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The prognostic nutritional index is prognostic factor of gynecological cancer: A systematic review and meta-analysis

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A R T I C L E I N F O

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A B S T R A C T

Background and aims: Many reports have shown that the prognostic nutritional index (PNI) is associated with the progression of malignant tumors. We comprehensively evaluated the prognostic significance of the PNI in patients with gynecological cancer.
Methods: We identified relevant studies by searching PubMed, Embase, the Cochrane Library, and the Web of Science. The hazard ratio (HR) and odds ratio (OR) with 95% confidence interval (CI) were used to explore the correlation between PNI and overall survival (OS), progression-free survival (PFS), and the characteristics of gynecological cancer. All analyses were performed using Review Manager ver. 5.2 software.
Results: We included nine studies with 2373 patients. The PNI correlated closely with the OS and PFS of gynecological cancer; the pooled HRs were respectively 2.66 (95% CI 1.56–4.55) and 2.43 (95% CI 2.07–2.86) on univariate analysis (UVA) and 1.88 (95% CI 1.10–3.20) and 1.92 (95% CI 1.52–2.44) on multivariate analysis (MVA).
Conclusions: The PNI is significantly associated with the prognosis of patients with gynecological cancer, and may, in fact, be independently prognostic.

1. Introduction

Gynecological cancers, especially cervical and ovarian cancer, constitute major public health problems worldwide. In the USA alone, 100,000 new cases are diagnosed annually, associated with approximately 30,000 deaths [1]. The symptomatology, the availability of screening tests, and whether patients are diagnosed early (endometrial cancer) or late (ovarian cancer) differ between the various cancers. However, regardless of the cancer type, diagnosis of late-stage cancers remains common [2,3]. As cancers grow, the metabolic demand rises. If left unchecked, this contributes to a progressive decline in nutritional status, which is often evident even when patients are first diagnosed. Malnutrition may cause 20% of gynecological cancer deaths [4,5]. Malnutrition is a state of nutrient deficiency, excess, or imbalance, negatively affecting bodily function or form [6]. Here, we use the term to indicate nutrient deficiency, cachexia, and undernutrition. Although malnutrition embraces both over- and under-nutrition, most studies on gynecological cancer patients undergoing surgery focus on undernutrition, characterised by energy/protein deficiencies and/or a decrease in the fat-free mass that eventually reduces physical and/or mental capacity and triggers adverse clinical outcomes [7]. Those with chronic diseases in addition to gynecological cancer are particularly predisposed to the risk of malnutrition. Up to 40–80% of all cancer patients experience malnutrition at some stage during their disease [8]. In contrast, cachexia is a complex metabolic syndrome caused by cancer. Cachexia differs from malnutrition, being rather a hypercatabolic state associated with accelerated muscle loss attributable to a chronic inflammatory response. Although weight loss is common in malnourished cancer patients, the weight loss caused by cachexia is not attributable to inadequate caloric intake alone. Most malnourished patients can be fed aggressively to increase caloric intake, but the weight loss of cachexia is not easily reversed [9].

Recent studies in Australia and the USA have shown that 20–53% of gynecological cancer patients present with at least mild malnutrition at diagnosis [10,11]. The prevalence of malnutrition is even higher in developing nations (62–88%) [12–14]. Malnutrition prior to treatment increases the risk of adverse events during surgery and poor long-term outcomes [15,16]. The prognostic nutritional index (PNI), a predictor of nutritional status, has been evaluated in terms of cancer prognosis. Many studies have reported that the PNI may be associated with the prognosis of gynecological cancer [17–25]. Therefore, we performed a meta-analysis comprehensively analysing the prognostic role played by

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the PNI in patients with such cancers. To identify associations between the PNI and clinicopathological characteristics, we calculated the incidence of low- and high-PNI status among gynecological cancer patients with different clinicopathological characteristics.

2. Methods and materials

2.1. Inclusion and exclusion criteria

2.1.1. Inclusion criteria

(1) Prospective and observational retrospective studies; (2) Patients pathologically diagnosed with gynecological cancer; (3) The PNI noted prior to therapy; (4) Overall survival (OS) and progression-free survival (PFS) recorded after treatment.

2.1.2. Exclusion criteria

(1) Non-human research/trial; (2) Abstracts, letters, editorials, expert opinions, reviews, case reports, or laboratory studies; (3) Patients with other primary tumours or any severe disease that might compromise survival or nutrition; (4) Lack of adequate data; (5) Duplicate articles or data.

2.2. Search strategy

We identified relevant studies by searching PubMed, Embase, the Cochrane Library, and the Web of Science to December, 2018. Our search terms and procedures were: (1) "nutrition" OR "biomarker*" OR "indicator*"; (2) "gynecological cancer*" OR "cervical cancer*" OR "ovarian cancer*" OR "endometrial cancer*" OR "gynecological carcinoma*" OR "cervical carcinoma*" OR "ovarian carcinoma*" OR "endometrial carcinoma*" OR "gynecological neoplasm"; and (3) "prognosis" OR "survival" OR "outcome". The retrieval formula was: (1) AND (2) AND (3). The databases were searched using these terms and English-language articles retrieved. Two investigators who underwent prior normative and unitive training independently screened all titles and abstracts after duplicates were excluded. When potentially relevant studies were found, the full texts were obtained.

The work has been reported in line with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and AMSTAR (Assessing the methodological quality of systematic reviews) Guidelines.

2.3. Quality assessment and data extraction

Two assessors independently evaluated the quality of all included studies using the nine-star Newcastle-Ottawa Scale (NOS) [26]. The total NOS scores of each study are listed in Table 1. The scores reflected the appropriateness of selection, and the comparability of the outcomes of case and control groups. An NOS score ≥6 indicated high quality. In addition, the risks of bias within and across all studies were calculated [27]. The same two reviewers extracted data after careful perusal of included articles; any disagreement was resolved by discussion. We recorded the year of publication, sample size, country, tumour type, PNI, age (median, range), the frequencies of low- and high-PNI subjects, the PNI cutoff, treatments, primary outcomes, and follow-up time using a standardized form (Table 1). Data were input into RevMan. 5.2 software [27].

2.4. Statistical analysis

The effect of PNI on prognosis was measured by estimating the hazard ratio (HR) between low- and high-PNI groups. The odds ratio (OR) (with the associated 95% confidence interval [CI]) was used to evaluate associations between the PNI and clinical features. Among-study heterogeneity was evaluated using the chi-square-based Q test [28]. A $P_{heterogeneity}$ (P_h) value ≤ 0.10 was considered to indicate significant heterogeneity, and the pooled HRs/ORs were estimated using a random-effects model (DerSimonian and Laird [29]). On the contrary, if heterogeneity was not evident ($P_h > 0.10$), a fixed-effects model (the Mantel–Haenszel method [30]) was used. Effects were considered to be significant if the pooled effect parameter (with the 95% CI) did not include unity. Both univariate and multivariate analyses were used to assess the impact of PNI on cancer prognosis. We also analysed the frequencies of low and high-PNI status in patients with different clinicopathological characteristics.

3. Results

3.1. Retrieval of literature and study characteristics

Duplicate studies were removed after initial retrieval of 1454 records; the titles and abstracts of the remaining 896 records were then screened, and 857 excluded and 39 full texts obtained. Of these, 30 were excluded (14 studied irrelevant cancers, 4 were review articles [31–34], 11 evidenced inappropriate aims or interventions, and 1 was a duplicate [35]); finally, nine studies including 2373 participants were included [17–25]. Of these, four including 1669 patients with ovarian cancer explored the prognostic utility of the PNI, one study dealt with gynecological cancer, and four including 674 patents focused on cervical cancer. Seven studies used the same method to calculate the PNI: albumin (g/L) + 0.005 × lymphocyte count (mm^3). Four works studied gynecological cancer patients who received surgery as initial treatment [17,19,24,25]. The search process and study summaries are shown in Fig. 1 and study characteristics in Table 1.

3.2. Quality assessment

Table 1 shows that two studies received a NOS score of 8, three a score of 7, two a score of 6, and two a score of 5; approximately 77.8% were thus of good quality. We drew risk-of-bias graphs; the risks for all studies were presented as percentages in Fig. 2, and the risk of bias for each study in Fig. 3. The graphs indicated that methodological quality was generally good, particularly in terms of "selection"; both the patient and control cohorts were representative. Also, the comparabilities and outcome assessments were associated with low risks of bias. Follow-up was associated with a high risk of bias. The required "demonstration that the outcome of interest was not present at the start of the study" was not always met (thus, bias was in play); other sources of bias were also apparent.

3.3. The prognostic utility of the PNI in terms of OS

Of the 11 studies above, nine provided data allowing the prognostic utility of the PNI to be evaluated via univariate analysis, and all 11 data-facilitating multivariate analysis. As shown in Figs. 4 and 5, the PNI was closely related to OS; the pooled HRs were 2.66 (95% CI 1.56–4.55; $P = 0.0003$) and 1.88 (95% CI 1.10–3.20; $P = 0.02$) on univariate and multivariate analyses (UVA and MVA) (respectively). Both analyses featured use of a random-effects model because of significant among-study heterogeneity ($P_h < 0.00001$, $I^2 = 87\%$ and $P_h < 0.00001$, $I^2 = 89\%$ respectively). Subgroup analysis further indicated that the PNI was significantly associated with the OS of cervical cancer patients [pooled HRs 3.67 (95% CI 2.48–5.44; $P < 0.00001$) on UVA and 2.96 (95% CI 1.87–4.70; $P < 0.00001$) on MVA], but this was not true for ovarian cancer patients (Table 2).

3.4. The prognostic utility of PNI in terms of PFS

Six studies contained data allowing evaluation of the prognostic utility of the PNI in terms of PFS. As no significant among-study

Table 1
The characteristics of included studies for the association between PNI and prognosis of gynecological cancers.

Study (author/ year)	Country	Tumor type	Participants	Calculation of PNI	Age (median, range)	Incidence of low and high-PNI	PNI cut-off	Treatment	Follow-up time (month)	NOS score	Primary outcomes
Feng Z et al., 2018	China	OC	875	Alb + 0.005 × L	56 (30–90)	low-PNI: 45.5% high-PNI: 54.5%	45.45	Surgery	41 (1–134)	8	OS
Haraga J et al., 2016	Japan	CC	131	Alb + 0.005 × L	61.5 (25–88)	NR	48.55	CCRT, RT	Every 1–2 months	6	OS, PFS
He X et al., 2018	China	CC	229	Alb + 0.005 × L	44 (28–79)	NR	45	Surgery	NR	5	OS
Ida N et al., 2018	Japan	RCC	79	Alb + 0.005 × L	52.4 (25–78)	NR	46.9	CCRT	15.0 (2–93)	7	OS
Miao Y et al., 2016	China	EOC	344	Alb + 0.005 × L	55 (45–84)	low-PNI: 29.4% high-PNI: 70.6%	45	CT	72 (61–97)	8	OS, PFS
Takushima Y et al., 1994	Japan	GC	30	Alb + 0.005 × L	NR	NR		MT	Every 3 months	5	OS
Yim GW et al., 2016	Korea	EOC	213	NR	53 (22–81)	low-PNI: 21.6% high-PNI: 78.4%		CT	35 (2–112)	7	OS, PFS
Zhang W et al., 2018	China	CC	235	NR	46 (29–78)	low-PNI: 76.2% high-PNI: 23.8%	50.38	Surgery	77 (32–96)	6	OS, PFS
Zhang W et al., 2017	China	OC	237	Alb + 0.005 × L	50 (24–76)	low-PNI: 57.8% high-PNI: 42.2%	47.2	Surgery	Every 2–4 months	7	OS, PFS

PNI, prognostic nutritional index; OC, ovarian cancer; CC, cervical cancer; RCC, recurrent cervical cancer; EOC: epithelial ovarian cancer; GC, gynecological cancer; Alb, albumin (g/L); L, lymphocyte count (per mm^3); CCRT, concurrent chemoradiotherapy; RT, radiotherapy; CT, chemotherapy; MT, multimodal treatment; NOS, Newcastle-Ottawa Scale; OS, overall survival; PFS, progression-free survival; NR, not report.

heterogeneity was evident, we used a fixed-effects model for analyses. Gynecological cancer patients with high pretreatment PNIs experienced better PFS [pooled HRs 2.43 (95% CI 2.07–2.86; $P < 0.00001$) on UVA (Fig. 6) and 1.92 (95% CI 1.52–2.44; $P < 0.00001$) on MVA (Fig. 7)]. Subgroup analysis indicated that the PNI was significantly associated with the PFS of cervical cancer patients [pooled HRs 2.59 (95% CI 2.00–3.34; $P < 0.00001$) on UVA and 2.54 (95% CI 1.41–4.58; $P = 0.002$) on MVA]. For ovarian cancer patients, the pooled HRs were 2.34 (95% CI 1.90–2.88; $P < 0.00001$) on UVA and 1.82 (95% CI 1.41–2.36; $P < 0.00001$) on MVA (Table 2).

3.5. Associations between other risk factors and OS

We explored whether OS was affected by 10 risk factors; the pooled results are listed in Table 3. OS was significantly influenced by age (HR 1.01; 95% CI 1.00–1.02), clinical stage (HR 2.99; 95% CI 2.03–4.39),

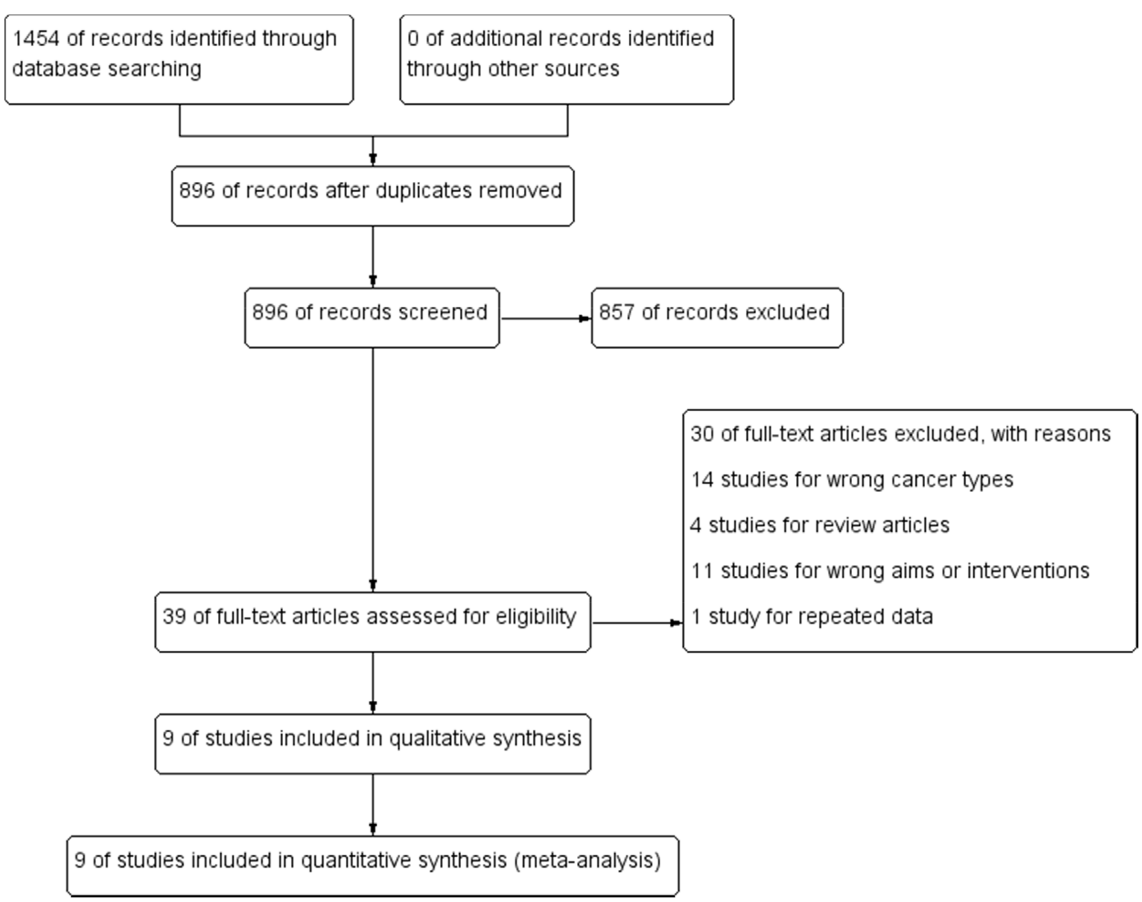

Fig. 1. Flow diagram of literature search and selection of included studies for meta-analysis.

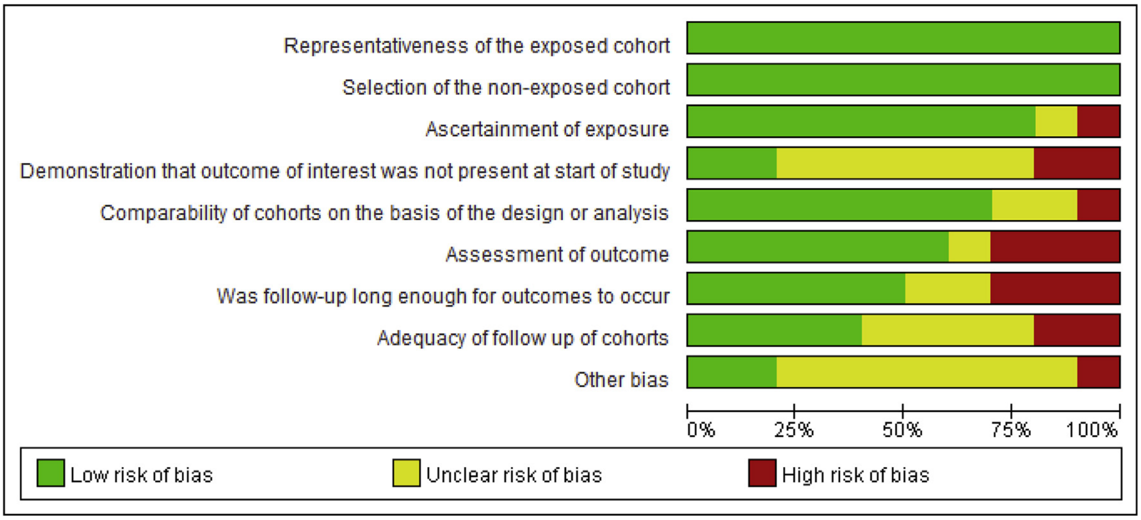

Fig. 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

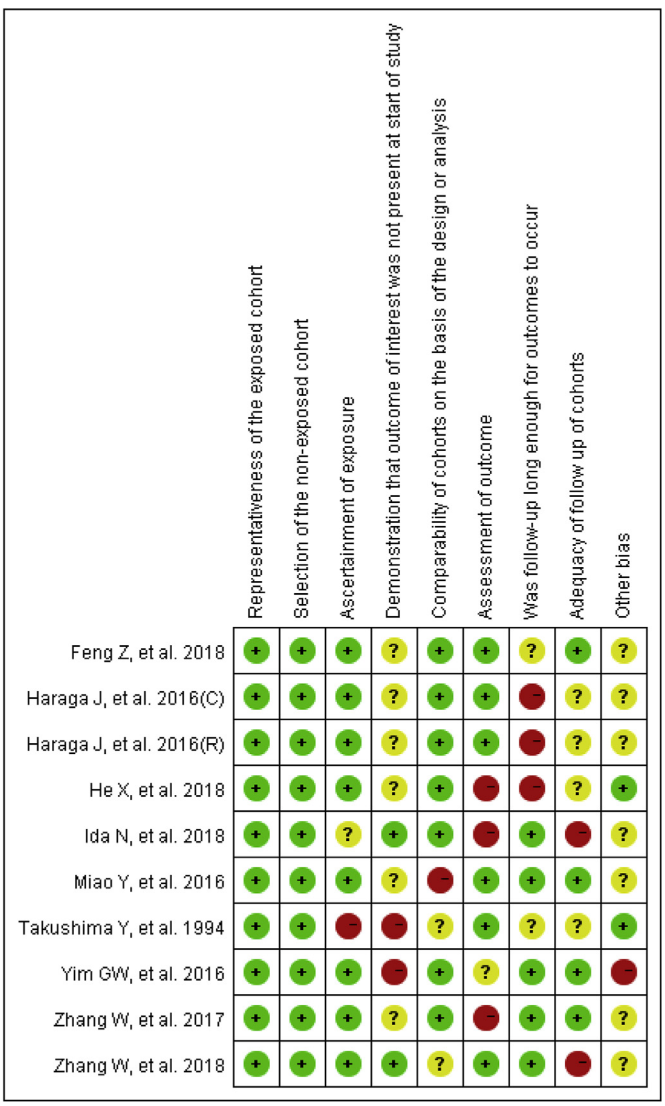

Fig. 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

residual disease (HR 1.66; 95% CI 1.18–2.33; MVA), maximum tumour size (MTS) (HR 2.32; 95% CI 1.58–3.41), body mass index (BMI) (HR 1.67; 95% CI 1.28–2.18), ascites status (HR 2.79; 95% CI 2.29–3.39), and CA125 level (HR 4.23; 95% CI 1.24–14.44). However, no significant association was found between OS and sensitivity to chemotherapy, residual disease (UVA), lymph node metastasis, or histological parameters.

3.6. Associations between other risk factors and PFS

We explored whether the PFS was affected by 10 risk factors; the pooled results are listed in Table 4. The PFS was significantly influenced by clinical stage (HR 2.41; 95% CI 1.50–3.89 on UVA and HR 1.95; 95% CI 1.11–3.42 on MVA), lymph node metastasis (HR 2.21; 95% CI 1.18–4.14; UVA), the MTS (HR 3.95; 95% CI 1.28–12.20 on UVA and HR 4.49; 95% CI 1.56–12.96 on MVA), ascites status (HR 2.42; 95% CI 2.02–2.91), tumour grade (HR 2.42; 95% CI 2.02–2.91), residual disease (HR 2.70; 95% CI 1.54–4.72), and CA125 level (HR 2.52; 95% CI 1.71–3.71), but not by lymph node metastasis (on MVA), histological parameters, BMI, or age.

3.7. The pooled results of associations between the PNI and other characteristics

We analysed the associations between the frequencies of low- and high-PNI patients and nine clinicopathological characteristics including tumour stage, ascites status, residual disease, chemosensitivity (associations evident), BMI, histological parameters, tumour grade, age, and CA125 level (no associations evident) (Table 5).

4. Discussion and conclusion

The high prevalence of malnutrition in gynecological cancer patients is of concern. In Australia and the USA, 20–53% of patients present with at least mild malnutrition [10,11]. Hertlein et al. found that only 22% of patients presented with normal nutritional status [36]. Malnutrition accounts for 20% of all cancer deaths [5]. The risk of malnutrition is greatest in ovarian cancer patients; this diagnosis is associated with a 67% risk of malnourishment compared to a figure of 21% for patients with other gynecological cancers [37]. Furthermore, patients with ovarian cancer were at a 19-fold greater risk of malnourishment than those with benign conditions [38]. Malnutrition in cancer patients is often attributable to an inability to ingest or absorb adequate nutrients. Surgery requires starvation; depending on the

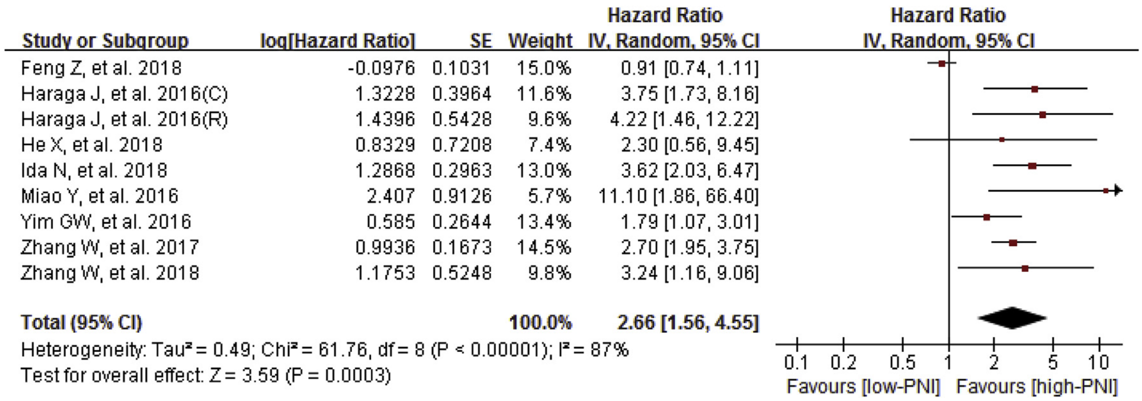

Fig. 4. Forest plot of the association between PNI and overall survival of gynecological cancers (UVA).

length of such starvation, protein catabolism may develop postoperatively. Anti-cancer treatment reduces appetite, further reducing food intake after surgery. If a bowel obstruction is in play, malabsorption becomes an issue. Metabolic demand increases as a cancer grows, triggering catabolism of stored protein. The combination of reduced food intake and absorption, and increased metabolic demand, can render the nutritional balance negative and diminish nutritional status [39].

Late cancer presentation is more common in non-Western countries; malnutrition thus affects many such patients. Malnutrition affects the prognosis of gynecological tumours [17–25,40–45]. The PNI, a predictor of nutritional status, is considered to be an important prognostic indicator in those with gynecological cancer. However, the findings remain controversial. Thus, we comprehensively evaluated the prognostic role played by the PNI in such patients. To the best of our knowledge, this is the first relevant meta-analysis. The data strongly support the idea that a low PNI compromises survival, as is true of those with gastric or colorectal cancer [33,34]. We found that the cancer stage, MTS, ascites status, and CA125 level correlated with both the OS and PFS; the PNI consistently predicted prognosis. Currently, the clinical stage is the most important indicator of tumour prognosis. However, the precise stage depends on pathological data obtained after surgery. The PNI can be calculated before surgery to predict prognosis, and may be used to guide treatment. We also sought associations between low PNI status and clinicopathological characteristics. The PNI correlated with tumour stage, ascites status, residual disease, and chemosensitivity; patients with advanced-stage tumours are exhausted.

Our work had certain limitations. First, most studies were retrospective observational works with uncontrolled (and thus potentially heterogeneous) baseline data; such studies are not optimal. Second, the clinical stages varied greatly; again, stage is the most important prognostic predictor. Given the heterogeneity among the small number of included studies, we could not perform subgroup analysis by TNM stage. Also, we found a significant association between low PNI status and stage; stage may thus influence our analysis of survival. Third, the mode of PNI calculation may affect our findings. Seven of the nine studies calculated the PNI as albumin (g/L) + 0.005 × lymphocyte count (mm^3), but two did not report how they calculated the PNI. Fourth, treatment was heterogeneous, perhaps creating bias. Four studies evaluated the prognostic utility of the PNI in patients undergoing surgery [17,19,24,25], but other patients received radiotherapy [18,20–23]. Finally, cancer prognosis is influenced by multiple factors including age, follow-up time, adjuvant therapy, tumour size, histological type, and venous involvement.

Given the limitations of retrospective studies, prospective studies (especially randomised clinical trials) are required to explore further the association between the PNI and gynecological cancer prognosis, and to clarify the significance of the PNI in patients of different clinical stages receiving various treatments. We found that the PNI correlated significantly with gynecological cancer prognosis, and can be used to predict outcomes.

Ethical Approval

Ethical Approval is not applicable.

Sources of funding

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Reviewregistry654.

Author contribution

The authors on this paper all participated in study design. All authors read, critiqued and approved the manuscript revisions as well as the final version of the manuscript. Also, all authors participated in a session to discuss the results and consider strategies for analysis and

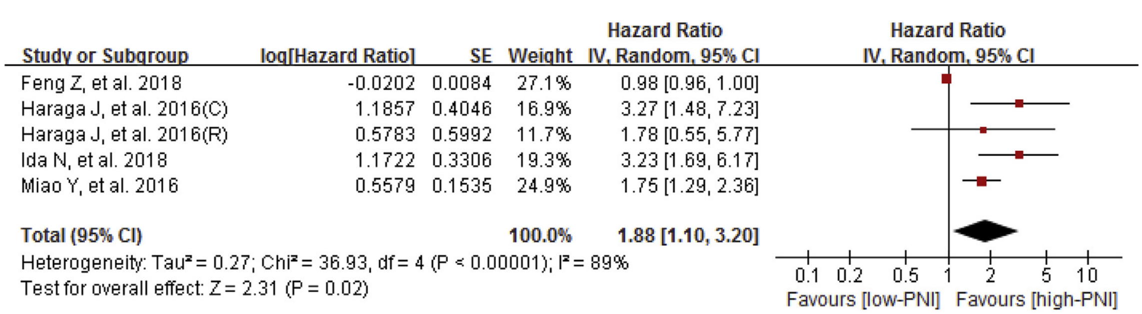

Fig. 5. Forest plot of the association between PNI and overall survival of gynecological cancers (MVA).

Table 2
The subgroup analysis of the association between PNI and survival of gynecological cancers.

Subgroups	Pooled results			heterogeneity		
	HR	95% CI	P value	I^2	P_h value	Analytical effect model
Overall survival						
Ovarian cancer (UVA)	2.02	0.95, 4.33	0.07	92%	< 0.00001	Random-effect model
Ovarian cancer (MVA)	1.28	0.73, 2.26	0.39	93%	0.0002	Random-effect model
Cervical cancer (UVA)	3.67	2.48, 5.44	< 0.00001	0%	0.99	Fixed-effect model
Cervical cancer (MVA)	2.96	1.87, 4.70	< 0.00001	0%	0.65	Fixed-effect model
Progression-free survival						
Ovarian cancer (UVA)	2.34	1.90, 2.88	< 0.00001	10%	0.33	Fixed-effect model
Ovarian cancer (MVA)	1.82	1.41, 2.36	< 0.00001	0%	0.66	Fixed-effect model
Cervical cancer (UVA)	2.59	2.00, 3.34	< 0.00001	5%	0.35	Fixed-effect model
Cervical cancer (MVA)	2.54	1.41, 4.58	0.002	0%	0.70	Fixed-effect model

HR, hazard ratio; CI, confidence intervals; UVA, univariate analysis; MVA, multivariate analysis.

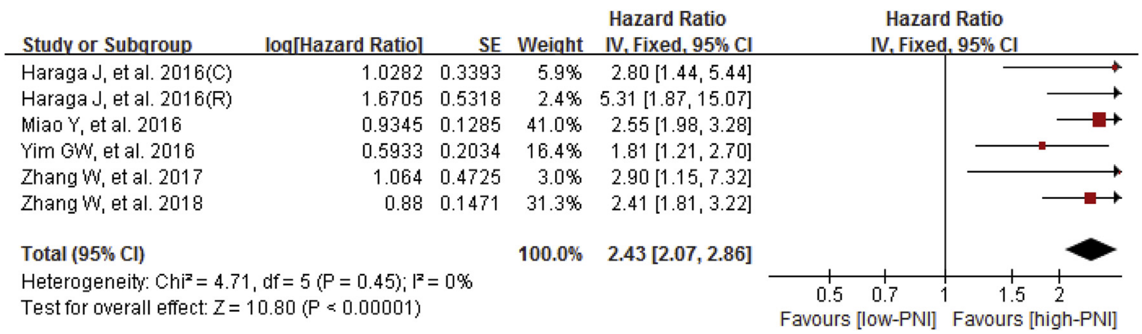

Fig. 6. Forest plot of the association between PNI and progression-free survival of gynecological cancers (UVA).

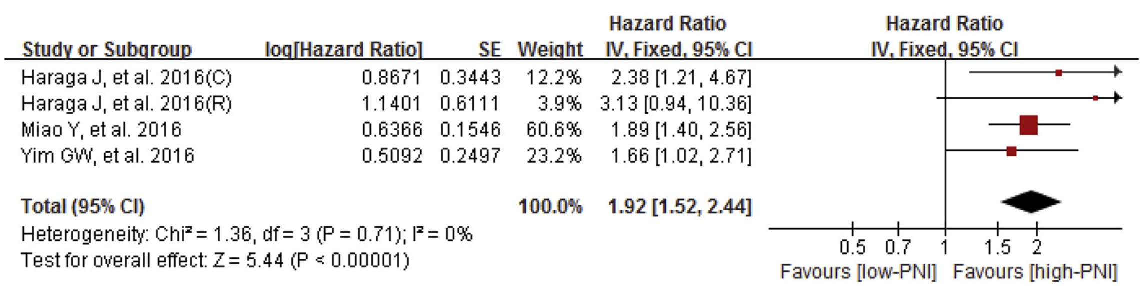

Fig. 7. Forest plot of the association between PNI and progression-free survival of gynecological cancers (MVA).

Table 3
The pooled results of the association between other risk factors and OS of gynecological cancers.

Subgroups	Number of participants	Pooled results			heterogeneity		
		HR	95% CI	P value	I^2	P_h value	Analytical effect model
Age	2133	1.01	1.00, 1.02	0.004	0%	0.83	Fixed-effect model
Stage	2160	2.99	2.03, 4.39	< 0.00001	79%	< 0.0001	Random-effect model
Chemo sensitivity	1349	1.80	0.16, 20.77	0.64	99%	< 0.00001	Random-effect model
Residual disease							
UVA	1906	1.60	0.77, 3.31	0.21	94%	< 0.00001	Random-effect model
MVA	557	1.66	1.18, 2.33	0.004	27%	0.24	Fixed-effect model
LN metastasis							
UVA	1384	1.51	0.64, 3.58	0.35	91%	< 0.00001	Random-effect model
MVA	606	1.29	0.95, 1.76	0.10	0%	0.45	Fixed-effect model
Histology							
UVA	1135	0.78	0.54, 1.12	0.18	65%	0.01	Random-effect model
MVA	475	0.77	0.13,4.42	0.77	92%	0.004	Random-effect model
MTS	726	2.32	1.58, 3.41	< 0.0001	25%	0.26	Fixed-effect model
BMI	1056	1.67	1.28, 2.18	0.0002	0%	0.81	Fixed-effect model
Ascites	581	2.79	2.29, 3.39	< 0.00001	48%	0.17	Fixed-effect model
CA125	581	4.23	1.24, 14.44	0.02	86%	0.007	Random-effect model

HR, hazard ratio; CI, confidence intervals; UVA, univariate analysis; MVA, multivariate analysis; LN, lymph node; MTS, maximum tumor size; BMI, body mass index.

Table 4
The pooled results of the association between other risk factors and PFS of gynecological cancers.

Characteristics	Number of participants	Pooled results			heterogeneity		
		HR	95% CI	P value	I^2	P_h value	Analytical effect model
Stage							
UVA	1291	2.41	1.50, 3.89	0.0003	88%	< 0.00001	Random-effect model
MVA	710	1.95	1.11, 3.42	0.02	83%	0.0006	Random-effect model
LN metastasis							
UVA	841	2.21	1.18, 4.14	0.01	74%	0.010	Random-effect model
MVA	606	1.16	0.86, 1.56	0.32	0%	0.56	Fixed effects model
Histology	1056	0.93	0.79, 1.10	0.39	12%	0.33	Fixed effects model
MTS							
UVA	497	3.95	1.28, 12.20	0.02	65%	0.06	Random-effect model
MVA	262	4.49	1.56, 12.96	0.005	0%	0.33	Fixed effects model
BMI	1056	1.51	0.94, 2.41	0.09	70%	0.009	Random-effect model
Age	1029	1.01	0.99, 1.03	0.36	0%	0.96	Fixed effects model
Ascites	581	2.42	2.02, 2.91	< 0.00001	27%	0.24	Fixed effects model
Grade	557	2.42	2.02, 2.91	< 0.00001	27%	0.24	Fixed effects model
Residual disease	794	2.70	1.54, 4.72	0.0005	81%	0.006	Random effects model
CA125	581	2.52	1.71, 3.71	< 0.00001	62%	0.11	Fixed effects model

HR, hazard ratio; CI, confidence intervals; UVA, univariate analysis; MVA, multivariate analysis; LN, lymph node; MTS, maximum tumor size; BMI, body mass index.

Table 5
The pooled results of the association between PNI and characteristics of gynecological cancers.

Characteristics	Number of participants	low-PNI			high-PNI		
		OR	95% CI	P value	OR	95% CI	P value
Age	632	0.96	054, 1.71	0.89	1.74	0.46, 6.61	0.41
Stage	678	0.46	0.24, 0.85	0.01	2.19	1.17, 4.09	0.01
CA125	705	0.16	0.01, 3.91	0.26	6.31	0.26, 155.67	0.26
Ascites	1012	0.23	0.12, 0.44	< 0.00001	4.37	2.30, 8.32	< 0.00001
Residual disease	577	0.38	0.30, 0.49	< 0.00001	2.63	2.04, 3.39	< 0.00001
Chemo sensitivity	492	0.47	0.36, 0.61	< 0.00001	2.15	1.64, 2.80	< 0.00001
BMI	481	0.78	0.58, 1.06	0.11	1.28	0.94, 1.73	0.11
Histology	272	0.92	0.66, 1.29	0.65	1.11	0.39, 3.16	0.84
Grade	227	0.98	0.46, 2.09	0.96	1.02	0.48, 2.18	0.96

OR, odds ratio; CI, confidence intervals; BMI, body mass index.

interpretation of the data before the final data analysis was performed and the manuscript written. XFY Wang mainly contributed to the study design, data analysis and quality assessment. YP Wang mainly contributed to the literature search and manuscript writing. All authors have the appropriate permissions and rights to the reported data.

Conflicts of interest

The authors declare no relevant conflict of interest.

Trial registry number

None.

Guarantor

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Provenance and peer review

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Appendix A. Supplementary data

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