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Chemotherapy-Induced Reduction of Neutrophil-to-Lymphocyte Ratio Is Associated With Better Survival in Pancreatic Adenocarcinoma: A Meta-Analysis

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Abstract

Objectives: Numerous studies have suggested that an increase in neutrophil-to-lymphocyte ratio (NLR) before treatment is associated with worse survival in pancreatic adenocarcinoma (PAC). The aim of this study was to investigate the prognostic value of treatment-induced NLR change among PAC patients so as to better identify the characteristics of those who can benefit more from treatment.

Methods: This meta-analysis was undertaken using the PRISMA statement. Previously published studies between the correlation of NLR change and patients' survival were searched in Pubmed, Embase, and Web of Science databases. RevMan 5.3 was used to conduct statistical analysis.

Results: A total of 1213 patients with PAC from 6 retrospective studies were included in this meta-analysis. Four studies investigated the HR of pre-treatment NLR, demonstrating its prognostic impact on overall survival (OS) (HR = 2.21, 95%CI: 1.45-3.36). One study reported that an elevated post-treatment NLR was associated with poorer OS (HR = 1.28, 95%CI = 1.08-1.52). Pooled analysis indicated that NLR reduction might predict favorable survival in both the overall population (HR = 1.52, 95% CI: 1.34–1.73) and the subgroup treated with chemotherapy (HR = 1.50, 95% CI: 1.32-1.70).

Conclusion: Treatment-induced NLR change can act as an early predictor for PAC. Patients with reduced NLR after chemotherapy are expected to have better survival.

Keywords

pancreatic adenocarcinoma, neutrophil-to-lymphocyte ratio, systemic inflammatory response, prognosis, meta-analysis

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Introduction

Pancreatic adenocarcinoma (PAC) is one of the most aggressive malignancies with high incidence. PAC is the fourth leading cause of cancer-related death worldwide.[1] The 5-year survival for PAC is less than 8%, while the 5-year survival for those who undergo radical resection is much higher (up to 27%).[2] However, only 20% of patients at the time of diagnosis are eligible for surgery.[3,4] Chemotherapy and neoadjuvant chemoradiation are other vital strategies in the multimodality treatment for PAC.[2,5,6] Yet, the efficacy and long-term outcome are still unsatisfactory.[6,7] Thus, identifying new prognostic factors for PAC is crucial for a better selection of patients that will *benefit most* from this treatment.

Previous studies have revealed that systemic inflammation response participates in tumorigenesis by promoting angiogenesis, cell proliferation, tissue invasion, and metastatic dissemination.[8] So far, many systemic inflammation markers have shown predictive value in PAC, including neutrophil-to-lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), C-reactive protein to albumin ratio (CRP/Alb), Glasgow Prognostic Score (GPS), and modified Glasgow Prognostic Score (mGPS). Yet, most of the studies are focusing on investigating the correlation of pre-treatment systemic inflammation markers and prognosis after treatment. Whether the marker changes in response to treatment can be predictive remains unclear.

NLR is considered the most valuable marker for predicting PAC prognosis.[9,10] Thus, the aim of this meta-analysis was to investigate the prognostic value of pre- and post-treatment NLR change in patients with pancreatic adenocarcinoma, especially among the patients treated with chemotherapy.

Methods

This study was designed in conformity with the guidelines of the 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.

Literature Search

Pubmed, Web of Science, and Embase databases were searched for relevant articles published before May 2020 using the following search terms: "(neutrophil to lymphocyte ratio OR neutrophil-lymphocyte ratio OR neutrophil/lymphocyte ratio OR NLR) AND (pancreatic adenocarcinoma OR pancreatic cancer)", "AB = (neutrophil to lymphocyte ratio OR neutrophil-lymphocyte ratio OR neutrophil/lymphocyte ratio OR NLR) AND TI = (pancreatic adenocarcinoma OR pancreatic cancer)", and "(neutrophil to lymphocyte ratio or neutrophil-lymphocyte ratio or neutrophil lymphocyte ratio or NLR).ab. and (pancreatic adenocarcinoma or pancreatic cancer).ti.", respectively. Moreover, references of retrieved studies and reviews were also searched. Only studies published in the English language were reviewed.

Inclusion and Exclusion Criteria

The inclusion criteria were the following: (1) PAC diagnosed with pathologic methods; (2) NLR was tested at least 2 times: at baseline (at diagnosis, at admission, or right before treatment), and after treatment; (3) the correlation of NLR change (ΔNLR) and survival was investigated; (4) the values of hazard ratios (HR) and 95% confidence interval (CI) could be directly extracted or calculated with the method reported by Tierney et al.[11]

The exclusion criteria were: (1) other pathologic types of pancreatic cancer or neoplasms; (2) reviews, case reports, letters, conference abstracts, or laboratory studies; (3) indirect analysis between ΔNLR and survival; (4) insufficient information for pooled HRs.

Data Extraction

The following information was collected: first author's surname, research region, publication year, study design (prospective or retrospective), sample size, tumor type, and staging, treatment, outcome measure, the timing of NLR tests, classification of NLR change, and their distribution; if the multivariate analysis were conducted and whether the results were positive or negative, and eventually HR, 95%CI. The results of multivariate analyses were predominantly used; otherwise, the results of univariate analyses could be extracted. Two investigators independently assessed articles and extracted all data; consensuses were reached by discussion. If there were further disagreements, a third reviewer was invited.

Quality Assessment

The quality assessment of included studies was evaluated by 2 reviewers (X Luo and N Jiang) independently by the Newcastle-Ottawa Scale (NOS) for cohort studies. This tool consists of 3 dimensions, including the selection of the study groups (0-4 points), the comparability of the groups (0-2 points), and the ascertainment of or outcome (0-2 points). NOS scores range from 0 to 9; a higher score indicates better quality.

Statistical Analysis

This meta-analysis was conducted using RevMan (version 5.3; The Cochrane Collaboration). The heterogeneity of pooled results was measured by Cochrane's Q test and Higgins I-squared statistic. Significant heterogeneity was defined as $p < 0.1$ or $I^2 > 50\%$; thus, the random effect model was applied; otherwise, the fixed-effect model was used for included studies without significant heterogeneity. Next, the software was used to generate a forest plot so as to demonstrate pooled results. In addition, the funnel plot was constructed for testing publication bias.

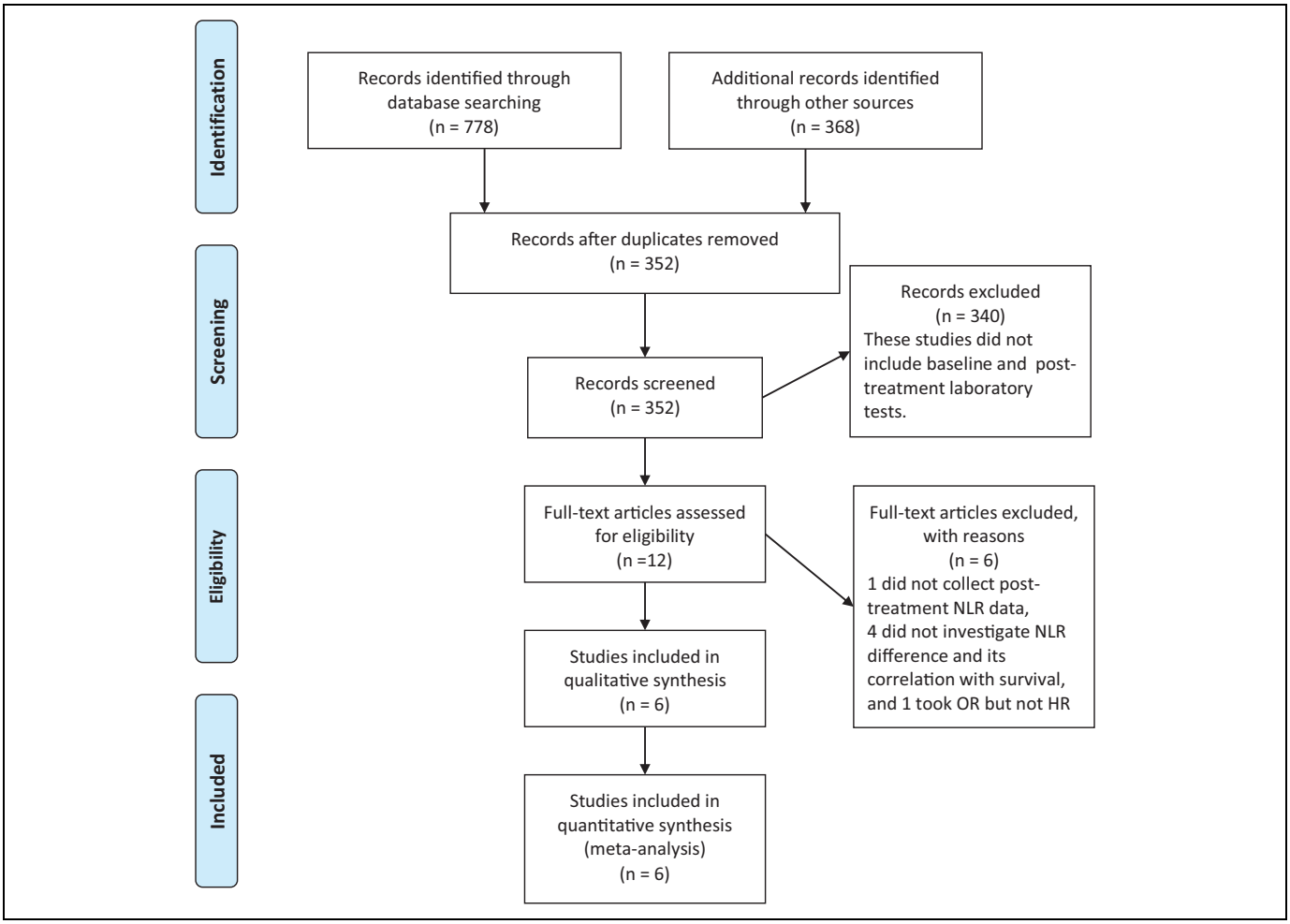

Figure 1. Flow chart of selection and inclusion of studies.

Results

Selection and Characteristics of Included Studies

A total of 12 studies were identified since they seemed to have explored the impact of laboratory tests before and after a period of therapy. After the full-text screening, 1 article, which did not collect post-treatment NLR value,[12] 4 articles, which did not calculate NLR difference and did not analyze the correlation between NLR change and long-term survival,[13-16] and 1 article that took odds ratio (OR) to reflect the prognostic value of NLR change on pancreatic adenocarcinoma treatment[17] were excluded. Finally, 6 studies were included in this meta-analysis[18-23] (**Figure 1**). The characteristics of the included studies are summarized in **Table 1**.

Prognostic Value of NLR Change

Since the heterogeneity test revealed minor heterogeneity ($I^2 = 0\%$, $P = 0.45$) between the studies, a fixed-effects model was chosen for the analysis. A pooled HR of 1.52 (95% CI: 1.34–1.73) showed that elevated post-treatment NLR was correlated with shorter OS in patients (**Figure 2A**). Since our focus was on the role of NLR change in patients treated with chemotherapy, subgroup analysis was conducted among chemotherapy-specific studies regardless of the significant heterogeneity (**Figure 2B**). Pooled data of the subgroup treated with chemotherapy (HR = 1.50, 95% CI: 1.32-1.70) was consistent with that of the overall population.

Prognostic Value of Pre-Treatment and Post-Treatment NLR

HR of baseline NLR could be extracted from 4 out of the 6 included studies.[18,19,22,23] Considering that the heterogeneity was significant ($I^2 = 83\%$, $P < 0.01$), the random-effects model was used. Meta-analysis results showed that elevated baseline NLR was associated with poorer OS (HR = 2.21, 95% CI: 1.45-3.36) (**Figure 2C**). Moreover, one study investigated the association between post-treatment NLR and OS, as well as the prognostic impact on survival of post-treatment NLR (HR = 1.28, 95% CI = 1.08-1.52).[20]

Table 1. Characteristics and Quality of Included Studies.

Study	Country	Study design	Sample size	Disease	Disease stage	Treatment	Outcome measure	Sampling time 1	Sampling time 2	Grouping	Distribution	Multivariate analysis	Results	NOS Score
Chen 2017[18]	China	retrospective	132	PDAC	locally advanced and metastatic	palliative chemotherapy	OS	baseline	after 2 cycles of chemo	Increased(ΔNLR>0) Decreased(ΔNLR≤0)	50 82	yes	positive	9
Choi 2016[19]	Korea	retrospective	396	PAC	metastatic	palliative chemotherapy	OS	baseline	after 1 cycle of chemo	Increased(ΔNLR≥0) Decreased(ΔNLR<0)	120 261	yes	positive	9
Eyff 2018[20]	Brazil	retrospective	135	PAC	Stagel-IV	palliative chemotherapy (subgroup, n = 49)	OS	baseline	after 2 cycles of chemo	Increased(ΔNLR>0) Decreased(ΔNLR<0)	21 10	yes	negative	9
Glazer 2016[21]	America	retrospective	62	PDAC	borderline resectable	neoadjuvant chemoradiation	OS	baseline	after neoadjuvant therapy	Increased* Stable	19 43	yes	positive	9
Luo 2015[22]	China	retrospective	403	PAC	locally advanced and metastatic	palliative chemotherapy	OS	baseline	after 1 cycle of chemo	Increased Decreased	211 146	yes	positive	9
Teo 2013[23]	Ireland	prospective	85	PDAC	locally advanced and metastatic	palliative chemotherapy	OS	baseline	after 4 weeks of chemo	Increased(ΔNLR≥0) Decreased(ΔNLR<0)	38 27	yes	negative	7

*Increased NLR in this study was defined as an increase of standard deviation of baseline NLR, and the remaining were classified as stable NLR. Abbreviations: PAC-pancreatic adenocarcinoma; PDAC-pancreatic ductal adenocarcinoma.

Publication Bias

The absence of studies in the lower left quadrant was noticed by visual inspection, indicating a potential bias in this meta-analysis, despite only 6 studies were eventually selected (**Figure 3**).

Discussion

To the best of our knowledge, this is the first systemic review assessing NLR change in response to treatment in PAC patients. Based on our meta-analysis, we found the prognostic significance of NLR change in PAC. Patients with elevated NLR (measured within 1 or 2 months after the initiation of treatment) had a shorter survival. Similarly, patients with increased NLR, who were treated with chemotherapy alone, had a higher HR of death. Several clinical studies have indicated that elevated baseline NLR is correlated with poorer survival in pancreatic cancer treated with surgery,[24] chemotherapy, radiotherapy,[25] and mixed therapy,[26] while some other studies reported controversial conclusion.[27] Moreover, 3 meta-analyses investigated the effect of pre-treatment NLR for the prediction of pancreatic cancer patients.[9,28,29] In addition, elevated NLR at baseline has been identified as a prognostic factor of poorer clinical outcomes in some other cancer types, including non-small cell lung cancer,[30,31] esophageal cancer,[32] gastric cancer,[33] ampullary cancer,[34] colorectal cancer,[35] and breast cancer.[36] Thus, in solid tumors, the prognostic value of pre-treatment NLR has been generally recognized.

By comparing the prognostic value of NLR change and pre-treatment NLR by pooled HRs, it was not possible to come to a final conclusion. Many studies assessing pre-treatment NLR's role were excluded as we only included papers that reported both pre-treatment and post-treatment NLR, which additionally limited the interpretation of results. We found 3 meta-analyses that reported on pre-treatment NLR in pancreatic cancer.[9,28,29] The cut-off values of elevated pre-treatment NLR were 2.0 in one study,[9] and 2-5[28] and 2.3-5[29] in the other 2. The pooled HRs of 3 studies were 1.147 (95%CI: 0.147-1.180) by fixed effect model, 1.737 (95%CI: 1.502-2.009) by random effect model,[9] 1.59 (95%CI: 1.41-1.78) by fixed-effect model,[28] and 2.61 (95% CI: 1.68-4.06) by random effect model,[29] respectively. Moreover, Formica *et al* found that high NLR helps select metastatic pancreatic cancer patients benefitting from oxaliplatin and gemcitabine.[37] In addition, the difference between pre-treatment and pos-treatment NLR may reflect treatment response. We hypothesized that patients who experienced NLR decrease might benefit more from the current regimen. Validation studies are being designed.

Most of the included studies had 1 or 2 cycles of monitoring for the collection of post-treatment data. Besides systemic inflammation markers, timing has shown to be a predictive factor for prognosis. Neutropenia, as well as NLR decrease, indicate systemic inflammation receding.[38,39] The timing of neutropenia is an independent predictor of prognosis in metastatic colon cancer patients who received mFOLFOX6.

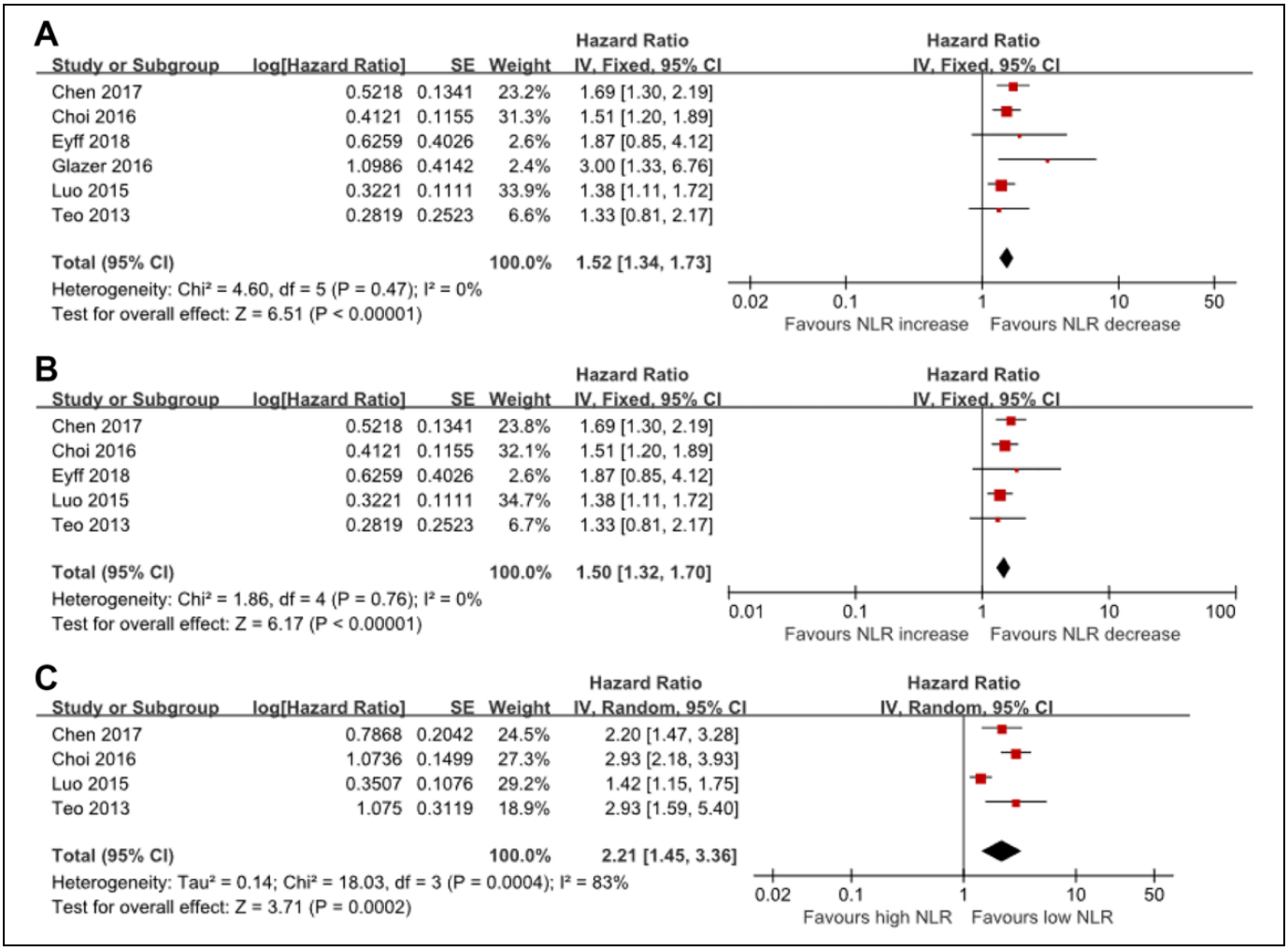

Figure 2. Forest plot of HR and 95%CI for the association between **(A)** NLR change and OS, **(B)** NLR change and OS in the subgroup of patients who receive chemotherapy, **(C)** pre-treatment NLR and OS.

Moreover, patients with early-onset and late-onset chemotherapy-induced neutropenia (CIN) had longer survival than patients without CIN.[38] The earlier detection and subgroup identification are of greater clinical significance.

The prognostic significance of systemic inflammation markers warrants future studies on the cluster of markers. A combination of NLR and CRP might have a predictive effect on patients with gastric cancer.[40] A novel systemic inflammation response index (SIRI) was reported for predicting PAC patients who receive chemotherapy, defined as the multiplication of neutrophil count and monocyte count divided by lymphocyte (SIRI = N*M/L).[41] The dynamic change of CA19-9 has been found to be associated with pancreatic cancer in several studies.[42,43] Combined CA19-9 and NLR are better prognostic marker than either alone in metastatic pancreatic cancer patients.[44]

This study has a few limitations. First, all of the included studies were retrospective and thereby more prone to bias, i.e. publication bias and language bias (see asymmetric funnel plots). Second, only 6 studies were included, indicating the prognostic value of NLR change; thus, more prospective clinical studies are required to validate its predictive effect. Third, the criteria for elevated NLR in response to treatment deserve more attention. Usually, it is calculated by latter NLR minus prior one, but Glazer *et al* took the standard deviation of pre-treatment NLR into consideration.[21] To determine a definition of NLR change in response to treatment would help to better understand its prognostic value. Last but not least, confounding factors in this study cannot be ignored, e.g. the role of neutrophil counts[38,39] or disease stage. Selected studies examined different disease stages (resectable, borderline resectable, locally advanced, and metastatic tumor), which leads to different treatment choices.

In conclusion, we found that reduced NLR in response to treatment is associated with improved OS in pancreatic adenocarcinoma patients. Neutrophil and lymphocyte counts were both routinely measured; thus, inexpensive laboratory tests could be used for an easily accessible identification of pancreatic patients' prognosis.

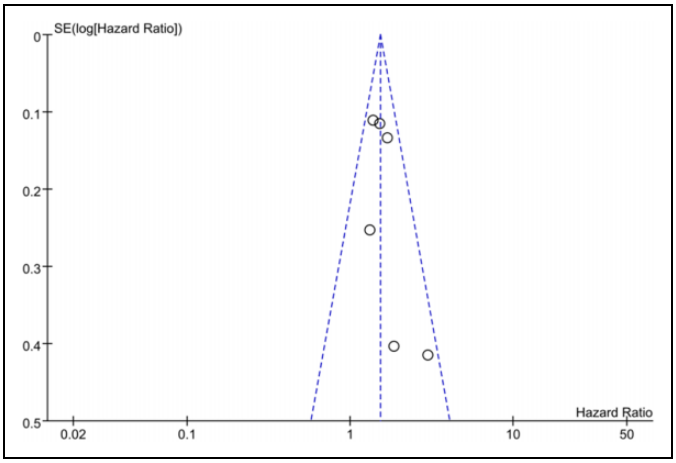

Figure 3. Funnel plot of included studies.

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Author Contribution

Xin Luo, Bo Yu and Nan Jiang are authors contributed equally to this work.

Declaration of Conflicting Interests

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Previous Communication of Work

This work has not been previously communicated to a society or meeting.

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