patients receiving chemotherapy according to the original article description. The surgical resection group was defined as those patients who underwent surgery. Distant tumor metastasis was defined as either originally reported or TNM Ⅳ stage. Elevated CA199, CRP, and low albumin levels were defined as originally reported. A poor performance status was defined as those with two-point scores or more. Tumor differentiation was separated into two groups, those with poor differentiation were grouped as poor, and the remainders were moderate. The OS, CSS, and disease free survival (DFS) were used as reported in the original article.

Qualitative assessment

All of the studies included in this research were assessed by referring to the Newcastle-Ottawa quality assessment scale (NOS) for cohort studies[18].

Meta-analysis

All calculations of the extracted data were performed using Stata 11.0; eligible studies were divided into two groups to evaluate the relationship between the NLR and the outcome of patients using the data for OS or CSS. Hazard ratios (HRs) and 95% confidence intervals (CIs) were pooled to obtain the effective value. If HRs and 95%CIs were directly provided in the original studies, crude data were used; otherwise, they were extracted from the survival curves according to the methods reported by Tierney *et al*[19]. For the analysis of the correlation between high NLR and clinicopathological features, odds ratios (ORs) and the 95%CIs were pooled to obtain the effective value. Heterogeneity between studies was evaluated using the χ^2 and I^2 tests. If $I^2 \geqslant 50\%$ and $P < 0.1$, there was significant heterogeneity; afterwards, subgroup analysis was performed using a random-effects model to combine the effective value. If there was no heterogeneity, a fixed-effects model was used to pool the HRs or ORs. An HR > 1 indicated a poor prognosis in patients with a high NLR; an OR > 1 demonstrated that a high NLR was correlated with poor tumor differentiation, a high incidence of distant tumor metastasis, poor performance status, high level of CRP, high levels of CA199, and low levels of albumin. The pooled HR or OR was considered to be statistically significant at $P < 0.05$ if 95%CIs did not overlap "1". Publication bias was evaluated in each combined study using Egger's test; significant bias existed if $P < 0.05$.

RESULTS

Selection and characteristics of studies

After searching comprehensive literature and checking references lists, 66 studies that mentioned the association between the NLR and pancreatic cancer were reviewed, of which 55 were excluded because they are either reviews, reference abstracts, or irrelevant to the patient outcomes. One study on the association between the NLR and DFS was acceptable; however, it was excluded because there was only one publication with a DFS assessment, meaning that there was not enough data for pooling[20]. Finally, ten studies conducted in five countries (China, United Kingdom, Australia, Ireland, and Japan) met the inclusion criteria[21-30]. One of them reported two groups of pancreatic cancer patients, and the relationship between the NLR and CSS was available in each group[30]; therefore, 11 groups, consisting of 1804 patients, were eligible for the meta-analysis. The basic characteristics of the included studies are shown in Table 1. The NLR cutoff values ranged from 2.3 to 5, and the sample sizes ranged from 65 to 474. The prognostic impact of high NLR on the OS was evaluated in eight studies (Figure 1A). Three studies evaluated the NLR for outcomes of patients who had undergone surgery, chemotherapy, radiotherapy or the combination of these treatments (grouped as the mixed treatment group)[22,24,26]; four studies that evaluated NLR for palliative chemotherapy outcomes were classified as the chemotherapy group[21,23,27,28]; and one study that evaluated the NLR for outcomes of patients who had undergone surgical resection was defined as the surgical resection group[25]. The prognostic impact of high NLR on the CSS was assayed in three groups of patients (Figure 1B). The HR data for nine groups were provided in the original multivariate analysis, while the data for the other two groups were deduced from survival curves. The scores of all groups, which were estimated by the Newcastle-Ottawa quality assessment scale, indicated that a favorable methodology was used in each study.

Prognostic impact of the NLR on the OS

HRs from eight groups of patients were combined to evaluate the prognostic impact of the NLR on OS. We found that a high NLR was a poor prognostic marker for pancreatic cancer patients because it had an unfavorable impact on the OS (HR = 2.61, 95%CI: 1.68-4.06, $P = 0.000$, Figure 1A), and significant heterogeneity was observed among these groups ($\chi^2 = 45.71$, $I^2 = 84.7\%$, $P = 0.000$). When subgroup analysis was conducted according to therapy, the following interesting results were observed: combined data from three groups of patients with different therapies indicated that high NLR significantly correlated with poor OS (HR =

Table 1 Baseline characteristics of the included studies

Ref.	Country	Treatment	NLR cutoff, *n*	HR estimation	Outcome measured	Sample/high NLR, *n*	HR(95%CI)	Study quality (points)
Martin *et al*[21]	Austria	Chemo	5	HR	OS	124/64	1.6 (1.07-2.4)	8/9
Wang *et al*[22]	China	Mix	5	HR	OS	177/32	2.537 (1.313-4.902)	6/9
Xue *et al*[23]	Japan	Chemo	5	HR	OS	252/40	1.92 (1.27-2.9)	6/9
Sugiura *et al*[24]	Japan	Mix	4	Survival curve	OS	83/36	6.4 (2.85-14.34)	8/9
Bhatti *et al*[25]	United Kingdom	Sur	4	HR	OS	84/13	1.2 (1.01-1.449)	7/9
Aliustaoglu *et al*[26]	Japan	Mix	5	Survival curve	OS	65/9	5.42 (2.96-9.91)	7/9
Teo *et al*[27]	Ireland	Chemo	3	HR	OS	85/58	2.93 (1.59-5.64)	5/9
An *et al*[28]	China	Chemo	5	HR	OS	89/16	4.489 (1.372-14.692)	7/9
Szkandera *et al*[29]	Austria	Mix	2.3	HR	CCS	474/271	1.24 (1.01-1.51)	7/9
Stotz *et al*[30]	Austria	Mix	5	HR	CCS	261/79	2.532 (1.64-3.91)	6/9
Stotz *et al*[30]	Austria	Sur	5	HR	CCS	110/37	1.611 (1.024-2.534)	7/9

Studies evaluated mixed treatment (Mix), chemotherapy (Chemo), or surgical resection (Sur). Study quality is listed using the results of the Newcastle-Ottawa questionnaire. HR: Hazard ratio; OS: Overall survival; CSS: Cancer specific survival; NLR: Neutrophil to lymphocyte ratio.

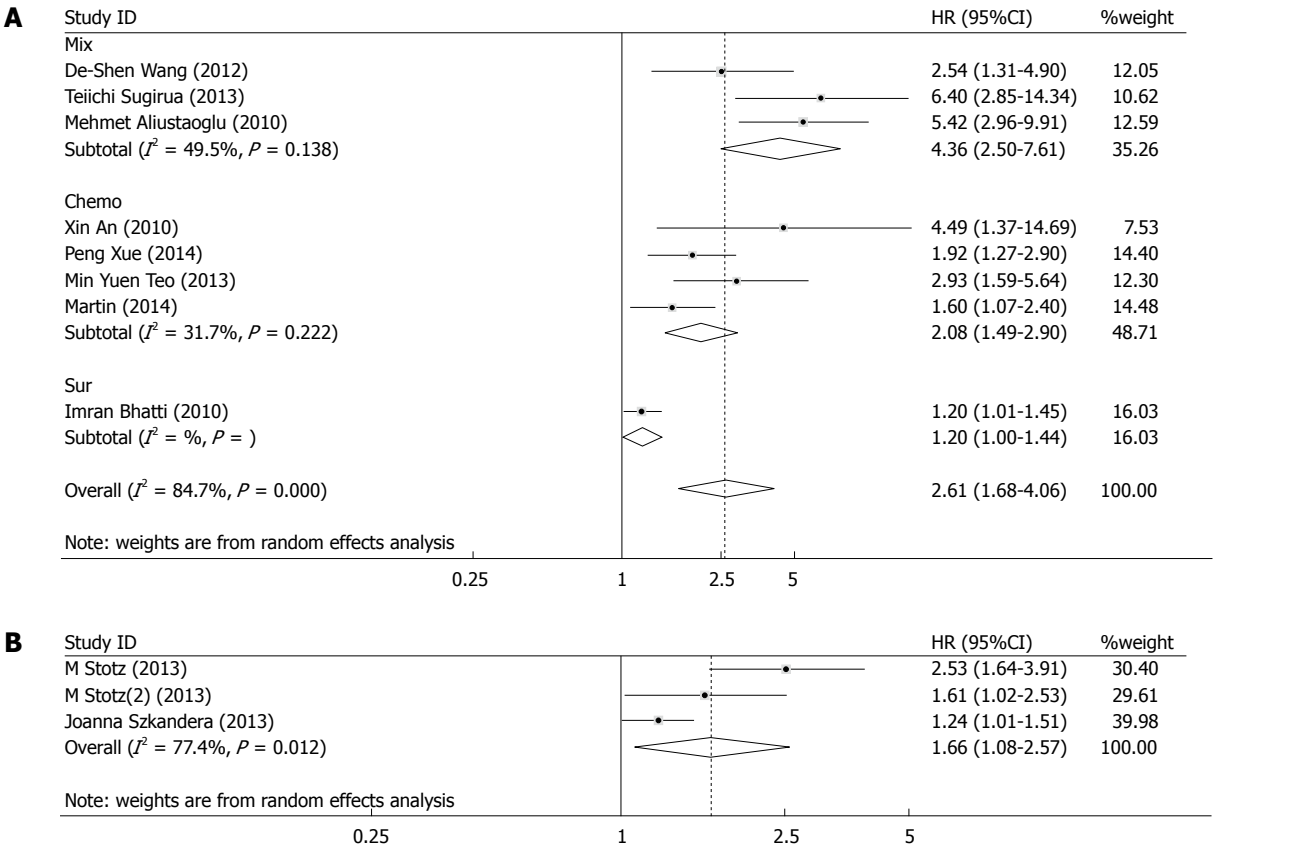

Figure 1 Forest plots. A: Meta-analysis of the association between high neutrophil to lymphocyte ratio (NLR) and overall survival; B: Meta-analysis of the association between high NLR and cancer specific survival. Results are presented as individual and combined hazard ratios (HR) and 95%CI. Chemo: Chemotherapy; Sur: Surgical resection; Mix: Mixed treatment.

4.36, 95%CI: 2.50-7.61, P = 0.000, Figure 1A), and there was no significant heterogeneity (χ^2 = 3.96, I^2 = 49.5%, P = 0.138). The combined data from four groups revealed that high NLR significantly correlated with poor OS in patients undergoing chemotherapy (HR = 2.08, 95%CI: 1.49-2.9, P = 0.000, Figure 1A), and no significant heterogeneity was detected (χ^2 = 4.39, I^2 = 31.7%, P = 0.222, Figure 1A). Data from one group demonstrated that high NLR significantly correlated with poor OS of patients undergoing surgical resection (HR = 1.2, 95%CI: 1.00-1.44, P = 0.048, Figure 1A).

Prognostic impact of the NLR on the CSS

Significant heterogeneity was observed in three groups of patients when the prognostic impact of the NLR on the CSS was evaluated (χ^2 = 8.84, I^2 = 77.4%, P = 0.012, Figure 1B). The synthesized HR data with a random-effects model revealed that high NLR was associated with poor CSS (HR = 1.66, 95%CI:

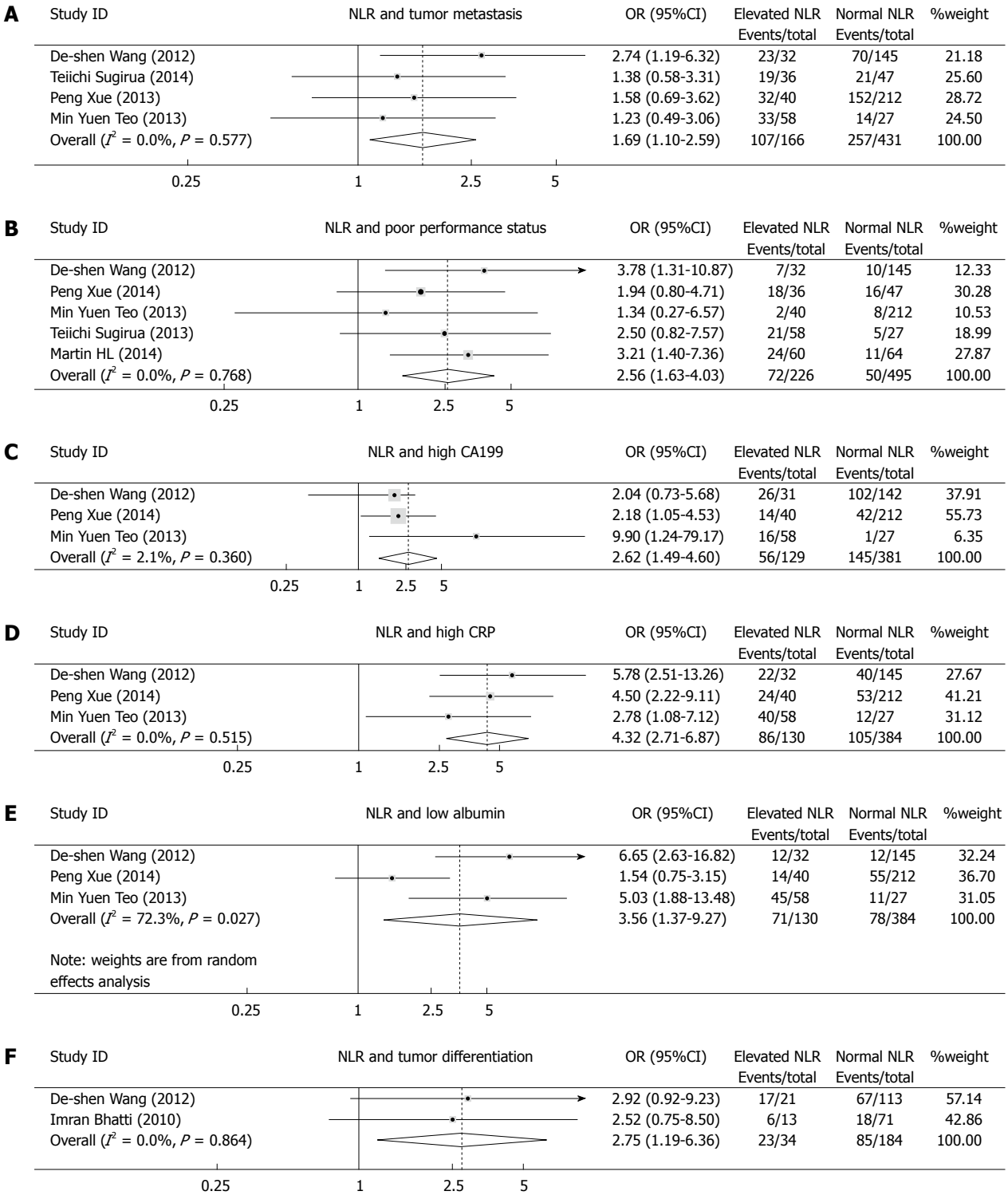

Figure 2 Forest plots. A: Meta-analysis of the association between high neutrophil to lymphocyte ratio (NLR) and tumor metastasis; B: Meta-analysis of the association between high NLR and poor performance status; C: Meta-analysis of the association between high NLR and high carbohydrate antigen 199 (CA199); D: Meta-analysis of the association between high NLR and high C-reactive protein (CRP); E: Meta-analysis of the association between high NLR and low albumin; F: Meta-analysis of the association between high NLR and tumor differentiation. Results are presented as individual and combined odds ratio (OR) and 95%CI.

1.08-2.57, P = 0.021, Figure 1B).

NLR and tumor clinicopathologic parameters

The correlation between the NLR and tumor distant metastasis was reported in four studies, and the combined data indicated that high NLR was associated with a high incidence of distant tumor metastasis (OR = 1.69, 95%CI: 1.10-2.59, P = 0.016, Figure 2A). Five studies reported a connection between high NLR and poor performance status; conjoined data showed that high NLR was associated with poor performance status (OR = 2.56, 95%CI: 1.63-4.03, P = 0.000, Figure

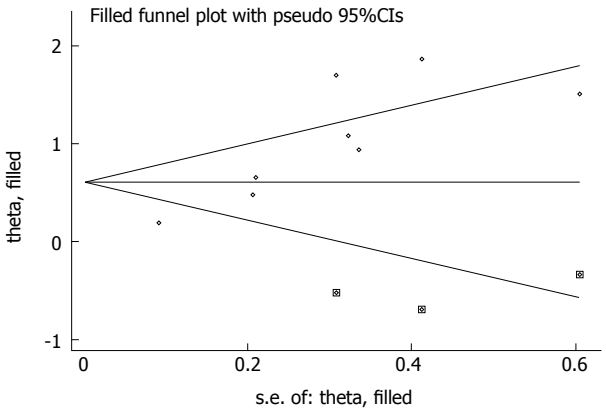

Figure 3 Funnel plot adjusted using a trim and fill method for overall survival. Diamonds: Included studies; diamonds in squares: Presumed missing studies.

2B). Three studies reported a correlation between high NLR and high CA199, high CRP, or low albumin. The synthesized data from these reports showed that high NLR was related to high CA199 (OR = 2.62, 95%CI: 1.49-4.60, *P* = 0.000, Figure 2C), high CRP (OR = 4.32, 95%CI: 2.71-6.87, *P* = 0.000, Figure 2D), or low albumin (OR = 3.56, 95%CI: 1.37-9.27, *P* = 0.009, Figure 2E). The association between the NLR and tumor differentiation was reported in two studies, and pooled data showed that high NLR was correlated with poor tumor differentiation (OR = 2.75, 95%CI: 1.19-6.36, *P* = 0.016, Figure 2F).

Publication bias

Publication bias was assessed using the Begg's funnel plot and Egger's linear regression test. Studies evaluating the impact of high NLR on the OS in patients yielded an Egger's test score of *P* = 0.009, indicating a significant publication bias. Therefore, it was necessary to use a trim and fill method to recalculate the combined HRs. The stability of the assembled data was revealed because the results did not change significantly (HR = 1.84, 95%CI: 1.22-2.78, *P* = 0.004, Figure 3). Studies evaluating the impact of high NLR on CSS showed an absence of publication bias (*P* = 0.237); moreover, reports assessing the correlation of high NLR with high CA199 (*P* = 0.291), high CRP (*P* = 0.638), low albumin (*P* = 0.207), poor performance status (*P* = 0.414), high incidence of tumor distant metastasis (*P* = 0.322), or tumor differentiation (*P* = 0.317) also showed no publication bias.

DISCUSSION

The systemic inflammatory response from cancer cells is involved in cancer progression and malignant transformation[10]. Increasing evidence shows that infiltration of the neutrophils around the tumor is associated with poor survival of patients, whereas lymphocyte infiltration predicts better prognosis. Furthermore, lymphocyte infiltration in advanced stages of pancreatic cancer is, to some extent, lower than that in the early stages[31,32]; therefore, elevated NLR may be a potential indicator for the prognosis of pancreatic cancer.

In our meta-analysis, we evaluated the prognostic value of NLR in patients with pancreatic cancer. Combined HRs revealed that elevated NLR is associated with poor OS as well as CSS in patients with pancreatic cancer, either receiving mixed treatment or chemotherapy. The mechanism underlying the potential prognostic value of NLR is mainly due to the significance of the infiltrated neutrophils and lymphocytes. The systemic inflammatory response from cancer cells promotes the infiltration of neutrophils, which provides a favorable tumor environment for cancer progression by secreting interleukin-2 (IL-2), interleukin-6 (IL-6), interleukin-10 (IL-10), tumor necrosis factor α (TNF-α) and vascular endothelia growth factor (VEGF)[33,34]. VEGF, as a known pro-angiogenic factor, especially promotes angiogenesis and contributes to cancer development. However, increased TNF-α and IL-10 levels lead to a decrease in the lymphocyte count as well as lymphocyte dysfunction[35-37]. It is well known that lymphocytes are important in the immune defense against cancer cells[38]. The infiltration of CD^{4+} T cells is essential for the immune activation of CD^{8+} T cells[39], and activated CD^{8+} T cells can induce apoptosis of cancer cells and exert cytotoxic activity against them[40]. Furthermore, the number of CD^{4+} help T cells is relatively low compared to CD^{8+} suppressor T lymphocytes in pancreatic cancer[41]. A decreased lymphocyte count results in an inadequate immunologic reaction to cancer cells, resulting in a poor prognosis. In general, the relative ratio of elevated neutrophils and decreased lymphocytes could be a scientific marker for evaluating the systemic inflammatory response and outcome of individuals; NLR, as a potential indicator of prognosis, is valuable to some degree.

We also evaluated the relationship between the elevated NLR and clinicopathological features; synthesized data suggested that increased NLR was significantly associated with distant tumor metastasis, poor tumor differentiation, high CRP, high CA199, low albumin, and poor performance status. Of all these factors, distant tumor metastasis and tumor differentiation, which are traditionally poor predictors of patients with pancreatic cancer, are correlated with oncologic phenotypes[42]. High CRP level, a systemic inflammatory marker, was reported as a prognostic indicator in a variety of cancers[43-45]. We found that elevated NLR was associated with high CRP, contributing to a poor OS and CSS in patients with pancreatic cancer. Low albumin level, as an independent prognostic marker, has been demonstrated in renal cell carcinoma[46]; the serum albumin level is modulated by systemic inflammation and the prognostic role of serum albumin combined with CRP has been reported in various cancers[47]. In our meta-

analysis, we showed that high NLR is associated with low albumin, which also indicated that NLR is a potential indicator of the prognosis. Finally, we also found that increased NLR was connected with low albumin and poor performance status, both of which were correlated with the physical condition of the individual patients[48]. To the best of our knowledge, the systemic inflammatory response is related to the progressive nutritional decline in patients and subsequent poor outcomes. We found that elevated NLR was associated with low albumin and poor performance status, which accounts for a poor OS and CSS in patients with pancreatic cancer. Interestingly, a large cohort study reported a newly derived NLR (dNLR) composed of white cell and neutrophil counts had similar prognostic value as the NLR in various cancer types[49]. The prognostic role of dNLR was also verified in pancreatic cancer[29]. Future studies and clinical practice should pay more attention to this universally available dNLR.

It is worth noting that there are still some defects in our meta-analysis. First, there was heterogeneity among studies evaluating the relationship between the NLR and OS or CSS. However, we supposed that heterogeneity is due to the non-uniform cutoff value of NLR (range: 2.3-5). There is clinical heterogeneity because studies differ in treatment. Second, this non-uniform cutoff value may not be applicable for clinic use; therefore, our study warrants further confirmation in large sample cohort studies with a definitive NLR cutoff value. Third, there is potential publication bias because all of the included studies reported positive results; however, when a trim and fill method was used, the recalculated results indicated the stability of the combined data. Because only English publications were included, language bias also needs to be considered.

In conclusion, we found that elevated NLR is associated with poor OS and poor CSS in patients with pancreatic cancer. Because pretreatment blood testing is inexpensive and routinely measured in the clinic, NLR may be a widely used indicator to evaluate the prognosis of pancreatic cancer. Additionally, NLR might potentially and extensively be used as a novel predictive factor in pancreatic cancer; however, our selected studies that evaluated the prognostic role of NLR were all retrospective analysis. Additional large cohorts of prospective studies are needed to confirm the NLR as a potential predictor of prognosis in pancreatic cancer. Additionally, targeting systemic inflammation may also be a useful strategy for pancreatic cancer patients with increased NLR.

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COMMENTS

Background

As the prognosis of pancreatic cancer is poor, biomarkers for evaluating the survival of pancreatic cancer patients are still unsatisfactory. It is necessary to explore inexpensive and routinely measured predictors of the prognosis.

Research frontiers

A meta-analysis was used to evaluate the prognostic significance of the neutrophil to lymphocyte ratio in pancreatic cancer.

Innovations and breakthroughs

This is the first comprehensive and detailed meta-analysis for evaluating the prognostic value of the neutrophil to lymphocyte ratio and its association with the clinicopathological features in pancreatic cancer.

Applications

The meta-analysis showed that the neutrophil to lymphocyte ratio (NLR) is associated with a poor prognosis of pancreatic cancer patients, and NLR might be a novel predictor of prognosis in pancreatic cancer.

Peer-review

This is an interesting, well-designed meta-analysis of the NLR that is associated with poor prognosis and clinicopathological features in pancreatic cancer. The NLR might be a novel marker of the survival evaluation in pancreatic cancer.

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