Systematic Review and Meta-Analysis

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Prognostic significance of preoperative prognostic nutritional index in ovarian cancer

A systematic review and meta-analysis

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Abstract

Background: The prognostic significance of preoperative prognostic nutritional index (PNI) in ovarian cancer (OC) is uncertain, and this study is aimed to clarify the prognostic significance.

Methods: We used 4 common databases for conducting a systematic review and meta-analysis, and eligible studies were included in the analysis. The association of preoperative PNI with overall survival (OS), progression-free survival (PFS), and clinicopathological parameters was analyzed.

Results: A total of 2050 patients with OC receiving the surgical treatment were analyzed in this study. Patients with low PNI tended to have a shorter OS (hazard ratio [HR] = 1.82, 95% CI = 1.30–2.55, $P < .01$) and PFS (HR = 1.91, 95% CI = 1.53–2.39, $P < .01$) compared with those with high PNI. Besides, low PNI was significantly associated with more advanced International Federation of Gynecology and Obstetrics stage ($P < .01$), the occurrence of ascites ($P < .01$), larger residual tumor ($P < .01$), insensitive to chemotherapy ($P < .01$), and higher CA125 ($P < .01$) compared with high PNI in OC.

Conclusion: Low preoperative PNI is associated with shorter OS, shorter PFS, and worse clinicopathological parameters in OC. Low preoperative PNI is an unfavorable prognostic indicator of patients with OC.

Abbreviations: CI = confidence interval, CSS = cancer-specific survival, HR = hazard ratio, NOS = Newcastle-Ottawa Scale, OC = ovarian cancer, OR = odds ratio, OS = overall survival, PFS = progression-free survival, PNI = prognostic nutritional index.

Keywords: meta-analysis, ovarian cancer, prognosis, prognostic nutritional index

1. Introduction

Ovarian cancer is one of the most common causes of women's mortality worldwide.[1] Despite significant improvement of diagnosis and therapy, many patients with ovarian cancer (OC) suffer from a poor prognosis, especially those at advanced stage.[2] To deal with this dilemma, researchers begin to seek biomarkers to assist the clinical-decision making and predict the prognosis of OC.[3–5] Unfortunately, no optional biomarker with satisfactory sensibility and specificity has been recognized to predict the prognosis of OC up to now.

The abnormal condition of nutrition and immunologic status place a vital role in tumorgenesis and progression.[6,7] Prognostic nutritional index (PNI), calculated using the following method: $10 \times$ serum albumin (g/dL) $+ 0.005 \times$ total lymphocyte count (per mm^3) in peripheral blood, can both reflect the nutrition and immunologic status of patients with cancers.[8] The prognostic value of pretreatment PNI has been verified in several tumors, such as pancreatic cancer,[9] liver cancer,[10] and colorectal cancer.[11] Recently increasing evidence showed that preoperative PNI might predict the prognosis of ovarian cancer patients. However, due to the limited sample size and contradictory results of existing studies, the prognostic significance of PNI is still uncertain at this point.[12–17] Therefore, for the first time, we conducted this systematic review and meta-analysis to clarify the association between preoperative PNI and prognosis of OC.

2. Materials and methods

This study has been approved by the review board of our hospital and was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[18]

2.1. Eligibility criteria

The inclusion criteria were as follows: Participant: patients with OC receiving the surgical treatment; Intervention: Patients with high level of preoperative PNI; Control: Patients with low level of

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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preoperative PNI; Outcomes: clinicopathological parameters and survivals, including overall survival (OS), cancer-specific survival (CSS), and progression-free survival (PFS); Study design: retrospective or prospective studies. The exclusion criteria included duplications, cell or animal experiments, reviews or case reports, studies without full-texts, and studies without sufficient data.

2.2. Literature search and selection

We comprehensively searched the PubMed, Web of Science, Embase, and Wanfang Database on February 16, 2020. The search strategy was as follows: ("prognostic nutritional index" OR "PNI") AND ("ovarian cancer" OR "ovarian carcinoma" OR "carcinoma of ovary") AND ("survival" OR "prognosis"). The references of retrieved studies were also checked to avoid missing relevant studies. Then, study selection was conducted by 2 authors independently using the eligibility criteria, and any disagreement would be solved by group discussion.

2.3. Data collection and risk of bias

We extracted the following items from included studies: the first author, published year, country of enrolled patients, study design, age, histology of OC, number of patients, the cutoff value of PNI, International Federation of Gynecology and Obstetrics (FIGO) stage, outcomes, median duration of OS, and analysis model of OS, and chemotherapy. With respect to prognostic outcomes such as OS, CSS, and PFS, we extracted hazard ratio (HR) with 95% confidence interval (CI) from included studies. If HR and 95% CI were not directly reported, we would calculate both of them as described by *Tierney*.[19] We used the Newcastle–Ottawa Scale (NOS), which contained 3 components (selection, comparability, and outcome), to evaluate the risk of bias of included studies. The study with the value of NOS less than 6 was considered to have a high risk of bias.[20]

2.4. Statistical analysis

The analyses were performed using Stata 12.0 (StataCorp, College Station, TX) and Review Manager 5.3 (Cochrane Collaboration, London, UK). The data of OS, CSS, and PFS was pooled using HRs and corresponding 95% CI, and the data of clinicopathological parameters was pooled using odd ratio (OR) and 95% CI. Besides, we used Q and I^2 statistics to evaluate the heterogeneity across studies. We used the random-effect model if there was significant heterogeneity across studies ($P < .10$ or $I^2 > 50\%$), otherwise, a fixed-effect model was used. Subgroup analysis was carried out to determine the association between preoperative PNI and OS. Sensitivity analysis was conducted to test the robustness of final results by omitting one study at a time and then calculating the combined HR. Begg test and Egger test were performed to evaluate the publication bias among included studies. A 2-sided P value $< .05$ was considered as a significant association of preoperative PNI with prognosis in OC.

3. Results

3.1. Literature search and selection

As showed in Figure 1, a total of 136 records were obtained from common databases. After the removal of duplications, 62 records remained for further analysis. Forty-four records were directly excluded by scanning the titles or abstracts, and full-texts of remaining 18 records were carefully evaluated. Twelve records were excluded for irrelevant to this topic (n = 5), duplicated patients (n = 1), review type (n = 2), cell experiments (n = 3), and insufficient data (n = 1). At last, 6 studies were included into this systematic review and meta-analysis.[12–17]

3.2. Characteristics of included studies

As listed in Table 1, a total of 2050 patients with OC were included into the analysis, all patients were at first diagnosis and received the surgical treatment with or without chemotherapy.[12–17] Five studies were conducted in China[12,13,15–17] and 1 study was conducted in Japan.[14] Especially, Komura et al study contained 2 independent cohorts focusing on early-stage and advanced-stage OC, respectively.[14] The median age of patients ranged from 50 to 56 years old, and there were 563 patients at early FIGO stage (I/II) and 1487 patients at advanced FIGO stage (III/IV). Three methods were used to determine the cut-off value of PNI, including receiver operating characteristic curve,[14–16] cut-off finder (http://molpath.charite.de/cutoff),[13,17] and median value.[12] The cut-off value of PNI ranged from 42.9 to 48.8 across included studies. Regarding outcomes, OS, CSS, PFS, and clinicopathological parameters were reported among included studies. The median of OS ranged from 19.7 to 44.0 months in low PNI group and 37.1 to 68.8 months in high PNI group. The association of PNI with OS was evaluated using univariate analysis in 1 study[15] and using multivariate analysis in 5 studies.[12–14,16,17]

3.3. Association of preoperative PNI with OS

Five studies reported the OS and 1 study reported the CSS of OC patients, and all of them were included into the meta-analysis of association between preoperative PNI and OS in OC[12–17] (Fig. 2). A random-effect model was used for obvious heterogeneity among studies ($I^2 = 75\%$, $P < .01$), and patients with low PNI tended to have a shorter OS compared with those with high PNI (HR = 1.82, 95%CI = 1.30–2.55, $P < .01$). The Galbraith plot conducted by Stata 12.0 showed Feng et al study was the main source of heterogeneity (Fig. 3), and the heterogeneity reduced from 75% to 8% after the removal of Feng et al study. The association of PNI with OS remained significant after the removal of Feng et al study (HR = 2.02, 95% CI = 1.68–2.44, $P < .01$; $I^2 = 8\%$, $P = .36$) (Fig. 4).

To comprehensively evaluate the association between PNI and OS in OC, subgroup analysis was performed classified by the country, sample size, method of cut-off value, and analysis model. The association of PNI level with OS remained significant in most analyses ($P < .05$) except for studies conducted in other countries outside of China ($P = .06$) (Table 2).

3.4. Association of preoperative PNI with PFS

Three studies reported the association between preoperative PNI and PFS in OC,[14,16,17] and a fixed-effect model was used for the tiny heterogeneity ($I^2 = 20\%$, $P_{\text{heterogeneity}} = .29$). Pooled analysis showed low PNI was obviously associated with shorter PFS compared with high PNI in OC (HR = 1.91, 95% CI = 1.53–2.39, $P < .01$) (Fig. 5).

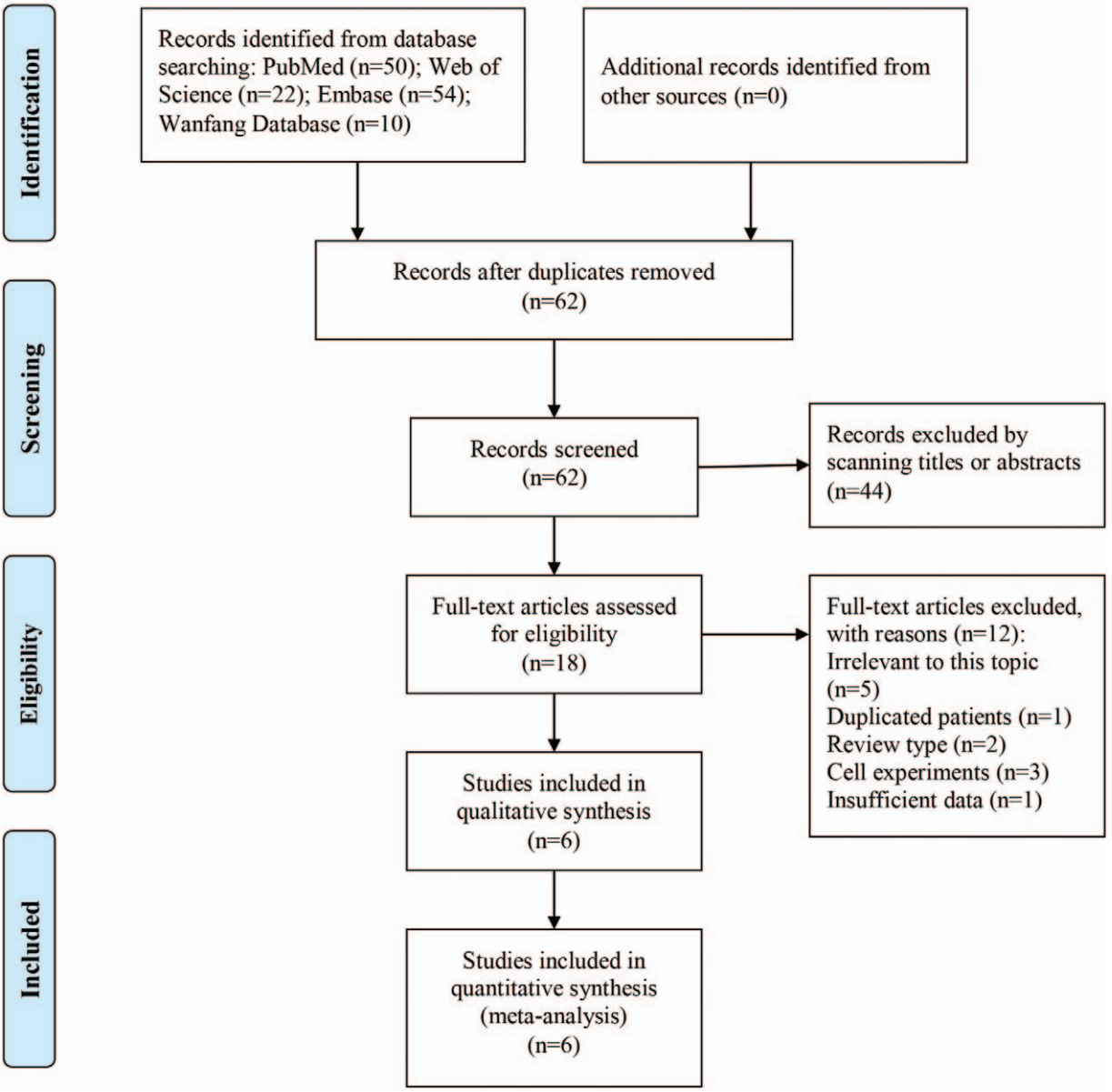

Figure 1. Flow chart of literature search and selectin.

3.5. Association of preoperative PNI with clinicopathological parameters

As listed in Table 3, low PNI was significantly associated with more advanced FIGO stage (OR = 1.05, 95% CI = 0.70–1.59, $P < .01$), the occurrence of ascites (OR = 3.67, 95% CI = 2.24–6.00, $P < .01$), larger residual tumor (OR = 2.89, 95% CI = 2.26–3.69, $P < .01$), insensitive to chemotherapy (OR = 2.15, 95% CI = 1.64–2.80, $P < .01$), and higher CA125 level (OR = 2.58, 95% CI = 2.02–3.29, $P < .01$) compared with high PNI in OC. There was no obvious association of PNI with age ($P = .80$), body mass index ($P = .07$), histology ($P = .81$), or tumor differentiation ($P = .96$).

3.6. Sensitivity analysis

Sensitivity analysis showed the pooled HR was not obviously affected by the exclusion of any single study in terms of OS (Fig. 6A) and PFS (Fig. 6B), which indicated our results were reliable.

3.7. Publication bias

Begg test and Egger test were performed to evaluate the publication bias, and results showed there was no obvious publication bias among included studies in the analyses of OS (Fig. 7A) (Begg test, $P = .73$; Egger test, $P = .40$), PFS (Fig. 7B) (Begg test, $P = 1.00$; Egger test, $P = .23$) and clinicopathological parameters (Begg test, $P > .05$; Egger test, $P > .05$) (Table 3).

4. Discussion

Prognostic value of pretreatment PNI has been confirmed in several human cancers,[9,10,21,22] however, the agreement on the prognostic significance of preoperative PNI in OC has not been

Table 1

Characteristics of included studies.

Study	Country	Study design	Age (year) (median, range)	Histology	Level of PNI (n) (total/low/high)	Cut-off value		FIGO stage(n) (I+II/III+IV)
						Value	Method	
Chen et al 2018 (12)	China	R	55 (15–80)	OC	86/41/45	43.0	Median	31/55
Feng et al 2018 (13)	China	R	56 (30–90)	HSOC	866/394/472	45.5	Cutoff finder	75/800
Komura et al 2019 (1) (14)	Japan	R	<51 (n=64)/≥51 (n=100)	EOC	164/44/120	44.7	ROC	164/0
Komura et al 2019 (2) (14)	Japan	R	<51 (n=37)/≥51 (n=104)	EOC	144/81/63	42.9	ROC	0/144
Liu et al 2017 (15)	China	R	53 (18–83)	OC	200/54/146	48.8	ROC	58/142
Miao et al 2016 (16)	China	R	55 (45–84)	EOC	344/101/243	45.0	ROC	168/176
Zhang et al 2017 (17)	China	R	50 (24–76)	OC	237/137/100	47.2	Cutoff finder	67/170

Study	Outcome	OS (median, month) (low/high)	Analysis model of OS	NOS	Chemotherapy
Chen et al 2018 (12)	CP,OS	19.7/37.1	M	8	NA
Feng et al 2018 (13)	CP,OS	44.0/64.0	M	8	Adjuvant platinum-based chemotherapy
Komura et al 2019 (1) (14)	CP,PFS,CSS	NA	M	9	Adjuvant chemotherapy: Paclitaxel (175 mg/m^2)+Carboplatin (area under the curve: 5)
Komura et al 2019 (2) (14)	CP,PFS,CSS	31.0/NA	M	9	Neoadjuvant platinum-based chemotherapy
Liu et al 2017 (15)	OS	37.5	U	6	Adjuvant platinum-based chemotherapy
Miao et al 2016 (16)	CP,PFS,OS	26.0/47.0	M	9	Adjuvant chemotherapy: Paclitaxel (175 mg/m^2)+Carboplatin (area under the curve: 5)
Zhang et al 2017 (17)	CP,PFS,OS	38.7/68.8	M	9	Adjuvant platinum-based chemotherapy

CP = clinicopathological parameters, CSS = disease-specific survival, EOC = epithelial ovarian cancer, FIGO = International Federation of Gynecology and Obstetrics, HSOC = high-grade serous ovarian cancer, M = multivariate, NA = not available, NOS = Newcastle–Ottawa Scale, OC = ovarian cancer, OS = overall survival, PFS = progression-free survival, PNI = prognostic nutritional index, R = retrospective, ROC = receiver operating characteristic, U = univariate.

reached for contradictory results and small sample size of existing evidence.[12–17] Komura et al[14] study analyzed 164 patients with early-stage OC, and authors failed to observe the statistical association of preoperative PNI with PFS ($P=.58$) and OS ($P=.99$). Similarly, Feng et al[13] also did not detect the relationship between preoperative PNI and OS using the multivariate analysis model ($P>.05$). Differently, shorter OS was found in patients with low PNI compared with patients with high PNI in OC in Zhang et al study[17] and Miao et al study.[16] To deal with this controversy, we performed this systematic review and meta-analysis, and our results showed, compared with patients with high preoperative PNI, patients with low preoperative PNI tended to have shorter OS ($P<.01$), shorter PFS ($P<.01$), and worse clinicopathological features, including more advanced FIGO stage ($P<.01$), the occurrence of ascites ($P<.01$), larger residual tumor ($P<.01$), insensitive to chemotherapy ($P<.01$), and higher CA125 level ($P<.01$) in OC. Therefore, our study showed low preoperative PNI was an unfavorable prognostic indicator of patients with OC, and preoperative PNI could serve as a predict biomarker for the prognosis of OC.

In the subgroup analysis of OS stratified by the country, we failed to observe the significant association between preoperative PNI and OS in other countries outside of China. However, this finding should be treated with caution because only Komura et al study containing 2 cohorts was included into the analysis.[14] Moreover, no significant relationship between preoperative PNI and prognosis was observed in patients at early stage in Komura et al study,[14] which reminded us that the prognostic value of preoperative PNI in early-stage OC was uncertain. Therefore, future studies should focus on the prognostic role of preoperative PNI in OC in other countries or in patients at early stage.

Although plenty of studies have shown PNI had the potential ability to predict the prognosis of cancers, the underlying mechanism remained unclear. The level of albumin can reveal the nutritional status of cancer patients, and low albumin level stands for the malnutrition of cancer patients, which can result in the poor prognosis and increase the cancer-related mortality.[23,24] A

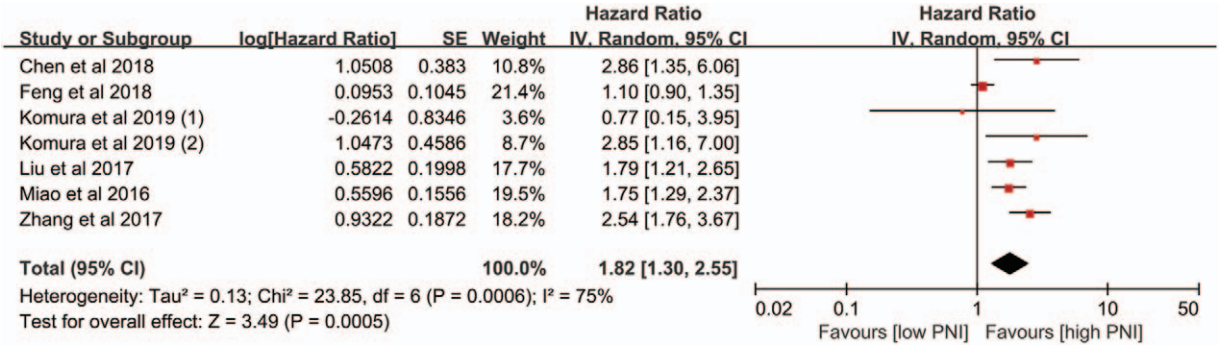

Figure 2. Meta-analysis of association between preoperative PNI and OS. OS = overall survival, PNI = prognostic nutritional index.

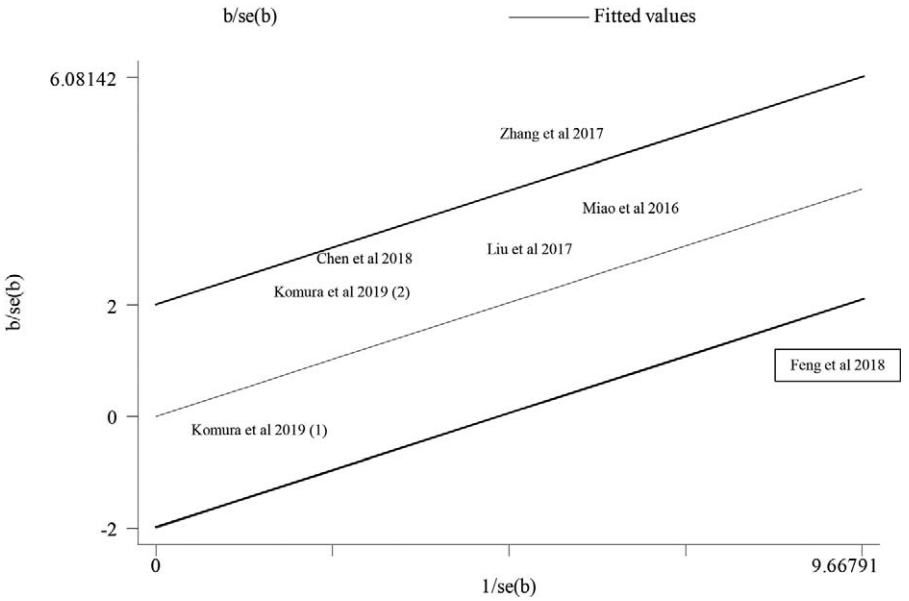

Figure 3. Galbraith plot for the source of heterogeneity.

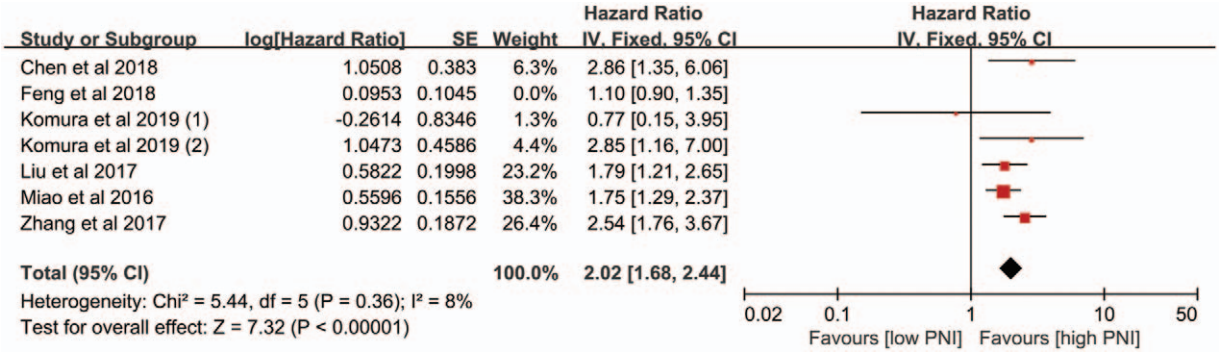

Figure 4. Meta-analysis of association between preoperative PNI and OS after the removal of Feng et al study. OS = overall survival, PNI = prognostic nutritional index.

Table 2

Subgroup analysis of association between preoperative PNI and OS.

Variables	Included cohort (n)	HR 95% CI	*P*	I^2 (%)	*P* for heterogeneity	Model
Country						
China	4	2.02 (1.66, 2.45)	<.01*	15	.32	Fixed
Others	2	2.10 (0.96, 4.63)	.06	47	.17	Fixed
Sample size (n)						
<200	3	2.47 (1.44, 4.26)	<.01*	9	.33	Fixed
≥200	3	1.97 (1.61, 2.41)	<.01*	25	.27	Fixed
Methods of cut-off value						
ROC	4	1.79 (1.42, 2.26)	<.01*	0	.56	Fixed
Others	2	2.60 (1.87, 3.61)	<.01*	0	.78	Fixed
Analysis model						
Univariate	1	1.79 (1.21, 2.65)	<.01*	NA	NA	Fixed
Multivariate	5	2.10 (1.69, 2.61)	<.01*	19	.29	Fixed

CI = confidence interval, HR = hazard ratio, NA = not available, OS = overall survival, PNI = prognostic nutritional index, ROC = receiver operating characteristic.
* $P < .05$ indicating significant association between OS and preoperative PNI.

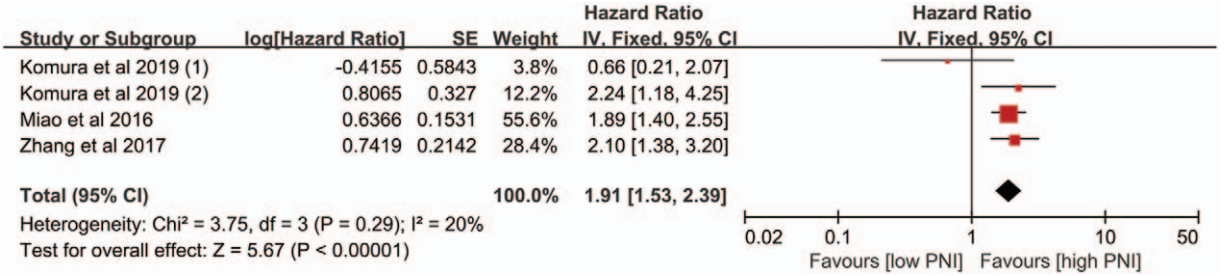

Figure 5. Meta-analysis of association between preoperative PNI and PFS. PNI = prognostic nutritional index, PFS = progression-free survival.

Table 3

Meta-analysis of association between preoperative PNI and clinicopathological parameters.

Variables	Included cohort (n)	Patients (n)	OR 95% CI	*P*	Heterogeneity	*P* for heterogeneity	Model	Begg test	Egger test
Age (old/young)	6	1841	1.05 (0.70, 1.59)	.80	67	.01	Random	0.71	0.96
FIGO stage (III+IV/I+II)	4	1533	3.67 (2.24, 6.00)	<.01*	58	.07	Random	0.12	0.06
Ascites (yes/no)	5	1728	4.19 (2.09, 8.38)	<.01*	83	<.01	Random	0.81	0.43
Residual tumor (large/small)	3	1447	2.89 (2.26, 3.69)	<.01*	0	.95	Fixed	0.30	0.56
Chemosensitivity (insensitive/sensitive)	2	1103	2.15 (1.64, 2.80)	<.01*	37	.21	Random	NA	NA
BMI (kg/m^2) (≥18.5/<18.5)	2	1084	0.64 (0.40, 1.04)	.07	0	.72	Fixed	NA	NA
Histology (serous/nonserous)	4	861	0.91 (0.42, 1.96)	.81	82	<.01	Random	1.00	1.00
Tumor differentiation (G3/G1+G2)	2	563	1.02 (0.48, 2.18)	.96	77	.04	Random	NA	NA
CA125 (high/low)	6	1821	2.58 (2.02, 3.29)	<.01*	45	.11	Fixed	0.13	0.07

BMI = body mass index, CA125 = carbohydrate antigen 125, CI = confidence interval, FIGO = International Federation of Gynecology and Obstetrics, LMR = lymphocyte-to-monocyte ratio, NA = not available, NLR = neutrophil-to-lymphocyte ratio, OR = odd ratio, PLR = platelet-to-lymphocyte ratio, PNI = prognostic nutritional index.

* *P* < .05 indicating significant association between PNI and clinicopathological parameters.

previous study containing 604 patients with OC showed low albumin was associated with higher complication rate and worse OS after the cytoreductive surgery.[25] On the other hand, it has already been proved that inflammation is associated with the proliferation, migration, immune escape, and chemoresistance of tumor cells.[26] Lymphocytes play an important role in cell-mediated immunity in cancers and can reflect systemic inflammation condition of cancer patients.[27] Several subtypes of lymphocytes have been proved to facilitate the tumor progression and induce the unfavorable outcomes of cancers.[28] PNI, calculated by the combination of albumin and lymphocytes, is considered a reflection of nutritional status and systemic inflammation affecting the cancer growth and metastasis of OC.

Several highlights of the current study should be noted. First, to the best of our knowledge, our study was the first systematic review and meta-analysis to determine the prognostic role of preoperative PNI in OC, which provided important evidence on the clinical decision-making. Second, a total of 2050 OC patients were analyzed in the current study, and this large population could benefit reaching a reliable conclusion. Third, comprehensive

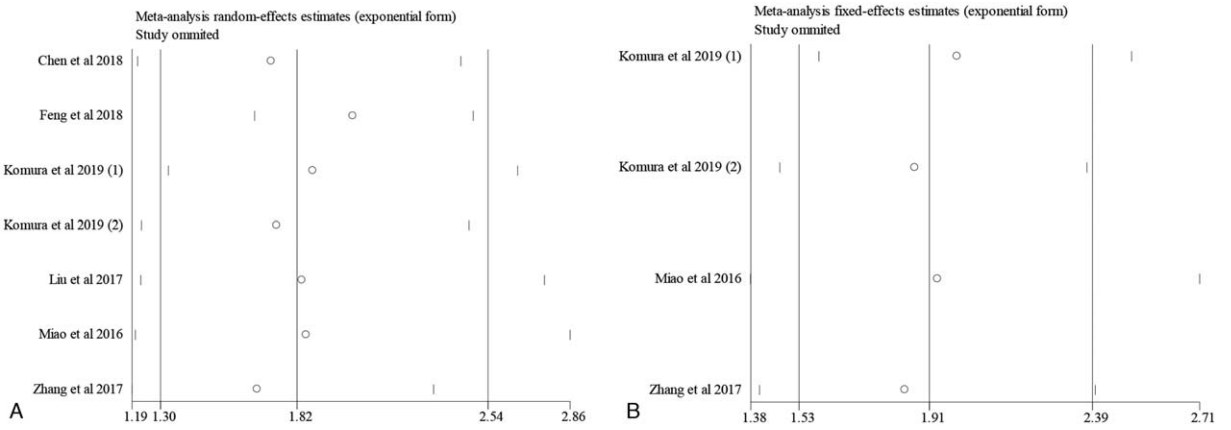

Figure 6. Sensitivity analysis of OS and PFS (A, OS; B, PFS). OS = overall survival, PFS = progression-free survival.

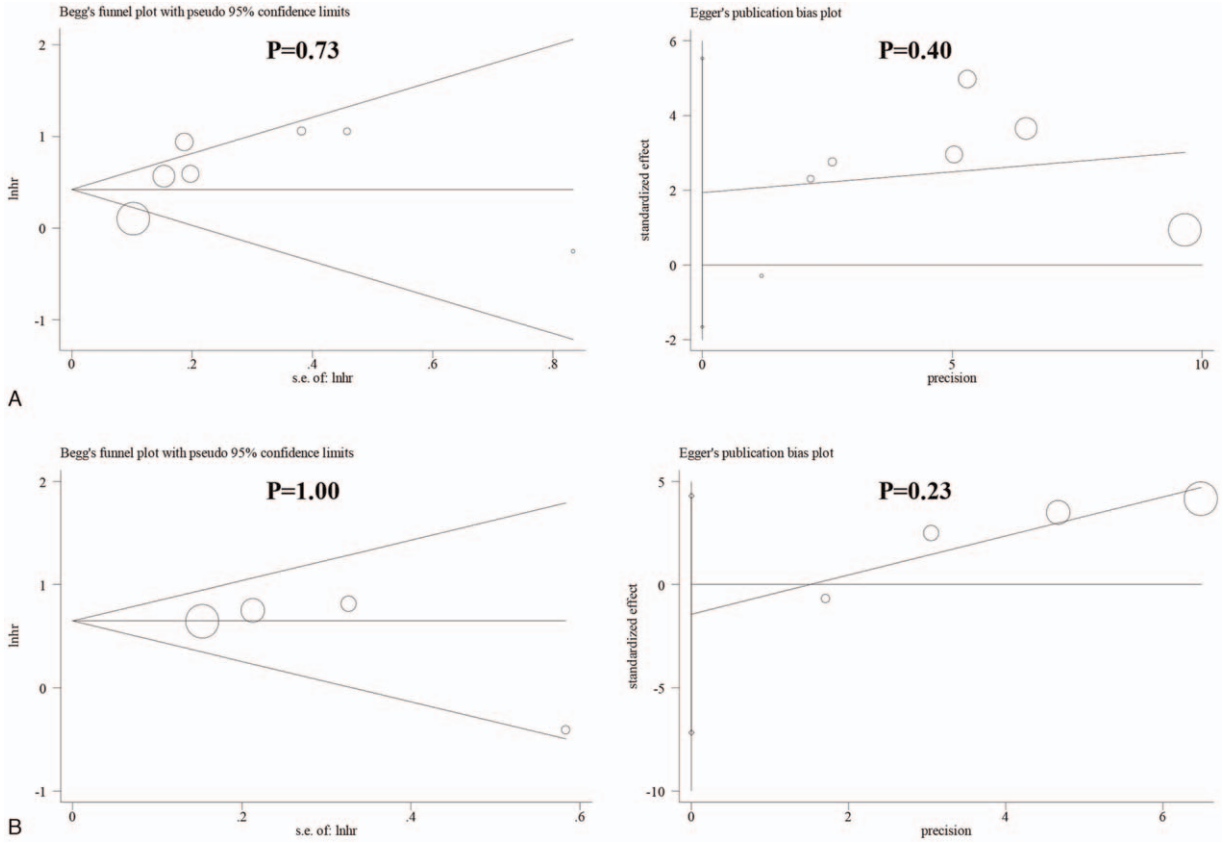

Figure 7. Publication bias of OS and PFS (A, OS; B, PFS). OS = overall survival, PFS = progression-free survival.

additional analyses (e.g., subgroup analysis, publication bias, and sensitivity analysis) were performed in the current study, and these additional analyses confirmed that our results were convincing.

Some limitations should be considered when interpreting our findings. First, although we did not set any restriction on the country during the literature search and selection, most of included studies were conducted in China and Japan, which might limit the application of our findings in other countries. Second, significant heterogeneity was observed in the analysis of OS, which might reduce the accuracy of results. However, heterogeneity decreased a lot after the removal of Feng et al study,[13] and the association of preoperative PNI with OS remained significant, which suggested our results were reliable and convincing. Third, although all patients received the surgical therapy with or without adjuvant chemotherapy, the unknown details of treatment might affect our results. However, as a meta-analysis, all data in the current study was extracted from published studies, and individual's data was unavailable for us, which stopped the further analysis. Forth, studies with positive results were more easily published, as a result, potential selection bias might exist. Thus, large-scale, multicenter, well-designed, and prospective studies are needed to confirm and expand on our findings.

5. Conclusion

Our study suggested that low preoperative PNI was significantly associated with shorter OS, shorter PFS, more advanced FIGO stage, the occurrence of ascites, larger residual tumor, insensitive to chemotherapy, and higher CA125 level compared with high PNI in OC. Therefore, preoperative PNI might be a promising prognostic indicator of OC.

Acknowledgments

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Author contributions

Study concepts and design: Shentao Lu; Literature search: Yan Dai and Mingbo Liu; Data extraction: Yan Dai and Li Lei; Manuscript preparation and revision: Yan Dai and Shentao Lu. All authors have participated sufficiently in the study and approved the final version.

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