Original Article
Low pretreatment prognostic nutritional index predicts poor survival of urologic cancer: an observational meta-analysis

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Abstract: Background: The pretreatment prognostic nutritional index (PNI) has been reported to be a potential prognostic marker of urologic tumors in succession, but the evidence is not decisive. In this study, meta-analysis was performed to better elucidate the prognosis of pretreatment PNI in patients with urologic tumors. Methods: Data from PubMed, Embase, and Web of Science databases were extracted and integrated from the matching articles (until October 12, 2017). Pooled hazard ratio (HR) and 95% confidence interval (CI) were collected and calculated for PNI of overall survival (OS) by Stata 12.0. Twelve studies involving 6786 cases met the criteria for inclusion and provided available data to evaluate the prognostic value of PNI in urologic cancer. Results: The pooled HR reached 1.72 (95% CI: 1.48-2.00, $P<0.001$) of OS by applying the fixed effect model on account of low heterogeneity in urologic cancer (I^2: 0; $P=0.509$, nine studies containing 4735 cases). Moreover, subgroup analyses indicated that the association between low PNI and worse OS in urologic tumors was stable despite variations in region, publication time, and cut-off value. Conclusion: Low pretreatment PNI could serve as an adverse predictor of prognosis in urologic cancer. It predicts poor survival of urologic cancer based on our research. Further prospective studies are necessary to verify the role of PNI in urologic cancer.

Keywords: Prognostic nutritional index, prognosis, urologic cancer

Introduction

Urologic cancers, including renal cell cancer, upper tract urothelial cancer, bladder cancer, and prostate cancer, are among the most common malignancies with an increased incidence each year worldwide. The estimated number of new cases and deaths of urologic cancer reached 150,350 and 33,170 in the United States in 2018, respectively [1]. Although surgical operation remains the primary option of treatment for urologic cancer, the long-term survival is still discontented mainly attributed to regionally advanced tumors, recurrence, and distal metastasis [2-4]. To date, TNM staging still has been regarded as the most standard tool to assess tumor prognosis and therapy strategy of cancer patients. Nonetheless, TNM staging cannot always accurately predict the

risk of disease recurrence [5]. Furthermore, emerging evidence verified that various biomarkers also have a significant value in tumor development and progression [6].

In general, evaluation and support of the nutritional and immune condition run through the entire oncotherapy [7]. Several different indexes have been utilized to assess the nutritional and immune situation of cancer patients. Specifically, low body mass index (BMI), preoperative weight loss, and hypoalbuminemia have all been demonstrated to be associated with adverse survival after surgery in patients with renal cell cancer [8]. The prognostic nutritional index (PNI) was reported by Buzby et al. in 1980 to evaluate the perioperative nutrition and predict the risk of postoperative complications after gastrointestinal surgery initially [9]. It

reflects the nutritional and immune condition of hosts because it is calculated based on combining the serum albumin concentration and total lymphocyte count in peripheral blood [9]. Recently, several studies have found that limited PNI before initial treatment was independently correlated with inferior survival in different types of cancer [10-12]. However, the inconsistent conclusion of pretreatment PNI in urologic cancer still existed [13]. Therefore, this meta-analysis was performed based on published studies to acquire a more credible result.

Materials and methods

Literature retrieval

A comprehensive search without limits was conducted in PubMed, Web of Science, and Embase databases. The following search terms were used: 1) "PNI" or "prognostic nutritional index"; 2) urologic cancer or prostate cancer or bladder cancer or renal cell carcinoma or renal cancer or urinary tract cancer or upper urinary tract urothelial carcinoma. The literature retrieval of this current meta-analysis was updated to October 12, 2017.

Selection criteria

Studies meeting the following criteria were included in our meta-analysis: 1) the involved patients were diagnosed pathologically with urologic cancer and did not have any other tumors; 2) PNI was obtained before any treatment; 3) the association between PNI and the survival of patients with urologic cancer was examined; 4) only the largest sample size article was included in cases of reduplicated studies based on the same patient population; and 5) retrospective study or randomized controlled trial was enrolled.

The study exclusion criteria were as follows: 1) studies were reviews, letters, case reports, animal studies, and duplicates; 2) hazard ratio (HR) and 95% confidence interval (CI) were not able to be extracted from the results.

Data extraction

Data were independently extracted from all eligible publications by two investigators according to the inclusion criteria. If inconsistent conclusion existed, a third investigator was required. The following items were sought from each publication: first author's last name, publication period, region, cancer type, sample size, cancer location, stage, follow-up time, cut-off value, main treatment, and HR with 95% CI for PNI of overall survival (OS).

Quality assessment

The quality of the 12 eligible studies included with the guideline of the Newcastle-Ottawa Scale (NOS), including selection, comparability, and outcome [14]. Studies with scores ≥6 were deemed as high-quality studies. Any inconsistencies were resolved by involving a third investigator.

Statistical analysis

All the data analyses were conducted using Stata 12.0 (STATA Corporation, College Station, TX, USA). HRs and 95% CIs of the ratio for low PNI over high PNI were extracted from each eligible study for OS. Meta-analysis was performed to evaluate the prognostic effect of PNI in patients with urologic tumors for OS. The pooled HR and 95% CI were estimated using the fixed effect model if no heterogeneity existed among included studies (P>0.1 and I^2<50%), otherwise, a random effect model was used [15]. Pooled HR >1 was considered indicative of worse survival outcome of patients with low PNI. If the 95% CI did not overlap 1, the result was considered statistically significant. Subgroup analyses were performed to investigate the association of pretreatment PNI with variables such as region, cut-off value and publication time. Moreover, sensitivity analyses were performed by sequential elimination of one study at a time to explore its potential impact on the heterogeneity. Funnel plots and Egger's test were further used to examine the influence of publication bias on the pooled OS. All statistical tests were two-sided and P<0.05 indicated statistical significance.

Results

### Literature retrieval and characteristics

The initial search identified 417 articles in available databases. After excluding 392 irrelevant or reduplicated articles, 25 studies were screened by reviewing the full text. Finally, 12 studies involving 6786 cases met the inclusion of this meta-analysis and provided available data that are summarized in **Table 1** [13,

Table 1. Characteristics of the included studies

Study	Year	Region	Study design	Patients (M/F)	Age (years)	Follow-up (months)	Tumor type	Tstage	N stage	Distant metas-tases	Treatment	Cut-off	Survival analysis	Determine the cut-off value	NOS score
Kim M	2014	South Korea	R	218/59	Median: 63.7; IQR: (57.4-70.6)	Median: 57.2; Range: (6.8-158.3)	UTUC	pTa, pTis, pT1-pT4	pN0, pNx, pN+	0	Nephro-ureterectomy	45	RFS, DSS	NA	6
Luccal	2015	Austria	R	257/173	Median: 65.5; IQR: (57-73)	Median: 40; IQR: (17-73)	RCC	pT1-pT4	N0	0	Radical or partial nephrectomy	48	DFS	Univariable Cox models	7
Hofbauer S L	2015	Austria	R	892/452	Median: 62; IQR: (53-70)	Median: 40; IQR: (18-73)	RCC	pT1-pT4	pN0, pNx, pN+	399	Radical or partial nephrectomy	48	CSS	Discrimination analysis	7
Jeon H G	2015	South Korea	R	1011/426	Mean: 54.2±11.7; Range: (20-85)	Mean: 68.6; Range: 1.2-212.6	RCC	pT1-pT4	pN0, pNx, pN+	106	Radical or partial nephrectomy	51	OS, CSS	Minimum p value approach	7
Kwon W A	2016	South Korea	R	99/26	Median: 58; IQR: (51-66)	Median: 45.3; IQR: 23.7-77.3	RCC	NA	NA	125	Targeted therapy	41	OS, PFS	Discrimination analysis	6
Broggi M S	2016	USA	R	204/115	Mean ± SD: (61.1±11.5)	-60	RCC	pT1-pT4	NA	71	Radical or partial nephrectomy	44.7	OS, RFS	ROC analysis	8
Fan L	2017	China	R	112/0	Median: 72; IQR: (66-77)	Median: 20.2; IQR: 14-22.9	PC	NA	NA	112	Abiraterone	50.5	OS	ROC analysis	7
Miyake M	2017	Japan	R	95/22	Median: 72; IQR: (61-77)	Median: 22; IQR: (10-64)	BC	pT0, pTa, pTis, pT1-pT4; cT2-cT4	pN0, ≥pN1; cN0, ≥cN1	0	Radical cystectomy	50	OS, DSS	Median	7
Kang M	2017	South Korea	R	241/83	Median: 55; IQR: (48-64)	Mean: 79.6	RCC	pT1-pT4	NA	0	Radical nephrectomy	45	OS, CSS	ROC analysis	6
Huang J	2017	China	R	279/146	Mean ± SD: 65.9±11.1; Range: (30-86)	Median: 38.5; IQR:(23-62)	UTUC	pTa, pT1-pT4	pN0, pNx, pN1-pN3	0	Radical cystectomy	46.78	OS, CSS	Minimum p value approach	6
Peng D	2017	China	R	436/80	Median: 37; IQR: (20-56)	Median: 66; IQR: (35-91)	BC	pT1-pT4	pN0, pN+	NA	Radical cystectomy	46.025	OS, PFS	ROC analysis	7
Peng D (1)	2017	China	R	952/408	Median: 55; Range: (14-87)	Median: 67; Range: (2-108)	RCC	pT1-pT4	pN0, pN+	61	Nephrectomy	47.625	OS, PFS	ROC analysis	7

R: retrospective; UTUC: upper urinary tract urothelial carcinoma; RCC: renal cell cancer; BC: bladder cancer; PC: prostate cancer; NA: not available; OS: overall survival; PFS: progression-free survival; DSS: disease-specific survival; CSS: cancer-specific survival; DFS: disease-free survival; RFS: recurrence-free survival; ROC: receiver operating characteristic curve; NOS: Newcastle-Ottawa scale.
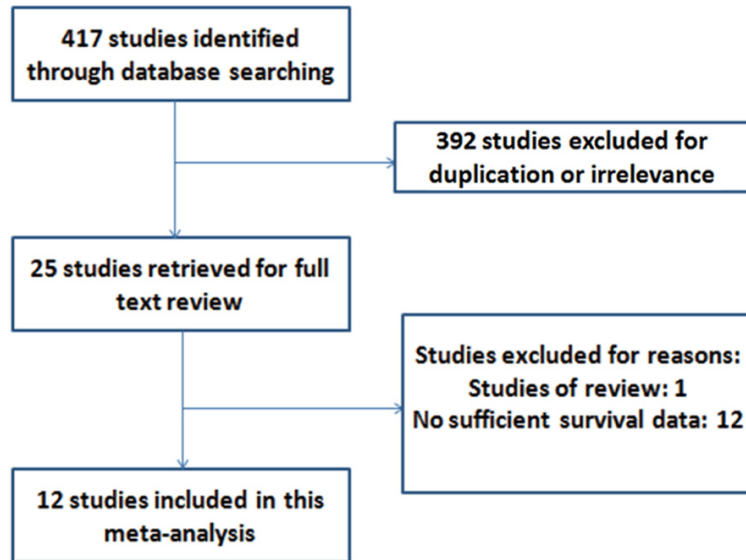
Figure 1. Flow diagram of the meta-analysis.

16-26]. The flow diagram of literature selection step is shown in **Figure 1**. These 12 retrospective studies were published between 2014 and 2017, indicating the increasing recent interest of this research. Among the included 12 studies, nine studies focused on Asian population, whereas three studies focused on Western population. Four types of urologic tumors were involved in our meta-analysis, including renal cancer (n=7), upper tract urothelial cancer (n=2), bladder cancer (n=2), and prostate cancer (n=1). Surgical resection was the dominating mode for treatment strategy. All enrolled literatures had relative high quality (NOS scores ≥6).

Relation of PNI and OS in patients with urologic cancers

In total, nine studies assessed the prognostic role of pre-treatment PNI for OS in urologic cancer. The pooled HR reached 1.72 (95% CI: 1.48-2.00, $P<0.001$, **Figure 2**) of OS applying the fixed effect model on account of low heterogeneity in urologic cancer (I^2: 0; $P=0.509$, nine studies containing 4735 cases).

Subgroup analysis

Subgroup analyses was stratified by region, publication time, and cut-off. The results are shown in **Table 2**. In both China and non-China studies, low PNI was linked to poor OS in uro-

logic cancer (China: HR=1.68, 95% CI: 1.36-2.07, $P<0.001$, fixed effect model; non-China: HR: 1.76, 95% CI: 1.42-2.19, $P<0.001$, fixed effect model, **Figure 3**). Similarly, parallel results in the two subgroup analyses (**Figures 4** and **5**) was obtained.
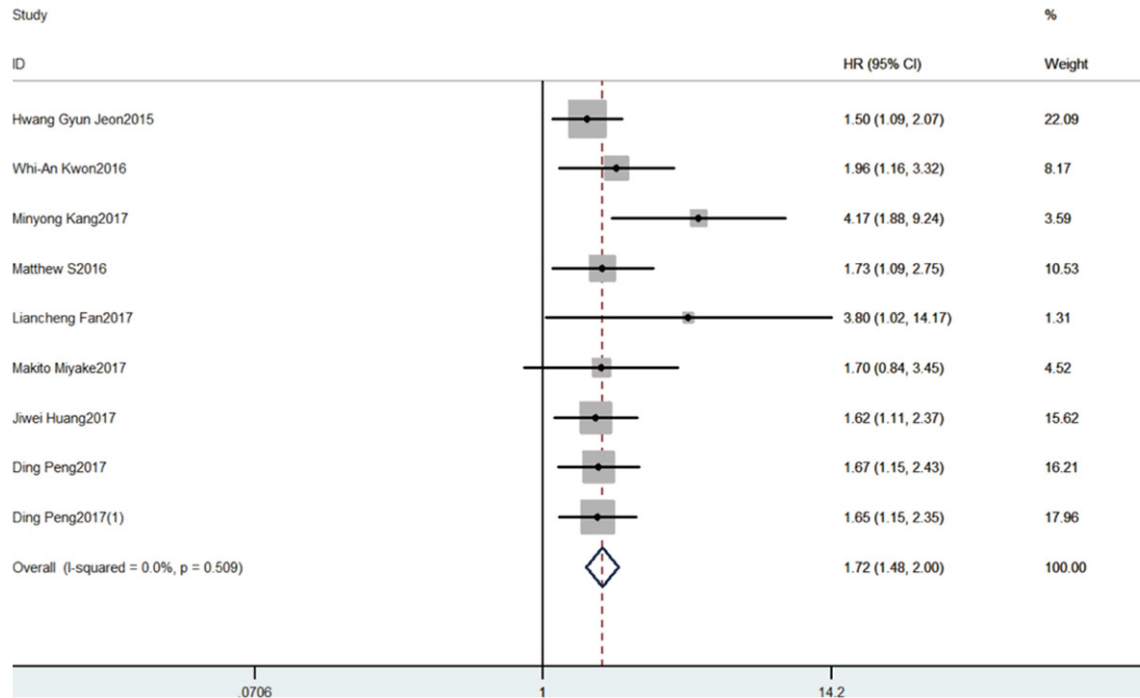
Publication bias

Visual inspection of funnel plots using Egger's tests revealed the absence of publication bias in the meta-analysis (**Figure 6**).

Discussion

Urologic cancer, a malignant neoplasm with high morbidity and mortality worldwide, still shows discontented long-term survival mainly attributed to regionally advanced tumors, recurrence, and distal metastasis [2-4]. Therefore, more novel and valid biomarkers are essential to assist clinicians for patient risk stratification, target treatment, and clinical research. The PNI is a simple and easily obtainable indicator based on combining serum albumin concentration and total lymphocyte count in peripheral blood [11]. Currently, emerging evidence demonstrates pretreatment PNI, which reflects human nutritional and immune status, to be remarkably associated with prognosis and oncologic outcomes in patients with various types of cancer [12, 27-29]. Research based on a meta-analysis according to Yang and colleagues could add to evidence that PNI is associated with poor prognosis in gastric cancer [30]. However, the prognostic impact of PNI in urologic cancer is still not determined based on pooled study until now.

To the best of our knowledge, this work is the first meta-analysis to systematically analyze the results of the relationship between the pretreatment value of PNI and urologic cancer outcomes. The current meta-analysis of nine cohort studies with 4735 individuals provides a convincing and stable result of an association between low pretreatment PNI and reduced OS. When stratified by region, publication time, and cut-off value, the results were also consis-

Figure 2. Forest plot of all included studies. The pooled HR of nine included studies was 1.72 (95% CI: 1.48-2.00, *P*<0.001, fixed effect model (I²=0).

Table 2. Subgroup analysis of the meta-analysis

Subgroup	Number of studies	Pooled HR	95% CI		*P*	Medol	I²	*P*
Region								
China	4	1.68	1.36	2.07	<0.001	Fixed effect	0.0%	0.676
Non-China	5	1.76	1.42	2.19	<0.001	Fixed effect	29.0%	0.228
Publication time								
Before 2017	3	1.64	1.30	2.08	<0.001	Fixed effect	0.0%	0.675
After 2017	6	1.78	1.46	2.16	<0.001	Fixed effect	19.6%	0.286
Cut-off								
>50	3	1.60	1.20	2.13	<0.001	Fixed effect	0.0%	0.398
<50	6	1.77	1.48	2.11	<0.001	Fixed effect	1.3%	0.408

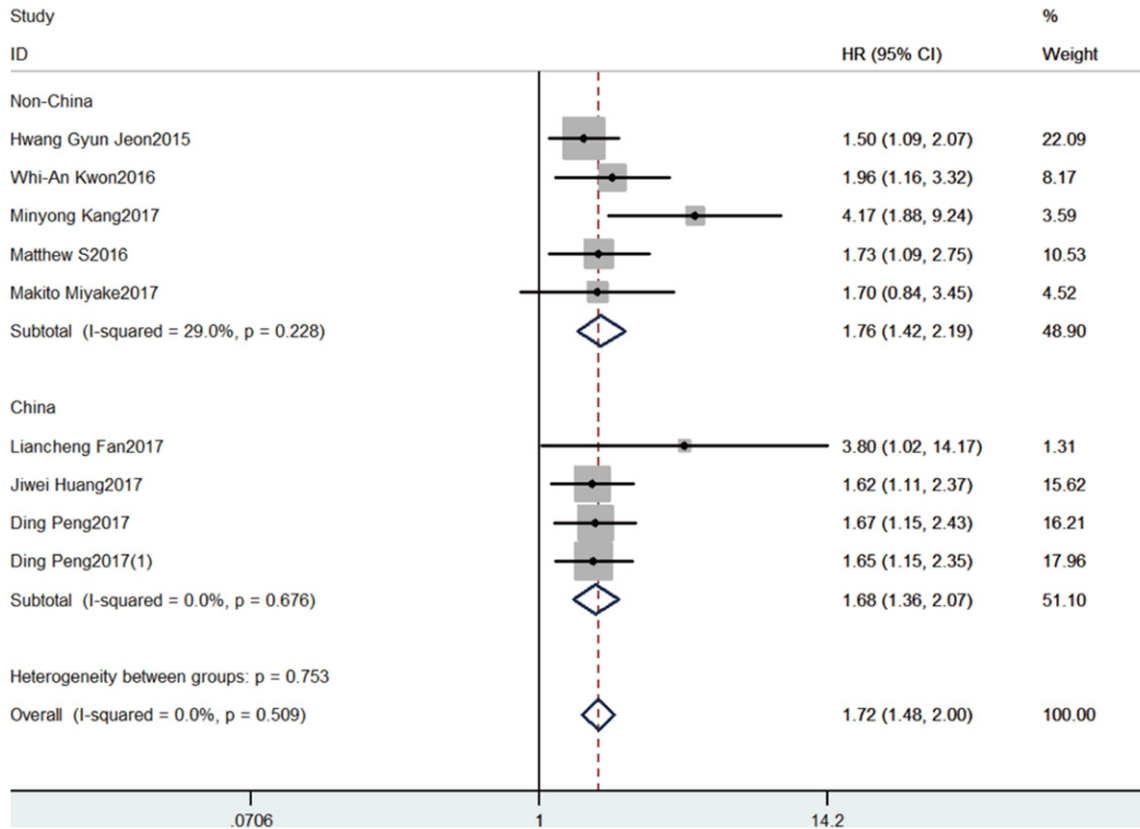HR: hazard ratio; 95% CI: 95% confidence interval.

tent. Of note, no significant heterogeneity and publication bias were observed.

Current evidence for the potential mechanisms may support our conclusion. A low PNI indicates a decrease in serum albumin and/or total lymphocyte count. Preoperative serum albumin is a valid indicator that has been identified by researchers to predict the outcomes of renal cell cancer [31], upper urinary tract urothelial carcinoma [32], and bladder cancer [33]. In addition, multiple studies have indicated that low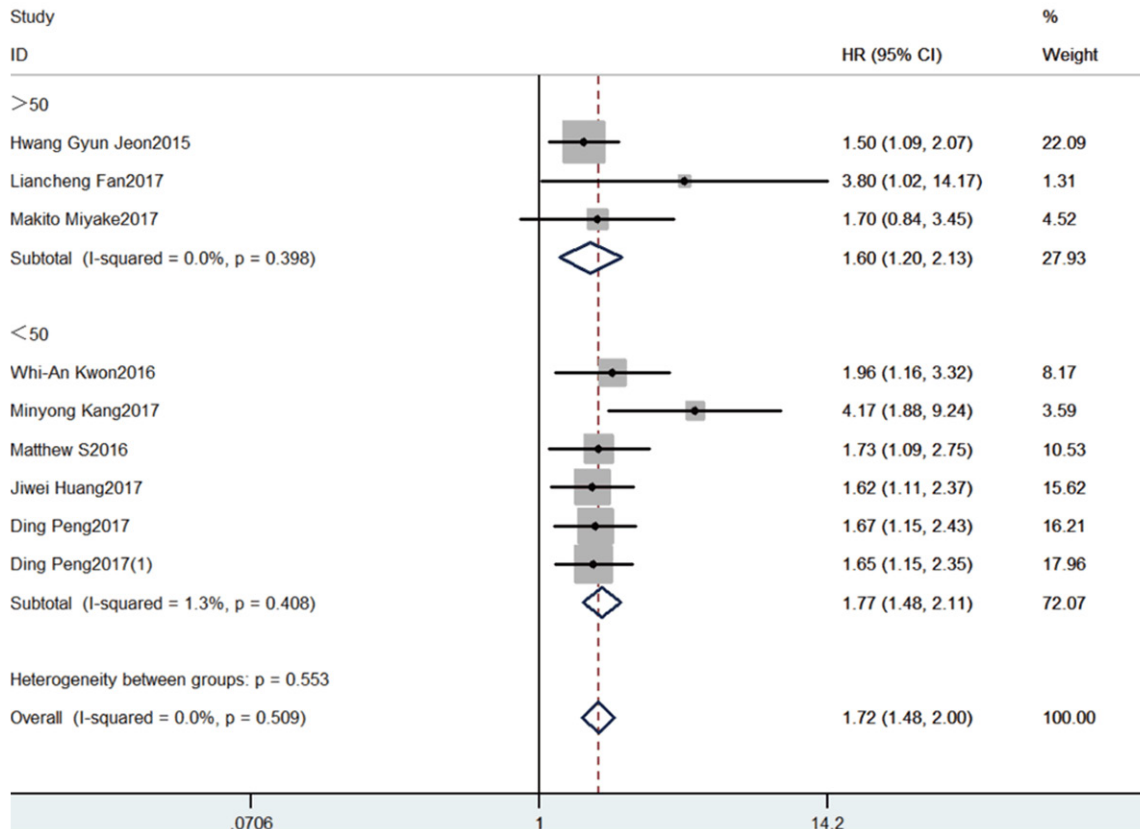 serum albumin was a significant risk for postoperative morbidity and mortality [34, 35]. Chronic inflammatory reaction, chronic malnutrition, and aberrant catabolism attributed to cancer can lead to hypoalbuminemia [32], resulting in edema, cachexia, organ dysfunction, and immunosuppression.

The total lymphocyte, another aspect of PNI, has a critical role in defense of cancer cells by initiating cytotoxic immune response and inhibiting cancer cell proliferation, invasion, and migration [6]. Actually, lymphocytopenias associated with worse clinical outcome in patients

PNI predicts survival of urologic cancer

Figure 3. Subgroup analysis for region. In China, the HR of PNI was 1.68 (95% CI: 1.36-2.07, *P*<0.001, fixed effect model). In non-China, a similar result was observed (HR: 1.76, 95% CI: 1.42-2.19, *P*<0.001, fixed effect model).

Figure 4. Subgroup analysis for cut-off value. The pooled HR of high cut-off value (>50) was 1.60 (95% CI: 1.20-2.13, *P*<0.001, fixed effect model) and pooled HR of low cut-off value was 1.77 (95% CI: 1.48-2.11, *P*<0.001, fixed effect model).
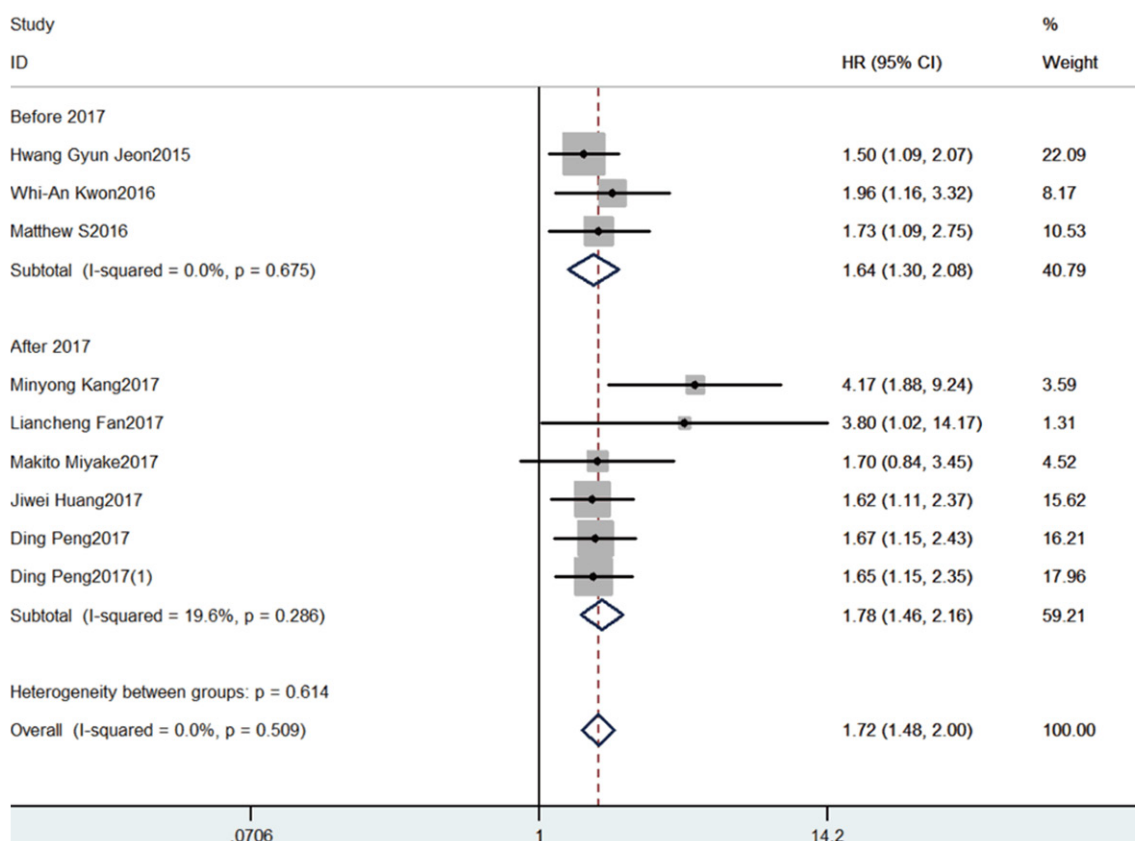
Figure 5. Subgroup analysis for publication time. In studies published before 2017, the HR of PNI was 1.64 (95% CI: 1.30-2.08, *P*<0.001, fixed effect model), and a consistent result was achieved in studies after 2017 (HR: 1.78, 95% CI: 1.46-2.16, *P*<0.001, fixed effect model).
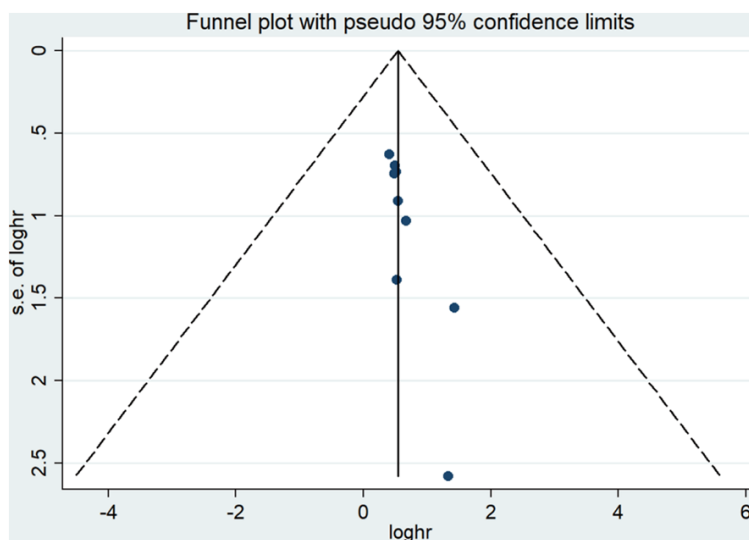
Figure 6. Funnel plot of included studies. No obvious publication bias was observed.

with diverse types of cancer [36, 37]. Lymphocytopenias identified as a sign of a pre-existing immunosuppressed condition as a result of impaired lymphocyte homeostasis and enhanced lymphocyte apoptosis [38]. Other scholars presented that cancer progression might start from peripheral blood into tumors and adjacent tissues, thus resulting in lymphocytopenia [39]. In other words, a low lymphocyte count might indicate a weakened defense against cancer, with a consequently poor prognosis [40]. In addition, a high neutrophil-lympho-

cyte ratio, another biomarker, has been found to be associated with an inferior outcome in many tumors [41, 42]. However, research from Joseph et al. showed that the prognostic value of a high neutrophil-lymphocyte ratio might actually be driven by lymphocytopenia rather than neutrophilia in bladder cancer [38].

As Koike et al. and Pinato et al. reported, PNI reflects not only the nutritional condition of a patient but also systemic inflammation, either from the tumor itself or as a host reaction, which could ultimately result in the decrease of lymphocyte and albumin [43, 44].

A study by Peng et al. revealed that low PNI was associated with advanced T stage, positive lymph node metastasis, distal metastasis, and cell differentiation [26]. Thus, from this observation, low PNI was associated with poor survival of urologic cancer.

Another area of concern is that whether limited PNI is an indicator of nutritional supplementation, which could minimize complications and prolong survival. In fact, preoperative nutritional supplementation was found to reduce the complication rate and prevent mortality in severely malnourished patients with gastrointestinal cancer [45]. Even if it delays therapy, a controlled intervention trial may be acquired to identify the outcome benefit of pretreatment nutritional supplementation in urologic cancer.

Although our study provided a more reliable result that PNI could act as a predictive biomarker of prognosis for urologic cancer, certain limitations still exist in our research. First, the enrolled articles were retrospective cohort studies and no prospective cohort studies were included. Second, the included trials were mostly from East Asia, especially China and South Korea. Third, it was not possible to perform other subgroup analyses because of the limited data of research.

Conclusions

Collectively, our meta-analysis showed that pretreatment PNI could be a promising indicator to predict disease progression of urologic cancer, and it is objective and easily obtainable. Moreover, prospective controlled trials are needed to validate the findings of this study.

Disclosure of conflict of interest

None.

Abbreviations

PNI, Prognostic nutritional index (=10 × serum albumin concentration (g/dl) + 0.005 × lymphocyte counts (number/mm^3)); HR, Hazard ratio; CI, Confidence interval; OS, Overall survival; BMI, Body mass index (BMI=kg/m^2); NOS, Newcastle-Ottawa Scale.

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