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Research article

Prognostic and clinicopathological role of prognostic nutritional index (PNI) in endometrial cancer: A meta-analysis

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ABSTRACT

Background: The effect of prognostic nutritional index (PNI) on predicting prognosis of endometrial cancer (EC) patients has been widely analyzed, but no consistent findings are obtained. We therefore performed a meta-analysis for determining accurate role of PNI in predicting EC prognosis.

Methods: We comprehensively searched PubMed, Web of Science, Embase, Cochrane Library, and CNKI databases from inception till January 5, 2024. Correlation between PNI and survival outcomes in EC was evaluated by pooled hazard ratios (HRs) and 95 % confidence intervals (CIs).

Results: There were altogether eight articles involving 3,164 patients enrolled into this meta-analysis. According to our pooled results, low PNI significantly predicted the dismal overall survival (OS) (HR = 1.72, 95%CI = 1.33–2.22, $p < 0.001$) and inferior progression-free survival (PFS)/disease-free survival (DFS)/recurrence-free survival (RFS) (HR = 2.49, 95%CI = 1.62–3.84, $p < 0.001$) for EC patients. Furthermore, as revealed by our pooled results, a decreased PNI was significantly connected to FIGO stage III-IV (OR = 2.06, 95%CI = 1.42–2.99, $p < 0.001$), tumor grade of G3 (OR = 1.68, 95%CI = 1.32–2.14, $p < 0.001$), presence of lymphovascular space invasion (LVSI) (OR = 1.72, 95%CI = 1.14–2.61, $p = 0.010$), and presence of myometrial invasion (MMI) (OR = 2.04, 95%CI = 1.51–2.77, $p < 0.001$) in EC.

Conclusion: According to our meta-analysis results, the decreased PNI is markedly related to poor OS and inferior PFS/DFS/RFS of EC patients. Additionally, decreased PNI was indicative of features implying tumor progression and development in EC.

1. Introduction

Endometrial carcinoma (EC) ranks the second place among commonly diagnosed gynecologic malignant tumor globally, in particular among some developed countries [1]. Based on GLOBOCAN, it is estimated that there were 417,367 newly diagnosed EC cases and 97,370 death cases in 2021 worldwide [1]. Current evidence showed that the diagnosis of EC is mainly made in uterus (almost 67 %), while 21 % and 8 % of cases present with regional and distant disease at diagnosis [2]. Surgery remains the main treatment for early EC, which includes vaginal surgery, laparotomy, open surgery, laparoscopic surgery, and robotic surgery [3]. The current treatment for advanced-stage EC is surgery followed by adjuvant therapy. Although advances in treatment of EC have been made, EC patients still show dismal prognostic outcome in the past several decades. The 5-year survival rate in patients with advanced

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EC is around 30 %–60 %, compared to 80 %–97 % in patients with early stages [4]. Prognostic biomarkers are important for clinical management and improvement of survival outcomes of individual EC cases [5,6]. Consequently, identifying new and creditable prognostic biomarkers for EC is of urgent necessity.

Nutritional status has been found to have a significant impact on the development and progression of cancer [7]. Numerous hematological parameters including controlling nutritional status score [8], albumin-to-globulin ratio [9], geriatric nutritional risk index [10], and systemic immune-inflammation index [11]are reported to be significant factors for predicting prognosis of different cancer types. prognostic nutritional index (PNI) is a nutritional parameter which is derived: PNI = 10 × serum albumin (ALB) [g/dL] + 0.005 × total lymphocyte (TL) counts [/mm^3]. At first, PNI was applied in assessing nutrition in patients receiving gastrointestinal surgery [12]. Subsequently, many articles reveal that decreased PNI is related to inferior prognosis of diverse cancers, such as head and neck squamous cell carcinoma [13], esophageal cancer [14], nasopharyngeal carcinoma [15], gastric cancer [16], and colorectal cancer [17]. Many studies also have investigated effect of PNI on prognosis in EC, whereas no consistent findings are obtained [18–25]. For instance, PNI is reported in some research as the prominent biomarker for EC prognosis [19,20,24,25]. However, some other researchers failed to define any relation of PNI with prognosis in EC [18,23]. Therefore, the present meta-analysis was carried out for identifying precise value of PNI in determining prognosis of EC patients.

2. Methods

2.1. Study guideline

The present meta-analysis was carried out in line with guideline of Preferred Reporting Items for Systematic Reviews and Meta-Analyses [26].

2.2. Ethics statement

Since analysis was made using published studies, neither ethical approval nor patient consent was necessary.

2.3. Literature retrieval

From inception to January 5, 2024, we systematically searched PubMed, Web of Science, Embase, Cochrane Library, as well as China National Knowledge Infrastructure databases using search strategies below, (prognosis or survival or outcome) and (prognostic nutritional index) and (endometrial cancer or endometrial carcinoma or endometrial neoplasm or endometrium carcinoma). There were no restrictions on publication language. Supplemental file 1 provides detailed search strategies for each database. In addition, we conducted a thorough review of references in relevant original and review articles in order to identify potentially relevant studies during our manual screening process.

2.4. Eligibility criteria

The following studies were included: (1) those including EC patients regardless of type of treatment; (2) those measuring PNI through blood test before treatment; (3) those investigating association of PNI with EC prognosis; and (4) available hazard ratios (HRs) and 95 % confidence intervals (CIs). Studies below were excluded: (1) reviews, conference abstracts, and comments; (2) animal studies; and (3) studies recruiting overlapped patients.

2.5. Information collection and quality evaluation

Two researchers (SM and ZZ) selected eligible articles independently; any discrepancy between these authors was settled through opinion from a third researcher (YL) till reaching a consensus. Data below were obtained in every qualified article: first author's name, year, country, number of patients, design, study period, age, tumor stage, treatment, PNI threshold, cut-off value determination, survival outcomes, follow-up, survival analysis types, HRs and 95%CIs. Enrolled study quality was estimated with the use of Newcastle-Ottawa Scale (NOS) [27]. NOS includes 3 domains: selection, comparability and outcomes, with the scores ranging from 0 to 9. Studies of $\geq$6 points were high-quality.

2.6. Statistical analysis

Relation of PNI with prognosis of EC was examined by pooled HRs together with 95%CIs. Cochran's Q test and Higgins I^2 statistics were employed to determine heterogeneities among articles. The random-effects model should be applied in the presence of obvious heterogeneity ($p < 0.10$ or $I^2 > 50$ %); or else, the fixed-effect model should be adopted. Subgroup analysis was carried out for detecting heterogeneity source. The relationships of PNI with clinicopathological factors of EC were evaluated by odds ratios (ORs) and 95%CIs. Impact of individual studies on total result was analyzed through sensitivity analysis, in which each article was removed each time to examine pooled effect estimate for rest articles. In addition, Begg's funnel plots and Egger's regression analysis were adopted for estimating publication bias. Statistical analysis was conducted using Stata software version 12.0 (StataCorp LP, College Station, TX, USA). $P < 0.05$ stood for statistical significance.

3. Results

3.1. Process of study retrieval

From Fig. 1, 122 studies were obtained initially, among which, 94 were maintained following removing duplicate records. By title- and abstract-reviewing, we eliminated 82 articles due to irrelevance or animal studies, for the rest 12 articles, their full-texts were read. Subsequently, four articles were further eliminated below, not on PNI (n = 3) and overlapped patients enrolled (n = 1). Ultimately, the current meta-analysis enrolled totally eight articles involving 3,164 patients [18–25].

3.2. Enrolled study features

Table 1 shows basic study features. They were published from 2019 to 2024 [18–25]. Six studies were published in English [18, 21–25] and two studies were in Chinese [19,20]. The sample sizes were 32–894 (median, 378.5). There were seven retrospective articles [18–20,22–25] and one study was a prospective trial [21]. Five studied included EC cases at stage I-IV of International Federation of Gynecology and Obstetrics (FIGO) [19,21–23,25], and one each enrolled patients with stage IVB [18], I-III [20], and IA-IB [24], separately. The threshold was 43.1–52.8 and the median value was 51.075. Researchers used receiver operating characteristics (ROC) curves to determine cut-off values in six studies [19,20,22–25], and one each applied the median value [18] and literature [21]. All eight studies reported significance of PNI in predicting overall survival (OS) [18–25], while five reported association between PNI and progression-free survival (PFS)/disease-free survival (DFS)/recurrence-free survival (RFS) [19–21,24,25] in EC. Seven studies provided the HRs as well as 95%CIs through multivariate regression [18–22,24,25] and one study used univariate

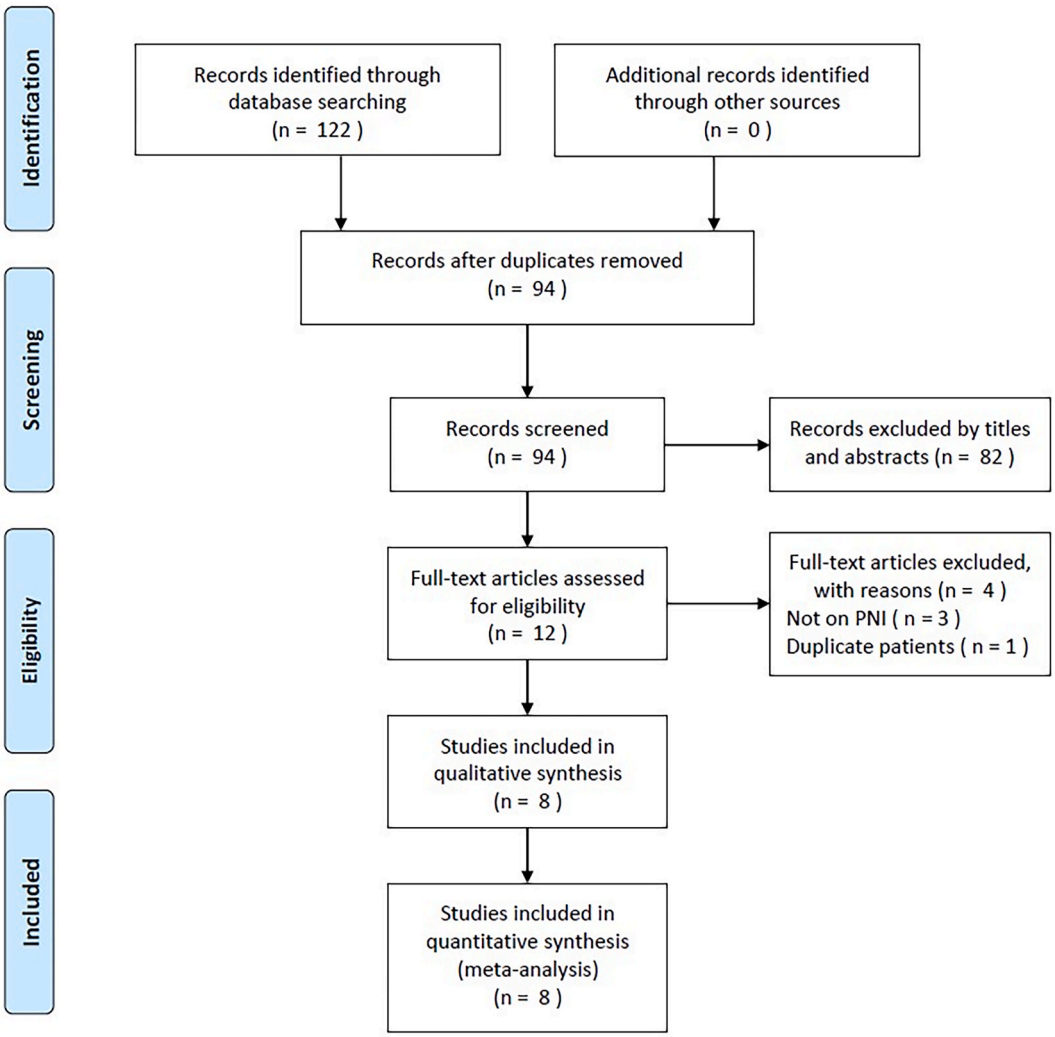

Fig. 1. PRISMA flow diagram of study selection process.

Table 1
Baseline characteristics of included studies in this meta-analysis.

Study	Year	Country	Sample size	Study period	Age (years) Median (range)	Study design	FIGO stage	Treatment	PNI cut-off value	Cut-off determination	Survival endpoints	Follow-up (months) Median (range)	Survival analysis	NOS score
Kiuchi, K.	2019	Japan	32	1997–2014	59.5 (36–83)	Retrospective	IVB	Mixed	43.1	Median value	OS	1–120	Multivariate	7
Zhao, F.	2021	China	101	2016–2018	40–75	Retrospective	I-IV	Surgery	45.0	ROC curve	OS, PFS	50.5(38–60)	Multivariate	8
Huang, B.	2022	China	156	2012–2017	54(28–78)	Retrospective	I-III	Surgery + CRT	51.95	ROC curve	OS, PFS	56.5(6–117)	Multivariate	7
Njoku, K.	2022	United Kingdom	439	2010–2016	67	Prospective	I-IV	Surgery	45.0	Literature	OS, RFS	1–60	Multivariate	9
Kim, Y. J.	2023	Korea	894	2005–2017	53	Retrospective	I-IV	Surgery	50.6	ROC curve	OS	1–180	Multivariate	8
Yuan, J.	2023	China	785	2012–2016	<60.5y: 607 ≥60.5y: 178	Retrospective	I-IV	Surgery	52.8	ROC curve	OS	1–60	Univariate	8
Zhang, N.	2023	China	387	2013–2017	55(26–84)	Retrospective	IA-IB	Surgery	51.55 for OS, 53.15 for DFS	ROC curve	OS, DFS	69(38–100)	Multivariate	7
Gen, Y.	2024	Korea	370	2010–2021	56(27–86)	Retrospective	I-IV	Surgery	52.74	ROC curve	OS, DFS	45(1–159)	Multivariate	8

FIGO, International Federation of Gynecology and Obstetrics; PNI, prognostic nutritional index; OS, overall survival; PFS, progression-free survival; DFS, disease-free survival; RFS, recurrence-free survival; CRT, chemoradiotherapy; NOS, Newcastle-Ottawa Scale; ROC, receiver operating characteristics.

analysis [23]. NOS scores were 7–9 (median, 8), which suggested high-quality studies. The detailed NOS scores of each included study are shown in Supplemental file 2.

3.3. PNI and OS of EC

All eight studies comprising 3,164 patients [18–25] mentioned significance of PNI in predicting OS of EC. We used the random-effects model owing to significant heterogeneity (I^2 = 80 %, p < 0.001). HR = 1.72, 95%CI = 1.33–2.22, p < 0.001 were obtained, suggesting low PNI as the factor significantly predicting OS of EC patients (Fig. 2; Table 2). As shown by subgroup analysis, decreased PNI significantly predicted the worse OS irrespective of region, study design, sample size, treatment, tumor stage, or threshold (p < 0.05; Table 2).

3.4. PNI and PFS/DFS/RFS in EC

A total of five studies consisting of 1,453 patients [19–21,24,25] presented the data on significance of PNI for predicting PFS/DFS/RFS of EC. The combined results indicated that low PNI showed marked relation to inferior PFS of EC (HR = 2.49, 95%CI = 1.62–3.84, p < 0.001) (Fig. 3). Based on subgroup analysis, a low PNI represented the significant prognostic marker of dismal PFS regardless of sample size, tumor stage, treatment, and threshold (p < 0.05; Table 3).

3.5. PNI and clinicopathological features for EC

There were 6 articles enrolling 2,347 cases [19–22,24,25] investigating the relation of PNI with clinicopathological features in EC. As shown by pooled results in Table 4, a low PNI showed significant connection to FIGO stage III-IV (OR = 2.06, 95%CI = 1.42–2.99, p < 0.001) (Fig. 4A), tumor grade of G3 (OR = 1.68, 95%CI = 1.32–2.14, p < 0.001) (Fig. 4B), presence of lymphovascular space invasion (LVSI) (OR = 1.72, 95%CI = 1.14–2.61, p = 0.010) (Fig. 4C), and presence of myometrial invasion (MMI) (OR = 2.04, 95%CI = 1.51–2.77, p < 0.001) (Fig. 4D).

3.6. Sensitivity analysis

To examine whether any one study influenced the overall results, we conducted sensitivity analysis. Through removing each study each time, OS (Fig. 5A) and PFS (Fig. 5B) results were not significantly influenced, suggesting that the overall results were uninfluenced by individual studies.

3.7. Publication bias

The publication bias was analyzed using Begg's test and Egger's linear regression test. As a result, no obvious publication bias was detected for OS (p = 0.174 and 0.096 upon Begg's and Egger's test separately; Fig. 6A and B) or PFS (p = 0.462 and 0.138 upon Begg's and Egger's test separately) in the current meta-analysis (Fig. 6C and D).

4. Discussion

Significance of pretreatment PNI for EC cases is previously analyzed, but no consistent findings are obtained. This work integrated data from eight articles with 3,164 cases to identify this issue [18–25]. Our results revealed that low PNI showed obvious relation to dismal OS and inferior PFS/DFS/RFS among EC cases. Based on subgroup analysis, PNI still significantly predicted the prognosis of OS

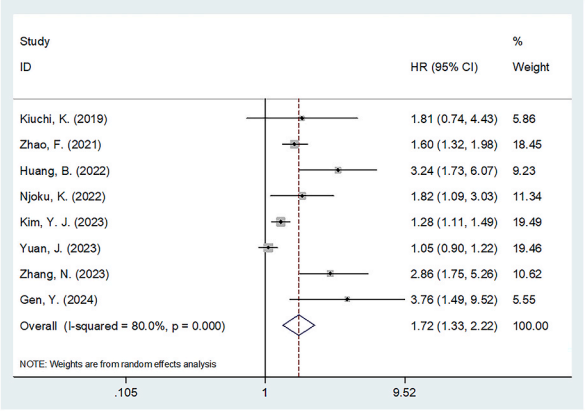

Fig. 2. Forest plot assessing the relationship between the PNI and OS in patients with EC.

Table 2
Subgroup analysis of the prognostic value of PNI for OS in patients with endometrial cancer.

Subgroups	No. of studies	No. of patients	Effects model	HR (95%CI)	p	Heterogeneity I^2(%)	Ph
Total	8	3,164	Random	1.72(1.33–2.22)	<0.001	80.0	<0.001
Geographical region							
Asian	7	2,725	Random	1.71(1.30–2.25)	<0.001	82.1	<0.001
Non-Asian	1	439	–	1.82(1.09–3.04)	0.022	–	–
Sample size							
<380	4	659	Random	2.23(1.41–3.54)	0.001	57.4	0.071
≥380	4	2,505	Random	1.45(1.08–1.94)	0.013	81.2	0.001
Study design							
Retrospective	7	2,725	Random	1.71(1.30–2.25)	<0.001	82.1	<0.001
Prospective	1	439	–	1.82(1.09–3.04)	0.022	–	–
Tumor stage							
I-IV	5	2,589	Random	1.42(1.12–1.81)	0.004	78.3	0.001
I/I-III/IV	3	575	Fixed	2.76(1.89–4.01)	<0.001	0	0.572
Treatment							
Surgery	6	2,976	Random	1.57(1.22–2.03)	0.001	81.2	<0.001
Mixed/Surgery + CRT	2	188	Fixed	2.67(1.60–4.47)	<0.001	8.0	0.297
Cut-off value of PNI							
<50	3	572	Fixed	1.64(1.36–1.97)	<0.001	0	0.879
≥50	5	2,592	Random	1.80(1.25–2.59)	0.002	85.9	<0.001
Survival analysis							
Univariate	1	785	–	1.05(0.90–1.22)	0.541	–	–
Multivariate	7	2,379	Random	1.92(1.46–2.54)	<0.001	70.1	0.003

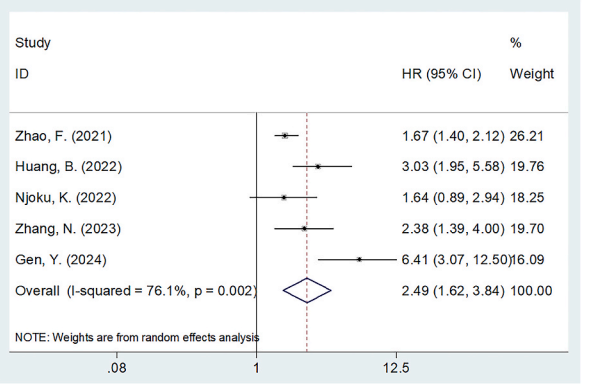

Fig. 3. Forest plot assessing the association between the PNI and PFS/DFS/RFS in patients with EC.

and PFS, regardless of sample size, tumor stage, treatment, and threshold. Moreover, we uncovered obvious correlation of decreased PNI with advanced tumor stage, higher tumor grade, presence of LVSI and MMI in patients with EC. These results suggested that EC cases showing low PNI could have higher malignancy degree and tumor progression. Collectively, the present work suggested low PNI as the reliable prognostic marker of poor long- and short-time survival outcomes for EC patients. Based on our knowledge, this study is the first meta-analysis to investigate significance of PNI for predicting EC prognosis.

PNI was calculated based on ALB level and TL counts. Therefore, a low PNI could be the results of low ALB levels and decreased TL counts. Although mechanisms related to the significance of PNI for EC remain to be further explored, they are interpreted as follows. On the one hand, it has been proven that serum ALB is a reliable indicator of nutritional status in patients [28]. As a result, malnutrition can negatively affect a person's immune system and, as a result, their cancer outcomes [29]. The presence of hypoalbuminemia indicates poor nutritional status, impaired immune function and antigen-presenting cells, which correlate with poor prognoses for cancer patients [30]. On the other hand, lymphocytes, particularly T-lymphocytes, are key regulators of anti-tumor immune activity [31]. It is well known that lymphocyte-dependent cellular immunity plays an important role in immunologically destroying cancer cells [32]. Anti-tumor immunity relies on immune surveillance, but tumor cells can escape detection by reducing $CD4^+$ and $CD8^+$ lymphocytes [33]. The presence of lymphopenia implied impaired host immunity to tumors, and has been correlated with disease severity [34]. Therefore, PNI served as the reliable marker of cancer prognosis based on ALB and TL counts.

The relationship of nutrition and inflammation is complex and the interaction between the in common in diseases [35,36]. Patients with acute and chronic illnesses often suffer from disease-related malnutrition (DRM) [35]. The primary causes of DRM are inflammation, undernutrition-driven catabolism, and an inadequate diet [37]. A growing body of evidence suggests that specific dietary interventions can promote tumor control by enhancing immune cells [38]. Many nutrition and inflammation assessment tools are also

Table 3
Subgroup analysis of the prognostic value of PNI for PFS/DFS/RFS in patients with endometrial cancer.

Subgroups	No. of studies	No. of patients	Effects model	HR (95%CI)	p	Heterogeneity I^2(%)	Ph
Total	5	1,453	Random	2.49(1.62–3.84)	<0.001	76.1	0.002
Geographical region							
Asian	4	1,014	Random	2.78(1.63–4.74)	<0.001	81.6	0.001
Non-Asian	1	439	–	1.64(0.90–2.97)	0.104	–	–
Sample size							
<380	3	627	Random	3.01(1.42–6.38)	0.004	87.4	<0.001
≥380	2	826	Fixed	2.02(1.36–3.00)	<0.001	0	0.358
Study design							
Retrospective	4	1,014	Random	2.78(1.63–4.74)	<0.001	81.6	0.001
Prospective	1	439	–	1.64(0.90–2.97)	0.104	–	–
Tumor stage							
I-IV	3	910	Random	2.46(1.19–5.10)	0.015	84.7	0.001
I/I-III/IV	2	543	Fixed	2.69(1.85–3.90)	<0.001	0	0.525
Treatment							
Surgery	4	1,297	Random	2.39(1.43–4.00)	<0.001	78.5	0.003
Mixed/Surgery + CRT	1	156	–	3.03(1.79–51.3)	<0.001	–	–
Cut-off value of PNI							
<50	2	540	Fixed	1.67(1.37–2.03)	<0.001	0	0.954
≥50	3	913	Random	3.43(2.02–5.83)	<0.001	59.9	0.083

Table 4
The correlation between PNI and clinicopathological features in patients with endometrial cancer.

Variables	No. of studies	No. of patients	Effects model	OR (95%CI)	p	Heterogeneity I^2(%)	Ph
FIGO stage (III-IV vs I-II)	5	1,960	Random	2.06(1.42–2.99)	<0.001	50.4	0.089
Tumor grade (G3 vs G1-G2)	5	2,191	Fixed	1.68(1.32–2.14)	<0.001	25.8	0.250
LVSI (yes vs no)	5	1,960	Random	1.72(1.14–2.61)	0.010	65.2	0.022
MMI (≥50 % vs <50 %)	3	910	Fixed	2.04(1.51–2.77)	<0.001	0	0.612

LVSI, lymphovascular space invasion; MMI, myometrial invasion.

widely used in cancer treatment [39]. In this meta-analysis, we also identified the association between PNI and advanced FIGO stage III-IV, tumor grade of G3, presence of LVSI, and presence of MMI, which indicated the progression and development of EC. These results suggested that EC patients with low PNI may experience high risk of disease progression and more comprehensive treatment strategies may be considered.

The role of PNI in predicting different cancer prognoses is extensively reported by meta-analysis. According to Zheng et al., the decreased baseline PNI was notably related to dismal OS and PFS of prostate cancer in the meta-analysis including 1,631 cases [40]. As discovered by Zhang and colleagues, the decreased PNI was linked with shortened OS and PFS in breast cancer from their meta-analysis involving 2,212 patients [41]. Based on the meta-analysis including 17 articles, the decreased PNI levels were significantly connected to dismal OS and PFS of gastrointestinal cancer patients receiving immune checkpoint inhibitors [42]. Tan et al. performed a meta-analysis incorporating 3,190 patients and revealed that ovarian cancer patients with low PNI had significantly shortened OS, PFS, and cancer-specific survival [43]. As found by Hung et al., the decreased PNI was related to inferior OS and PFS of glioma in the meta-analysis with 13 studies [44]. Our findings conformed to findings regarding PNI in other cancers.

PNI is an index based on laboratory test and is cost-effective. Considering that PNI is an effective prognostic marker for EC and many other cancer types, it should be routinely tested in management of cancer cases. Furthermore, during the follow-up of patients with EC, PNI is also a valuable indicator for cancer progression.

In the present study, there are some limitations to be noted. First, many enrolled studies are retrospective studies, so the potential bias was not inevitable. Second, there was significant heterogeneity in the pooled estimates, which may be caused by the inherent retrospective nature. Third, PNI threshold was non-uniform across eligible articles. Therefore, selection bias may be introduced in this meta-analysis. Fourth, this meta-analysis only examined pretreatment PNI of EC patients. Studies have also shown that post-operative PNI affects survival for cancer patients. As a result, the PNI is dynamic and some patients may have a higher PNI preoperatively but have a lower PNI after surgery. Therefore, the dynamic changes of PNI for prognosis of EC should be investigated in future studies. Due to the abovementioned limitations, large-scale prospective studies using standard PNI cut-off value are still needed to verify the findings.

5. Conclusions

In summary, according to our meta-analysis results, a low PNI is markedly related to poor OS and inferior PFS/DFS/RFS of EC patients. Additionally, decreased PNI was indicative of features implying tumor progression and development in EC.

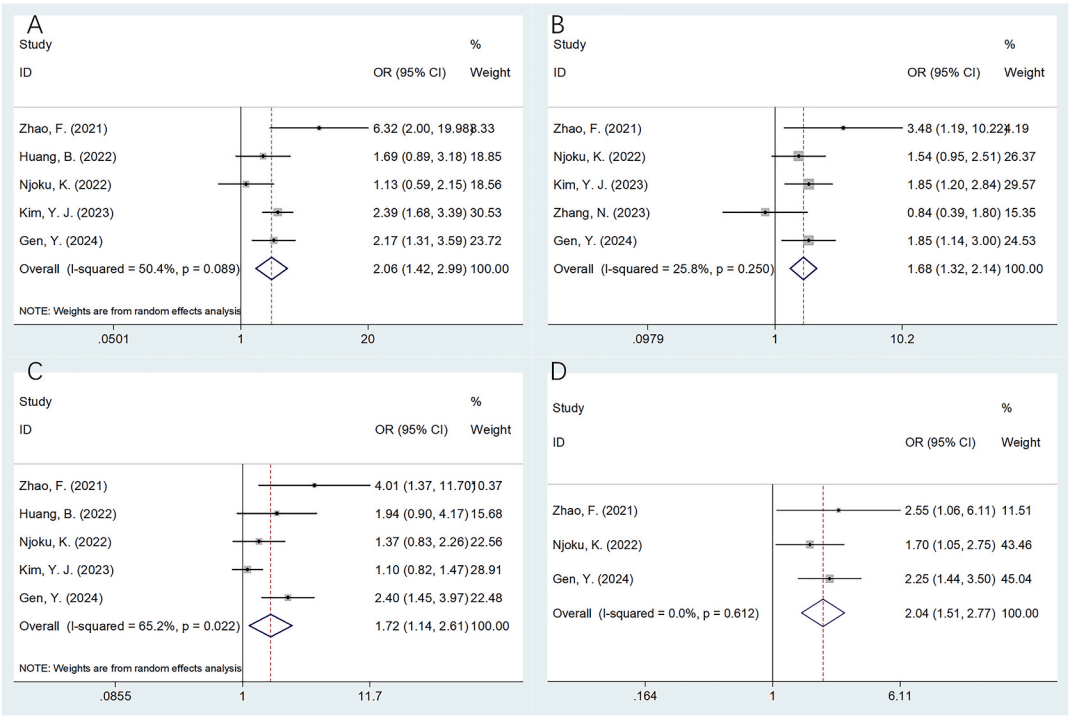

Fig. 4. Forest plots assessing the relationship between the PNI and clinicopathological factors in patients with EC. (A) FIGO stage (III-IV vs I-II); (B) tumor grade (G3 vs G1-G2); (C) LVSI (yes vs no); and (D) MMI (≥50 % vs <50 %).

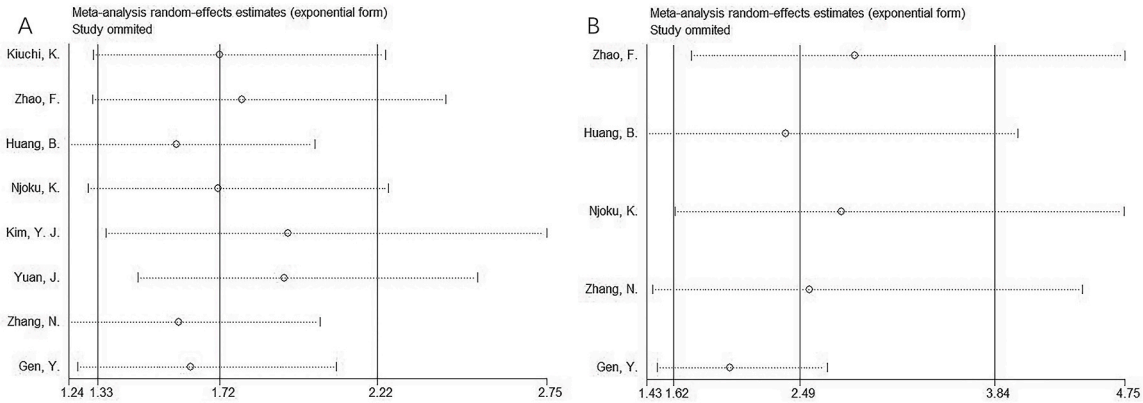

Fig. 5. Sensitivity analysis. (A) OS and (B) PFS/DFS/RFS.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Funding

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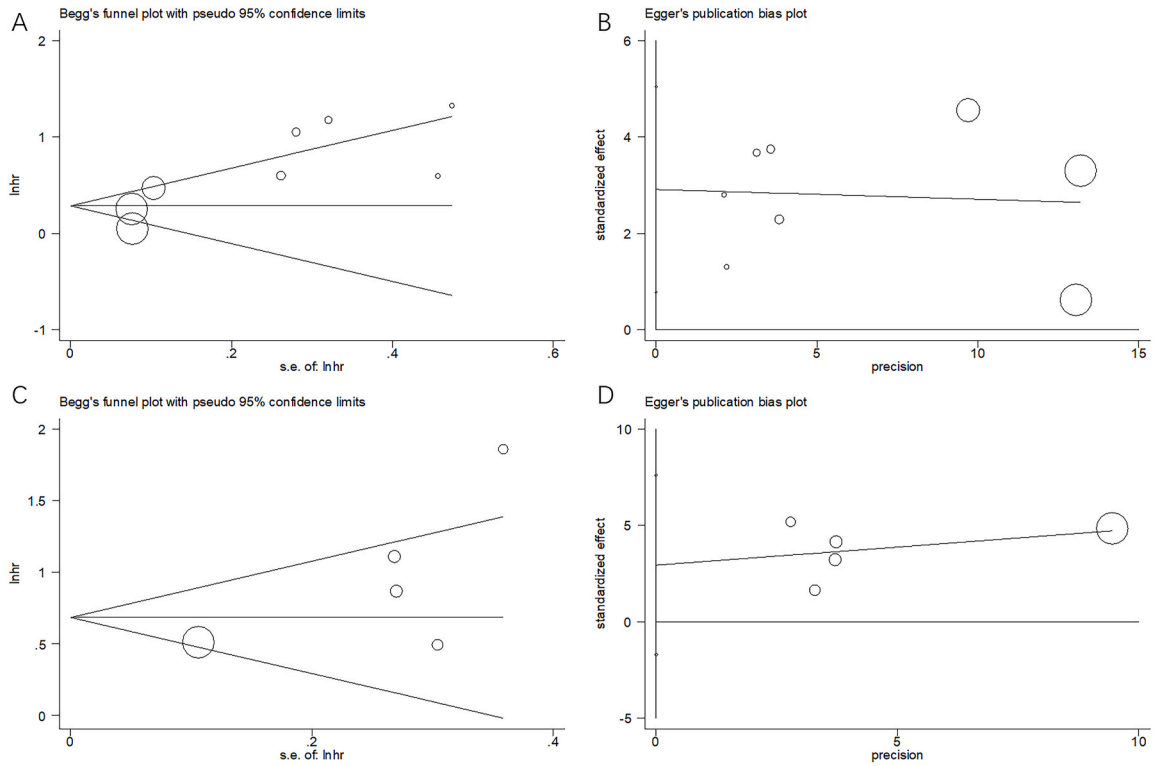

Fig. 6. Publication bias tests. (A) Begg's test for OS, p = 0.174; (B) Egger's test for OS, p = 0.096; (C) Begg's test for PFS/DFS/RFS, p = 0.462; and (D) Egger's test for PFS/DFS/RFS, p = 0.138.

Data availability statement

Data will be made available on request.

CRediT authorship contribution statement

Shuiying Mao: Writing – original draft, Validation, Supervision, Resources, Project administration, Formal analysis, Data curation, Conceptualization. **Zongxin Zhang:** Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Yun Li:** Writing – review & editing, Validation, Supervision, Software, Resources, Project administration, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

None.

Abbreviations

PNI	prognostic nutritional index
EC	endometrial cancer
HR	hazard ratio
CI	confidence interval
PFS	progression-free survival
TL	total lymphocyte

LVSI	lymphovascular space invasion
MMI	myometrial invasion
OS	overall survival
ALB	albumin

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e35211.

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