

The prognostic significance of NLR in non-metastatic renal cell carcinoma undergoing nephrectomy, A meta-analysis

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Abstract

INTRODUCTION Neutrophil to Lymphocyte ratio (NLR) has been reported to correlate with poor survivals in many tumors. However, the association between preoperative NLR elevation and survival outcome in non-metastatic renal cell carcinoma (RCC) undergoing nephrectomy remains controversial. The aim of this meta-analysis was to investigate the prognostic significance of elevated NLR in non-metastatic RCC.

EVIDENCE ACQUISITION We systematically searched PubMed, EmBase, and the Cochrane Library databases in may 2018. Cancer specific survival (CSS), disease-free survival (DFS) and overall survival (OS) were pooled by hazard ratio (HR) with corresponding 95% confidence interval.

EVIDENCE SYNTHESIS A total of 3,175 patients from 8 studies were analyzed. The results demonstrated that elevated pretreatment NLR was significantly related to poor CSS (HR 1.91, 95% CI=1.53-2.40), DFS (HR 1.38, 95% CI=1.09-1.74), and OS (HR 1.84, 95% CI=1.58-2.14) in patients with non-metastatic RCC.

CONCLUSION Elevated NLR indicates a poor long-term survival (CSS, DFS and OS) in non-metastatic RCC. Patients with elevated NLR are more likely to have poor prognosis than those with lower NLR.

Introduction

Renal cell carcinoma (RCC) was the most common malignant tumor, accounting for 2~3% of adult malignancies [1]. Based on ultrasound and computed tomography, Some incidental and early stage RCC can be detected. About 20% to 30% patients occur distant metastases after nephrectomy Because of unresponsive to chemotherapy and radiotherapy, some of them even died [2,3]. Therefore, to identify a significant biomarkers for clinical diagnosis and therapy of RCC is important.

It has been demonstrated that inflammatory response plays an essential roles in tumor development and progression[4]. The systemic inflammation have intimated connection with poor survivals of many tumors in human [5]. Increased of pro-inflammatory cytokines and signaling molecules in cancer patients might reflect both disease activity and the innate response of the host to the tumor[6]. There is accumulating evidence for the correlation between pretreatment systemic inflammation and worse survival in patients with RCC[7].

Previous research have shown that Neutrophil to Lymphocyte ratio (NLR) being used as a biomarker for the prognosis of RCC[8][9]. NLR was an indicator of general immune response to various stress, it has been proved to be a prognosis related marker in various

malignancies, including RCC [10][11][12]. Earlier meta-analysis on NLR in patients with metastasis renal cancer described that elevated baseline NLR remained an independent predictor of OS and PFS^[13]. However, the association between NLR and CSS, DFS, OS in non-metastasis RCC are inconsistent. Some studies demonstrated that NLR represented an independent risk factor for prognosis^{[14][15]}, while others did not ^{[16][17]}. Thus, it is necessary to perform a comprehensive systematic review and meta-analysis of published studies to determine predictive value of NLR for RCC.

Materials And Methods

Study Identification

A systematic literature search was performed in May 2018. Three electronic databases (PubMed, Embase, and the Cochrane Library) were searched to select relevant articles. The following key words were used: (“neutrophil lymphocyte ratio” or “neutrophil-lymphocyte ratio”, or “neutrophil to lymphocyte ratio”, or “neutrophil-to-lymphocyte ratio”, or “NLR”) and (“kidney neoplasm” or “kidney cancer” or “renal neoplasm” or “renal cancer” or “renal carcinoma” or “RCC”). At the same time, a MESH/EMTREE search for “Kidney neoplasms” were also performed. Two reviewers independently scanned the potential references for titles and abstracts to exclude irrelevant articles. When disagreements or questions appeared, it would be resolved by consulting another author. In addition, the reference list was assessed for additional relevant articles. We evaluated the remaining articles to identify research that covered the topic of interest. Then the full texts were estimated comprehensively. The selection process of the articles is shown in Figure 1.



Figure 1 Flow chart of study selection process. CSS, cancer specific survival; DFS, disease free survival; MFS, metastasis free survival; NLR, neutrophil-lymphocyte ratio; RCC, renal cell carcinoma.

Inclusion and exclusion criteria

The studies included in this meta-analysis must be met the following criteria: (a) the patients must have been diagnosed with non-metastatic RCC by a pathological and imaging examination. (b) Provided pretreatment NLR as a variable in outcome analysis and cut off value. (c) HR and 95% CI were reported for pretreatment NLR in CSS,

DFS and OS or could be calculated from the article data. A search must meet all three inclusion criteria for inclusion. The exclusion criteria were: (a) review articles, case reports, letters, editorial comments, conference abstract and studies irrelevant to our topic. (b) Overlapping or duplicate reports. (c) Lacking required outcomes data that could not be calculated from other information presented. (d) Those nonhuman research. A search meeting any of the four exclusion criteria was excluded.

Data extraction

The following data included in this meta-analysis were extracted by two independent reviewers: first author, year of publication, country, sample size, age, cut-off value of NLR. Disagreements or questions in data extraction were resolved by joint discussion. The basic features of the 8 studies were summarized in table 1.

Quality assessment for the included studies was conducted using the Newcastle-Ottawa Scale (NOS) ^[18]. This scale mainly concerned with three aspect (selection of patients, comparability of group, and assessment of outcomes). Studies with NOS scores ≥ 6 were considered to be high quality, and studies with NOS scores < 6 were considered to be low quality. Studies from conference abstracts were defined as low quality. All P value were two tailed, and $P < 0.05$ was considered statistically significant.

Table 1, Main characteristics of included studies in the meta-analysis

First author	Country	Follow-up time	Sample size	Age	Tumour type	Cut-off	Survival analysis	NOS score
Lucca I	Austria	Median 40 (17-73)	430	Median (IQR) 65.5(57-73)	Clear cell RCC	4.2	DFS	8
Wen RM	China	Median: 44	327	Mean \pm SD: 65.15 \pm 12.727	Clear cell :294 others 33	1.7	DFS OS	8
Martino MD	Austria	Median 37	280	Median (IQR) :63(54-72)	Non clear cell RCC	3.6	DFS	7
Pichler M	Austria	Mean : 44	678	Mean \pm SD: (63.7 \pm 11.9)	Clear cell RCC	3.3	MFS CSS OS	7
Grivas N	Greece	Median 69	114	median 64	Clear cell RCC 80	2.7	DFS OS	7
Chen Z	China	Median 69.2	416	median 56.3	Clear cell RCC	2.17	CSS OS	7
Gu LY	China	Median 19.9	103	Median 56	Clear cell RCC 83, other 20	4.1	OS	8
Viers BR	England	Median: 9.3	827	Median (IQR) :65(56-73)	Clear cell RCC	4	MFS CSS OS	8

CSS, cancer-specific survival; OS, overall survival; M/F, male, female; NA, not available; (M), the HR comes from multivariate analysis; MFS, metastasis free survival; RCC, renal cell carcinoma; NOS, Newcastle-Ottawa Quality Scale; (U), the HR comes from univariate analysis

Statistical analysis

HR with corresponding 95% CI were selected as common measurements to assess the strength of the association between NLR and prognosis in renal carcinoma. An HR value greater than 1 reflects a strong association between high NLR value and poor survival outcome. Between-study heterogeneity was evaluated using Cochran's Q test, P value and

Higgins I-squared statistic. If $P \leq 0.1$, it indicates significant heterogeneity between studies. A random effect model was used in the significant heterogeneity; otherwise, a fixed effect model was used. Funnel plots was used to assess the possibility of publication bias in the meta-analysis. Subgroup analysis were performed to explore the heterogeneity among studies according to predefined parameters: sample size (≥ 200 vs < 200), cut-off value defining 'elevated NLR' (> 3 vs < 3). Sensitivity analysis was performed to check whether individual study influenced the result by omitting studies included one by one. Meta-regression analysis was not employed due to the limited number of studies. All statistical analysis were performed using RevMan (version 5.3, Cochrane Library).

Results

Search result

The systematic search identified 348 relevant references. Overall, 102 duplicated articles were removed. After screening titles and abstracts. Among the remaining 246 records, 214 were excluded by abstract and title. The full texts of the remaining 32 ,a total of 24 full-tests articles were excluded, including 3 without available data, 1 with postoperation NLR study, 1 that enrolled overlapping patients, 5 review articles, 12 conference abstract, 2 unwanted prognostic indicator. Finally, 8^{[14][15][16][17][19][20][21][22]} studies were including in this meta-analysis.

Study characteristics

Detailed information on the 8 studies is listed in table 1. These studies were published between 2013 and 2017. Five studies were from western country, including 1 from Britain, 3 from Austria, 1 from Greece. The rest four studies were from eastern country. Sample size for the included studies ranged from 103 to 827 patients, and a total of 3,175 patients were included. The NLR cut-off values ranged from 1.7 to 4.2. Among them, 3, 4 and 6 studies investigated the relationship of NLR and CSS, DFS and OS, respectively.

NLR and CSS

The pooled analysis was conducted 3^{[15][17][22]} studies including 1,921 patients that reported HR for CSS. The main results of this meta-analysis were listed in Figure.2. The result showed that high pretreatment NLR was associated with

a worse outcome for CSS with the pooled HR of 1.91 (95% CI=1.53-2.40). Good homogeneity was observed among these studies ($I^2 = 44\%$, $P=0.17$).



Figure 2 Results of the meta-analysis on pooled HR values for CSS.

NLR and DFS

The relationship between NLR and DFS was explored in 4^{[14][16][19][20]} cohorts including 1,151 patients. As illustrated in Figure 3, the pooled estimate for high pretreatment NLR value was of statistical significance (HR 1.38, 95% CI=1.09-1.74) with significant heterogeneity ($I^2=58\%$, $P=0.07$), indicating that patients with high pretreatment NLR were associated with worse DFS.



Figure 3 Results of the meta-analysis on pooled HR values for DFS.

NLR and OS

Six cohorts covering 2,465 patients described the association between NLR and OS in RCC. As illustrated in Figure 4. The pooled HR for high pretreatment NLR value group was found to be 1.84 (95% CI=1.58-2.14) with low heterogeneity ($I^2=33\%$, $P=0.19$), indicating that there was significant difference between high and low pretreatment NLR values in RCC patients.



Figure 4 Results of the meta-analysis on pooled HR values for OS.

Subgroup, sensitivity analysis and publication bias

We explored the heterogeneity by conducting subgroup analysis to evaluate the prognostic significance of preoperative NLR on DFS of non-metastasis RCC. Statistically significant effects were obtained in all of the subgroup analyses, it involves sample size, published year and cut-off value of preoperative NLR. In the subgroup about sample size and cut-off value, there is no significant on heterogeneity. But in the subgroup of the of published year, statistically

significance were found in both published year ≤ 2015 (HR=1.93, 95% CI=1.34-2.76, P=0.0004, I²=0%) and published year ≥ 2015 (HR=1.18, 95% CI=1.05-1.34, P=0.007, I²=0%). The detailed results were shown in in Table 2.

A sensitivity analysis was performed in which each study was successively deleted to assess the influence of individual studies on the pooled HRs. This analysis shows that no obvious change for OS, DFS and CSS when we removed each article in turn. The detailed results were shown in in Table 3.

Funnel plots of the studies used in the meta-analysis were conducted for assessing the publication bias, and we could roughly assess the publication bias by seeing whether their shapes were of any obvious asymmetry. As showed in Figure 5, there were no evident publication bias by funnel plots. However, because the number of included studies was just six, the funnel plots may not be significant.



Figure 5 Funnel plots based on overall survival.

Table 2. Summary of subgroup analyses results of DFS.

subgroup	number of studies	HR	95% CI	P value	I ²	P value
cut-off value						
NLR≤ 3	2	1.33	1.07-1.66	0.01	37%	0.21
NLR ≥ 3	2	1.21	1.06-1.39	0.006	80%	0.03
sample size						
<math>< 200</math>	1	2.866	1.08-7.59	0.034	0	0
≥ 200	3	1.25	1.10-1.42	<math>< 0.0001</math>	72%	0.03
Year						
<math>< 2015</math>	2	1.93	1.34-2.76	0.0004	0%	0.4
≥ 2015	2	1.18	1.05-1.34	0.007	0%	0.74

Table 3. Summary of sensitivity analyses results

omitting studies	Pooled results of remaining studies			Heterogeneity	
OS	HR	95% CI	P value	I ²	p value
Pichler M 2013	1.89	1.61-2.23	<0.00001	41%	0.15
Viers BR 2014	1.94	1.52-2.48	<0.00001	44%	0.13
Grivas N 2014	1.82	1.56-2.12	<0.00001	40%	0.15
Wen RM 2015	1.87	1.59-2.19	<0.00001	45%	0.12
Gu LY 2016	1.81	1.55-2.10	<0.00001	20%	0.29
Chen Z 2017	1.79	1.53-2.08	<0.00001	0%	0.41
DFS					
Martino MD 2013	1.59	1.09-2.30	0.01	57%	0.1
Grivas N 2014	1.56	1.03-2.37	0.04	72%	0.03
Lucca I 2015	1.23	1.06-1.43	0.006	21%	0.28
Wen RM 2015	1.31	1.02-1.68	0.04	60%	0.08
CSS					
Pichler M 2013	1.97	1.54-2.50	<0.00001	69%	0.07
Viers BR 2014	2.23	1.35-3.69	0.002	68%	0.08
Chen Z 2017	1.80	1.43-2.28	<0.00001	0%	0.67

Discussion

The association between NLR and prognosis has been identified in various tumors. Semeniuk-Wojtas A have reported a meta-analysis about the prognostic significance of NLR in metastasis RCC^[13]. However, prognostic significance of preoperative NLR in non-metastasis RCC still uncertain. So we conduct this meta-analysis to investigate the clinical value of pretreatment NLR in non-metastasis RCC.

Based on the meta-analysis, we identified that elevated pretreatment NLR was closely associated with worse long-term survival (DFS, CSS and OS) in non-metastatic renal cell carcinoma. As there was significant heterogeneity existing among included studies of DFS, we conducted subgroup analysis. When groups were stratified by sample size, published year and NLR cut-off value, elevated NLR predicted poor DFS. Meanwhile, sensitivity analysis was performed to check whether individual study influenced the result. Although there was no pooled HR for CSS, DFS and OS, we found that when removing the study of Chen Z et al [15] from the CSS and OS estimate, the I^2 decreased from 44% to 0% and 33% to 0% respectively. The results proved that Chen Z et al [15] might be the source of heterogeneity of CSS and OS in this study.

The potential reasons for the correlation between NLR elevation and low survival outcome in RCC patients are complex and have not been well clarified. It has been widely accepted that inflammatory mediators can destabilize the cancer cell genome by directly inducing DNA damage or affecting DNA repair systems and altering cell cycle checkpoint, leading to accumulation of cancer initiation and progression [23]. The association between chronic inflammation and cancer are duplex, inflammation can induce tumorigenesis and metastasis by affecting cell proliferation, death, and angiogenesis through elevated levels of cytokines, nuclear factor κ B (NF- κ B), prostaglandins and micro RNAs. et al, tumors also can induce inflammatory reactions through express cytokines that recruit neutrophils and macrophages [24]. Recent study have indicated that NLR is an indicator of systemic inflammation and general immune response of the cancer [25,26]. Although there are some other systemic inflammation reaction biomarkers, such as CRP, cystatin-C and PLR, were reported to be used for prognostic indexes in RCC [9][27]. Our meta-analysis indicated that an increased pretreatment NLR predict worse long-term survival in patients with RCC. Heterogeneity is the quality or state of consisting of dissimilar or diverse elements, it was very important in meta-analysis process. In this study, there are no significant heterogeneity when pooled HR for CSS and OS, but when pooled HR for DFS, the heterogeneity proved high diversity.

In this study, we carefully calculated the possible association between elevated NLR and prognosis of non-metastasis RCC patients from the most recent studies. The aim of the study was to drive reliable conclusions for clinical applications of NLR. But certain limitation should be taken into consideration for the results. The main limitation was that only 8 studies (among them, 3, 4 and 6 studies investigated the relationship of NLR and CSS, DFS and OS) being analysis, so the conclusion of the study are preliminary and need to examine in the future studies. Besides, we can not avoid the selection bias, all the studies we selected were retrospective, which may influence the accuracy of the results. Furthermore, the heterogeneity and variability could be influence by NLR cut-off value. Although we proved that elevated NLR was associated with a poor prognosis in non-metastasis RCC patients. Further well-designed studies with a large sample size are needed to correct our limitations. Whether the NLR can be use as a potential biomarkers in clinical applications are needing further investigation.

Declarations

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgments

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Figures

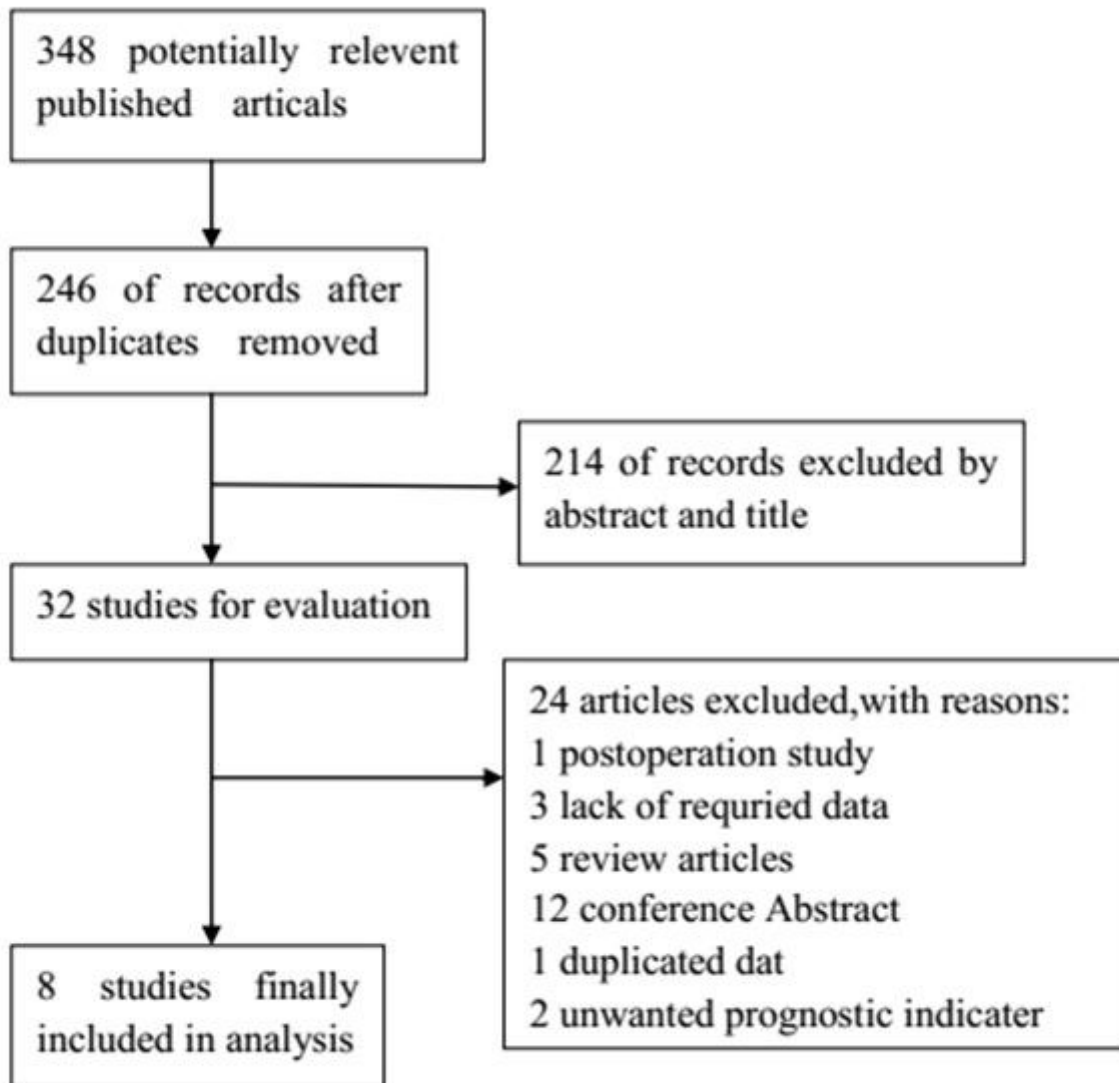


Figure 1

Flow chart of study selection from the PubMed, the Embase, and the Cochrane Library online databases for the NLR as prognostic in non-metastatic renal cell carcinoma patients, published in English from January 1, 2015 to May 31, 2018.

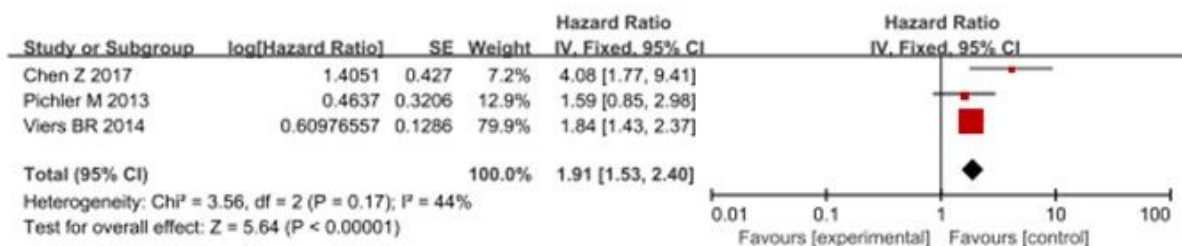


Figure 2

Forests plot of the association between neutrophil-lymphocyte ratio (NLR) and cancer specific survival (CSS) of non-metastatic renal cell carcinoma patients.

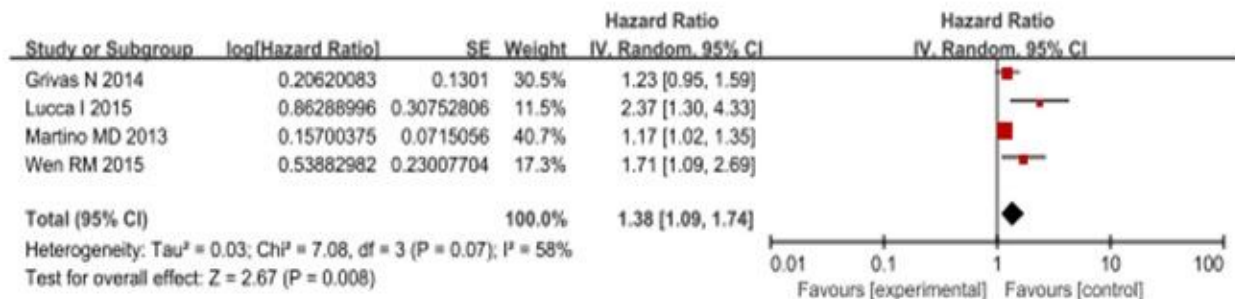


Figure 3

Forest plot for the association between neutrophil-lymphocyte ratio (NLR) and disease-free survival (DFS) of non-metastatic renal cell carcinoma patients.

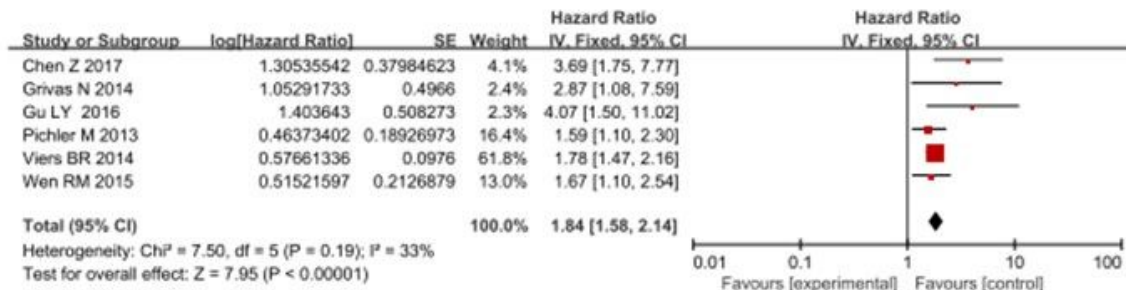


Figure 4

Forest plot for the association between neutrophil-lymphocyte ratio (NLR) and overall survival (OS) of non-metastatic renal cell carcinoma patients.

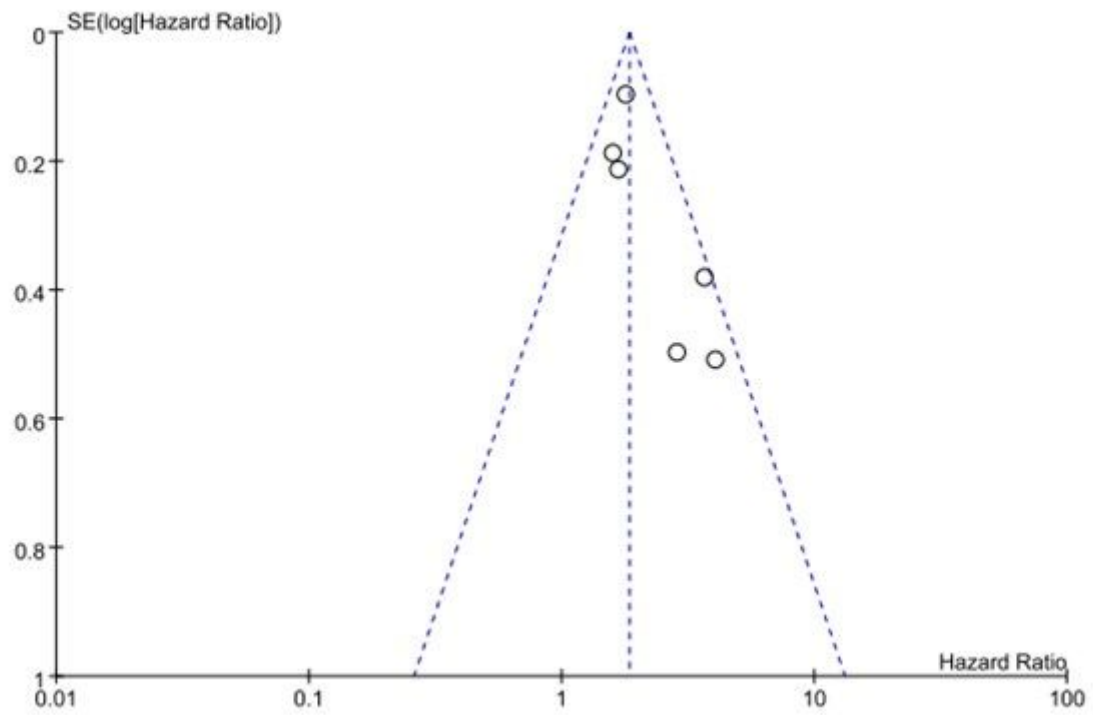


Figure 5

Funnel plots for detecting publication bias between neutrophil-lymphocyte ratio (NLR) and overall surviva (OS) of non-metastatic renal cell carcinoma patients