Predictive value of prognostic nutritional index for outcomes of cervical cancer: A systematic review and meta-analysis

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Abstract. Cervical cancer is a major global health concern. Prognostic markers for cervical cancer have traditionally focused on tumor characteristics. However, there is a growing recognition of the importaxnce of the nutritional status of the patient as a possible prognostic indicator. The present meta-analysis aims to estimate the role of the prognostic nutritional index (PNI) in predicting overall survival (OS) and progression-free survival (PFS) in patients with cervical cancer. Medline, Google Scholar, Science Direct and Cochrane Central databases were systematically searched for studies reporting PNI in patients with cervical cancer. Inclusion criteria were applied to select relevant studies and data extraction was performed by two independent investigators. Risk of bias was assessed by the Newcastle-Ottawa Scale (NOS). The present meta-analysis included 10 studies with 2,352 participants. The pooled analysis showed that in patients with cervical cancer PNI did not have a significant prognostic utility in predicting OS [univariate hazard ration (HR): 1.38; 95% confidence interval (CI): 0.77-2.48) or PFS (univariate HR: 1.12; 95% CI: 0.44-2.68). These results were consistent even after adjusting for other confounders using multivariate analysis (pooled HR: 1.06 for OS; 95% CI: 0.64-1.76; pooled HR: 1.22 for PFS; 95% CI: 0.65-2.30). Subgroup analyses were also performed based on region, PNI cut-off, sample size, grade of evidence and treatment protocol and did not demonstrate any significant prognostic value of PNI. The funnel plot demonstrated symmetry, suggesting the absence of publication bias. The present meta-analysis indicated that PNI does not have a significant prognostic utility in predicting OS or PFS in women with cervical cancer. Further research is warranted to explore alternative nutritional indicators and identify reliable prognostic markers in this patient population.

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Introduction

According to World Health Organisation (WHO) estimates, Cervical Cancer (CC) accounted for 604,000 new cases and 342,000 mortalities globally in 2020 alone. Of these new cases and fatalities, ~90% are from low-and middle-income nations and are identified at advanced stages (1). Such patients have markedly worse prognosis, higher recurrence and mortality rates compared with patients who are diagnosed at the early stages (2). Based on the guidelines of the International Federation of Obstetricians and Gynecologists (FIGO) tumour staging system, the prognostic markers for patients with CC include lymph node status, tumour size, histological grade and depth of invasion (3,4). Other characteristics, aside from the FIGO stage, can only be assessed following surgery. However, clinical staging, particularly in some patients with CC with advanced disease, is often inaccurate in predicting the prognosis (5). Therefore, identifying a vital pre-treatment parameter to assess the likelihood of survival and prognosis of CC is necessary before choosing a relevant clinical approach.

A number of malignancies are known to originate from areas of chronic inflammation, irritation and infection. Inflammation affects every stage of carcinogenesis from tumour initiation and progression to metastatic dissemination (6). The metabolic demand increases as malignancies spread and, if ignored, may lead to a gradual deterioration in nutritional status, which is frequently noticeable even before the patient is diagnosed. Studies have shown that ~20% of deaths from gynaecological cancer may be associated with malnutrition (7,8). Therefore, nutritional status is recognised as a vital determinant of the quality of life of survivors of cancer. Malnutrition, sarcopenia and cancer cachexia are linked to higher rates (20%) of post-treatment complications, poor clinical response, longer hospitalizations and shorter survival in 2022 (9). Several studies have shown that numerous factors, including nutritional and inflammatory indicators, predict the prognosis of various types of cancer. Studies from Western countries have shown that 20-50% of patients with gynaecological cancer present with malnutrition at diagnosis (10). This proportion is even higher in developing countries (62-88%) (11).

In recent years, the Prognostic Nutritional Index (PNI), a simple and readily available marker, has gained interest as a potential tool for assessing nutritional status and predicting clinical

outcomes in various malignancies (6). The PNI is calculated by combining serum albumin levels (g/l) with the total lymphocyte count ($x10^9$/l) using the formula: PNI=albumin+0.005 x lymphocytes (12,13). The PNI is often associated with the prognosis of several gastrointestinal and a few gynaecological types of cancer and its score reflects both the protein reserve (albumin) and cellular immunity (lymphocytes), providing a more comprehensive assessment of the nutritional-immune state (8). While several studies have explored the association between PNI and the prognosis of cervical cancer, the findings remain inconclusive (6,8,10). Thus, the aim of the current study was to evaluate the role of PNI in predicting the overall survival (OS) and progression-free survival (PFS) of women with cervical cancer.

Materials and methods

Research question. What is the predictive effect of PNI in predicting various clinical outcomes in adult patients (>18 years) diagnosed with cervical cancer?

Methods. The present study complied with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) framework 2020 (14). Ethical approval was not necessary as the present study undertook a secondary data analysis of the available literature. The present study was registered at PROSPERO, with the number: CRD42023423281.

Inclusion criteria. Prospective and retrospective studies conducted among women with cervical cancer reporting PNI prior to therapy were both included. Medline (https://www.ncbi.nlm.nih.gov), Google Scholar (https://scholar.google.com), Science Direct (https://www.sciencedirect.com) and Cochrane Central databases (https://www.cochranelibrary.com/central/about-central) were searched for articles available as free full text and published in English from inception to April 2023. Conference abstracts, narrative reviews, case reports and series and randomised control trials were excluded. Studies that reported on possible study treatments (concurrent chemoradiotherapy, radiotherapy, surgery) were included.

Type of intervention. The PNI was calculated using the equation: PNI=10 x albumin concentration (g/dl)+0.005 x total lymphocyte count (μl) (15). All studies that had used this accepted calculation of PNI were included in the present study.

Outcome definitions. The main outcomes included evaluated overall survival and progression-free survival.

Search strategy. Medline (https://www.ncbi.nlm.nih.gov), Google Scholar (https://scholar.google.com), Science Direct (https://www.sciencedirect.com) and Cochrane Central databases (https://www.cochranelibrary.com/central/about-central) were searched using the medical subject heading (MeSH) terms such as: 'Prognostic nutritional index' OR 'PNI' AND 'Cervical cancer' OR 'Cervical carcinoma' OR 'Cervical Ca' OR 'Cervical neoplasms' AND 'survival' OR 'Outcome' OR 'Progression-free survival' AND 'Observational studies' OR 'Retrospective studies OR 'Prospective studies' along with free text terms as a filter. Cross-references of primary studies were also searched for additional relevant articles.

Selection of studies. The two authors independently performed the preliminary title, abstract and keywords search screening. Full texts of the relevant articles and their abstracts were then screened for eligibility by both authors. All disagreements were resolved by discussion. The two authors individually extracted all data, monitored data entry and analysis and ensured quality.

Data extraction and management. The following information was retrieved from the eligible studies by the primary investigator: i) General information (authors and year of publication), ii) in the methods: Study design and setting, iii) in the participants section: The sample size and age distribution of participants, iv) in the intervention section: details of PNI such as cut-offs used, the formula used to calculate PNI, duration of follow up, and v) in the outcomes section: Overall survival and progression-free survival.

Risk of bias assessment in included studies. The two authors measured the risk of bias in relevant studies using the seven items Newcastle-Ottawa Scale (NOS) for observational studies. The NOS scale that has three domains (selection, comparability and outcome), was used to rate the studies. A study was graded as good quality if it had 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain (16).

Statistical analysis. Data were extracted, entered into Microsoft Excel and analysed using STATA 18 (StataCorp LLC). The primary and secondary outcomes data was summarized as hazards ratio (HR) with 95% confidence interval (CI) for outcomes on overall survival and progression-free survival. The estimates were pooled using a random effects model with Mantel-Haenszel method as the present study encountered considerate clinical heterogeneity and high statistical heterogeneity. In cases of missing data, the author(s) of the trial were contacted if possible. The prognostic effect of PNI on selected cancer outcomes were separately using univariate and multivariate estimates of HRs.

Assessment of heterogeneity. Between-study variance due to heterogeneity was assessed by the Chi square test and I^2 statistic. I^2 <25% was considered mild, 25-75%, moderate and >75% as substantial heterogeneity. Study details and pooled estimates were graphically represented by a forest plot. Publication bias was assessed using funnel plot.

Sensitivity analysis. Sensitivity analysis was performed for the risk of bias among the included studies. Hence, separate pooled estimates were obtained by analysing studies with various risk of bias scores according to NOS.

Results

Study selection. A total of 1,408 articles were identified by the search. Of them, 1,229 duplicates were removed and 54 were excluded at the stage of the preliminary title and abstract screening, as they did not match the inclusion criteria. A study performed by Haraga *et al* (17) in 2016, reported study outcomes on OS and PFS separately for individuals who were

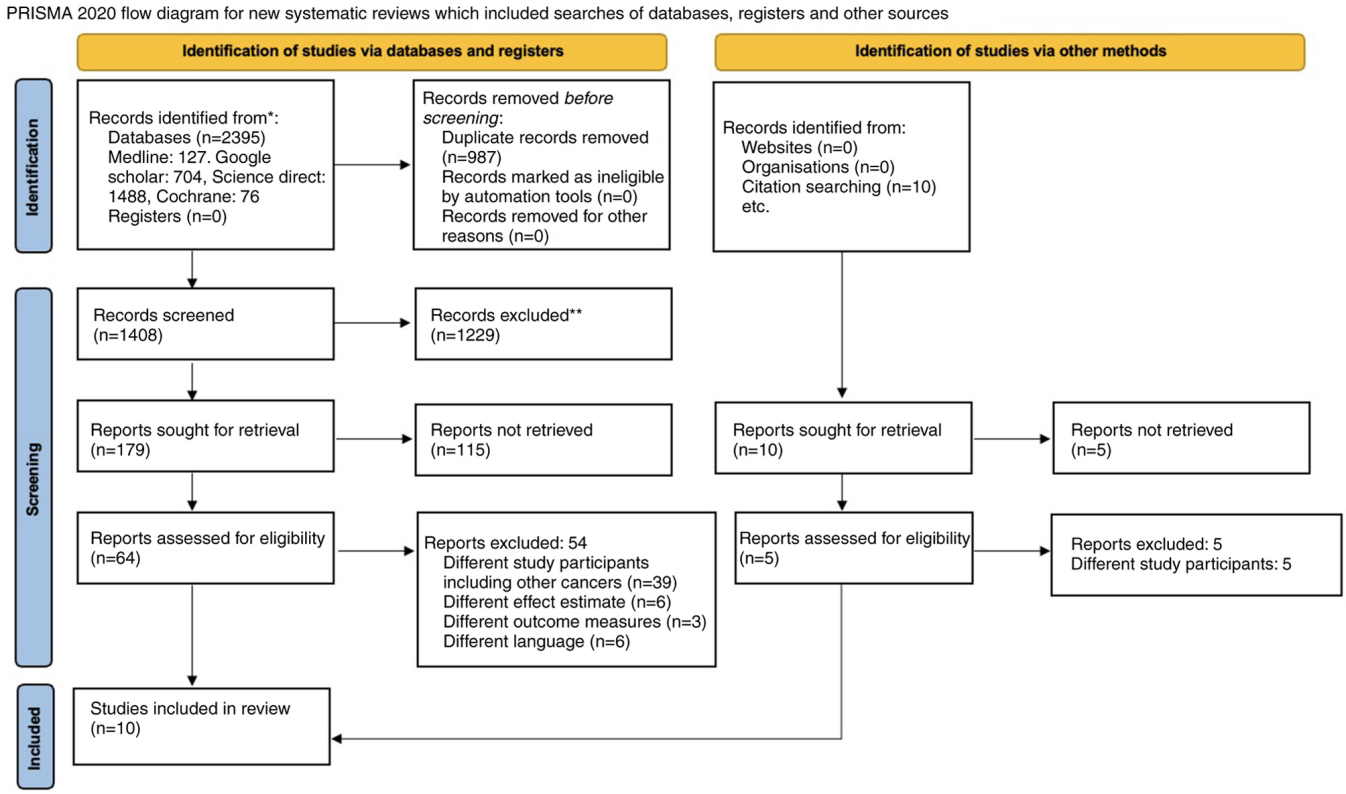

Figure 1. PRISMA 2020 flow diagram explaining the Search flow. PRISMA, preferred reporting items for systematic reviews and meta-analyses.

treated on concurrent chemoradiotherapy and radiotherapy respectively. Thus the data were included as two differences entries for the meta-analysis. Finally, nine articles were included in the systematic review and 10 articles were included in the meta-analysis (17-25). A total number of subjects in all studies was 2,352. The PRISMA 2020 flow diagram is explained in Fig. 1 and the search strategy is summarized in Table SI.

Characteristics of the included studies. Table I describes the characteristics of the included studies. Of the 10 included studies, seven studies were from China and the remaining three were from Japan [as Haraga *et al* (17) reported on both chemotherapy and radiotherapy treatment]. All studies included adult women diagnosed with cervical cancer with an age distribution between 25-88 years. All studies reported results in the English language. The number of patients in the included studies ranged between 79-698. All studies were of retrospective design and all reported on overall survival. A total of five studies reported on the progression-free survival. A total of four studies had surgery as a treatment option, while four had radiotherapy and two studies used concurrent chemo-radiotherapy as treatment. The PNI cut off determined by the included studies ranged between 45-55.

Excluded studies. Of 64 full-text potentially eligible articles, 54 studies were excluded. Of them, 39 studies were excluded because of the variability in the diagnosis of study participants (a mix of different gynaecological cancers), six studies had effect estimates other than HR, three studies reported on outcomes other than OS and PFS and six were in languages other than English.

Risk of bias in included studies. Table I summarizes the risk of bias in the included studies. The studies were categorised as high quality if NOS score ≥6, while studies with the lesser scores were categorised as low quality. Of the nine studies, eight were of high quality.

Prognostic utility of PNI and OS. The meta-analysis examined the association between pre-operative PNI and OS in patients with cervical cancer using data from 10 studies. Univariate analysis revealed a pooled hazard ratio (HR) of 1.38 [95% confidence interval (CI): 0.77-2.48; Fig. 2]. However, this result did not reach statistical significance, indicating no independent prognostic effect of PNI on OS at baseline. This was further supported by the non-significant pooled HR of 1.06 (95% CI: 0.64-1.76) in the multivariate analysis (eight studies), suggesting that PNI's predictive ability for OS might be mitigated by the influence of other prognostic factors included in the adjusted models (Fig. 3). Notably, high heterogeneity was observed in both univariate and multivariate analyses (I^2=88% and 83%, respectively; P<0.001), which required the use of a random-effects model for pooled estimate generation.

Prognostic utility of PNI and PFS. A total of six studies within the meta-analysis explored the association of PNI

Table I. Characteristics of included studies.

First author, year	Country	Sample size and age (median and range)	Type of study	PNI calculation	PNI cut off	Low and high PNI incidence	Treatment course	Follow up period (months)	Primary and secondary outcomes	Quality of study (NOS)	(Refs)
Gao *et al*, 2023	China	110 Age: Not reported	Retrospective	Albumin+0.005 x lymphocytes	47.35	Low PNI <47.35 High PNI >47.35	Radiotherapy	26 months	Overall survival and progression-free survival	6	(18)
Guo *et al*, 2023	China	109 Age: 53.95±9.56	Retrospective	Albumin+0.005 x lymphocytes	52.68	Low PNI <52.68 High PNI >52.68	Surgery	Not reported	Overall survival	7	(19)
Haraga *et al*, 2016	Japan	131 Age: 61.5 years (25-88)	Retrospective	Albumin+0.005 x lymphocytes	48.55	Not reported	Chemoradio-therapy	Once in every 1-2 months	Overall survival and progression-free survival	6	(17)
Haraga *et al*, 2016	Japan	131 Age: 61.5 years (25-88)	Retrospective	Albumin+0.005 x lymphocytes	48.55	Not reported	Radiotherapy	Once in every 1-2 months	Overall survival and progression-free survival	6	(17)
He X *et al*, 2018	China	229 Age: 44 years (28-79)	Retrospective lymphocytes	Albumin+0.005 x	45	Not reported	Surgery reported	Not	Overall survival	5	(20)
Ida N *et al*, 2018	Japan	79 Age: 52.4 years (25-78)	Retrospective	Albumin+0.005 x lymphocytes	46.9	Not reported	Concurrent chemoradio-therapy	Median: 15 months, range (2-93)	Overall survival	7	(21)
Jiang *et al*, 2021	China	583 Age: 49.05±9.208	Retrospective	Albumin+0.005 x lymphocytes	50.15	Low PNI ≤50.15 High PNI >50.15	Surgery	Mean follow up: 68.34±26.93	Overall survival and progression-free survival	7	(22)
Wang *et al*, 2023	China	178 Age: 52.46 (9.06)	Retrospective	Albumin+0.005 x lymphocytes	55	Low PNI ≤55 High PNI >55	Radiotherapy	Mean follow up: 50 months	Overall survival and progression-free survival	7	(23)
Zhang *et al*, 2018	China	235 Age: 46 years (29-78)	Retrospective	Albumin+0.005 x lymphocytes	50.38	Low-PNI: 76.2% High-PNI: 23.8%	Surgery	Median: 77 months, range (32-96)	Overall survival and progression-free survival	6	(24)
Zhang *et al*, 2021	China	698 Age: 51 years	Retrospective	Albumin+0.005 x lymphocytes	48.55	Low-PNI: >48.55 High-PNI: ≤48.55	Radiotherapy	Median: 56.2 months (range: 4.9-186.9 months)	Overall survival	6	(25)

PNI, prognostic nutritional index; NOS, Newcastle-Ottawa Scale.

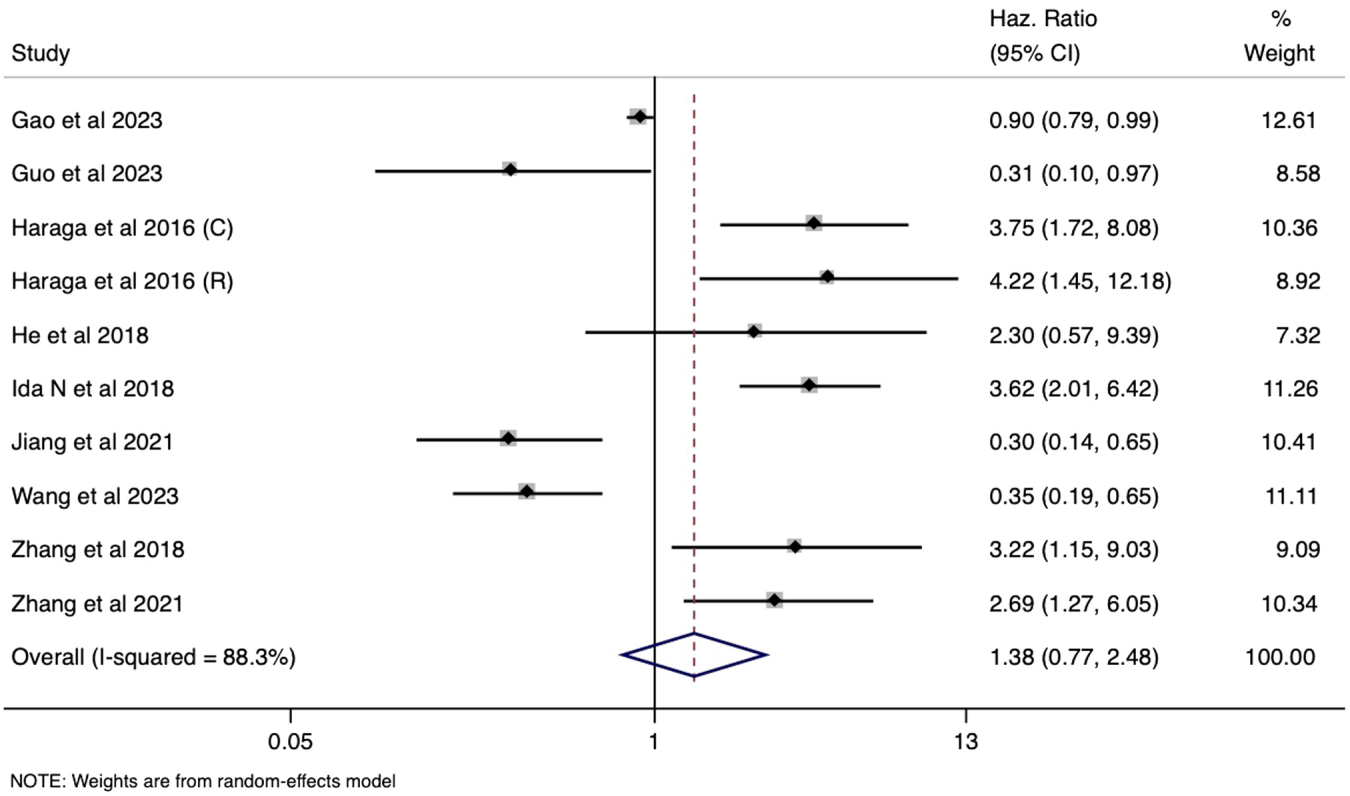

Figure 2. Forest plot showing prognostic utility of PNI (univariate analysis) for overall survival. PNI, prognostic nutritional index; Haz, Hazard; CI, confidence interval.

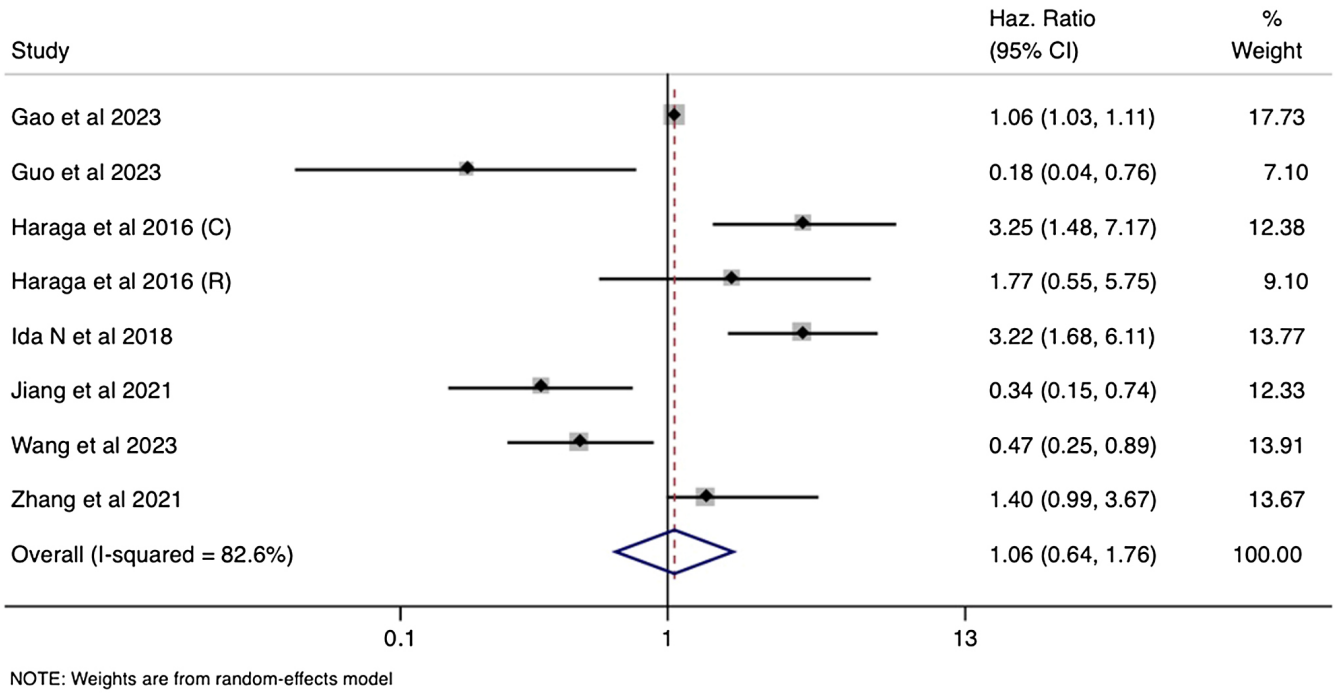

Figure 3. Forest plot showing prognostic utility of PNI (multivariate analysis) for overall survival. PNI, prognostic nutritional index; Haz, Hazard; CI, confidence interval.

with PFS in cervical cancer. As with OS, the univariate analysis yielded a non-significant pooled HR of 1.12 (95% CI: 0.44-2.86), suggesting no independent prognostic value of PNI for predicting PFS (Fig. 4). This lack of association persisted in the multivariate analysis (four studies), with a pooled HR of 1.22 (95% CI: 0.65-2.30) failing to reach statistical significance (Fig. 5). Since both univariate and multivariate analyses showed substantial heterogeneity (I^2=90% and 82%,

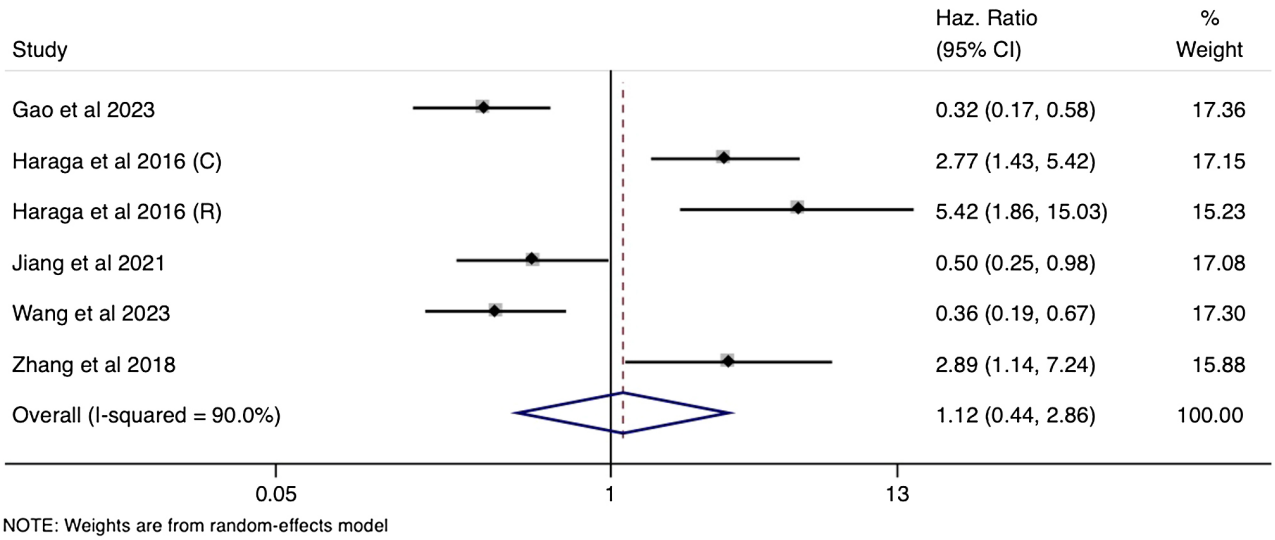

Figure 4. Forest plot showing prognostic utility of PNI (univariate analysis) for progression-free survival. PNI, prognostic nutritional index; Haz, Hazard; CI, confidence interval.

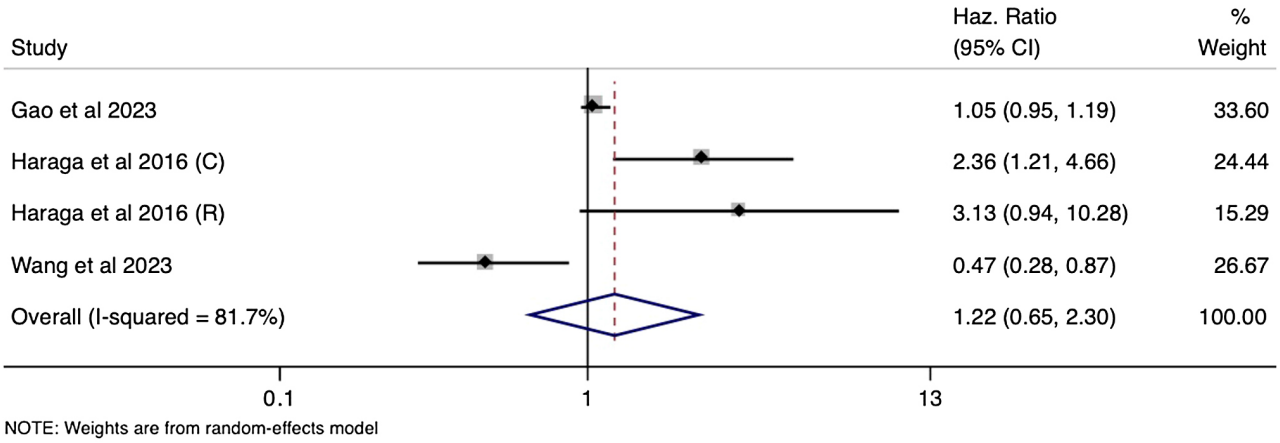

Figure 5. Forest plot showing prognostic utility of PNI (multivariate analysis) for progression-free survival. PNI, prognostic nutritional index; Haz, Hazard; CI, confidence interval.

respectively; P<0.001), a random-effects model was used for pooling the estimates.

Subgroup analysis. Due to variability in the treatment and estimated cut offs, a subgroup analysis was performed for the prognostic utility of PNI in determining OS (univariate and multivariate) and PFS (univariate) based on the region, PNI cut off used (≤48 and >48), sample size (≤150 and >150), grade of evidence and treatment protocol followed. PNI was efficient as a prognostic tool in predicting OS in studies conducted in Japan (univariate and multivariate) and in studies that report concurrent chemoradiotherapy as the treatment of patients with CC (univariate and multivariate). Other subgroups did not show any significant prognostic value for PNI (Figs. S1-8). Similar results were obtained in terms of the prognostic value of PNI in predicting PFS. Japanese studies and studies that used concurrent chemoradiotherapy indicated that PNI had a significant prognostic value (Figs. S9-12). The present study did not perform subgroup analysis for pooled multivariate HRs due to the limited number of studies (four).

Sensitivity analysis. A sensitivity analysis showed that there was not much difference in the pooled effect estimate between the overall risk estimate and the pooled estimate among high-risk studies. This suggests the robustness of the pooled estimate irrespective of the quality of individual studies. (Figs. S13-15)

Publication bias. Publication bias for the univariate analysis component of OS was evaluated using the funnel plot. The funnel plot showed symmetry among the included studies indicating absence of publication bias (Fig. 6).

Discussion

Cervical cancer is associated with a significant health burden worldwide. Identifying potential prognostic factors that can predict outcomes is crucial for guiding treatment decisions and improving patient care. In recent years, the prognostic nutritional index (PNI) has gained attention as a potential predictor of prognosis in various malignancies. The present

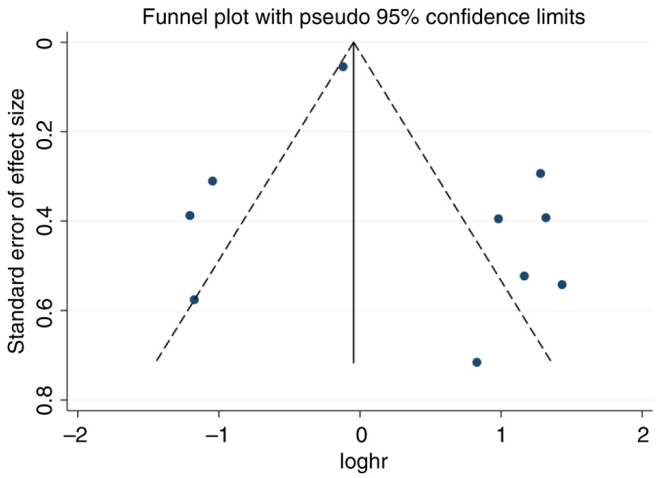

Figure 6. Funnel plot demonstrating publication bias.

analysis aimed to investigate the predictive value of the PNI for CC outcomes. It included nine articles and showed that PNI does not markedly determine OS of PFS in patients with CC. Subgroup analysis showed that PNI served as a useful prognostic tool in predicting OS in studies conducted in Japan and when the patients were treated with concurrent chemoradiotherapy.

Study results. The univariate analysis of the pooled hazard ratios (HRs) for OS revealed an insignificant prognostic utility of the preoperative PNI. The pooled HR was 1.38 (95% CI: 0.77 to 2.48), indicating that the PNI was not a significant predictor of overall survival. This finding was consistent with the multivariate analysis estimates provided by eight studies, which also showed an insignificant utility of the PNI in predicting OS after adjusting for other confounders. The pooled HR in the multivariate analysis was 1.06 (95% CI: 0.64 to 1.76). Similarly, the results of the present study demonstrated that the prognostic utility of the PNI in predicting PFS was insignificant. In the univariate analysis, the pooled HR for PFS was 1.12 (95% CI: 0.44 to 2.68), indicating that the PNI was not a significant predictor of PFS. A total of four studies provided multivariate estimates, which resulted in a pooled HR of 1.22 (95% CI: 0.65 to 2.30) for PNI in predicting PFS.

Malnutrition is seen at alarming rates among patients with gynaecological cancer. Studies from the USA and Australia have shown that almost 20 and 53% of patients with gynaecological cancers, respectively, suffer from at least mild malnutrition and ~20% of all mortality is linked to malnutrition (8,26). Inability to absorb sufficient nutrition frequently results in malnutrition among patients with cancer. Cancer treatment causes reduction in appetite, thereby reducing food intake. Surgery also necessitates starvation. Therefore, as a results of reduced food intake, protein catabolism develops postoperatively depending on the duration of starvation before surgery. This can be further worsened by bowel obstruction, leading to malabsorption. However, as the cancer progresses, there is an increased metabolic demand, triggering catabolism of stored proteins. All these factors build up the negative nutritional balance resulting in the deterioration of nutritional status (27).

Studies from various settings have shown that malnutrition serves as a prognostic determinant of several gynaecological cancers (20,21,28,29). Albumin, total protein, haemoglobin and transferrin are among the widely studied nutritional factors in patients with gynaecological cancers in general and CC in particular (30). Malnutrition and inflammation lead to the decrease in the levels of serum albumin, that reflect the nutritional state of the patient and the severity, course and prognosis. IL-6 has the ability to control albumin synthesis and lower serum albumin levels (31). Similarly, serum albumin levels that strongly correlate with body immunity and nutritional state, may rise and cause inflammation (32,33). In studies of lung, breast, colorectal, ovarian and cervical cancers as well as other malignancies, serum albumin has been found to be a reliable predictor of clinical outcomes (34). The present study used the PNI, a composite indicator calculated from serum albumin and lymphocyte levels.

Comparison with other studies. The present study demonstrated that PNI is not markedly linked with the OS or PFS of patients with cervical cancer. Its results differ from the conclusions of the previous meta-analysis on the same topic (35). However, our study population included only cervical cancer cases, whereas the previous study included all gynaecological cancers. Furthermore, while PNI is a well-established prognostic marker for ovarian and endometrial cancers, its predictive value for cervical cancers patients is still unclear. In addition, it was noted that some studies (18,22,23) have shown that PNI has poor prognostic utility in determining the survival of patients. Therefore, there is a need to identify additional comprehensive nutritional indicators to prognosticate cervical cancer outcomes. The present study results were in agreement with findings reported by individual studies performed in patients with cervical cancer (17,20,23). In our study, subgroup analysis did not show any significant prognostic values for PNI in predicting PFS.

There could be several factors that may explain the lack of significant prognostic value of PNI in predicting OS and PFS in patients with cervical cancer. Firstly, the PNI is calculated based on two components: Serum albumin levels and total lymphocyte count. While these markers reflect nutritional status and immune function, they may not fully capture the complex interplay between nutrition, inflammation and tumor biology in cervical cancer. Other nutritional indicators, such as body mass index, weight loss, or specific micronutrient levels, could potentially provide a more comprehensive assessment of the nutritional status and its impact on cancer outcomes. Therefore, considering alternative nutritional indicators in future studies may shed light on their potential prognostic value in cervical cancer. Additionally, the lack of standardized cut-off values for the PNI across the included studies may have contributed to the non-significant findings of the present study. Different studies may have utilized different cut-off values, leading to heterogeneity in the results. Establishing consensus on standardized cut-off values for the PNI in cervical cancer could potentially improve its prognostic utility and facilitate comparisons across studies.

The present study had several strengths. It is one of the few reviews that has attempted to generate evidence on the prognostic utility of PNI in OS and PFS of patients with CC.

While a previous review evaluated the use of PNI in gynaecological cancers, the present review is more comprehensive, has updated the results and is focused on cervical cancer alone (35). Additional subgroup and sensitivity analysis (using NOS) was performed that adds to the limited literature available. Funnel plot showed no publication bias which adds to the strength of the present study. The large sample size of the included studies added robustness to the results and increased generalizability. All studies were reviewed separately by the two authors. Furthermore, although the present study reported negative outcomes, it is important to note that the prognostic utility of the PNI in patients with cervical cancer is an area of continuing debate. Therefore, our robust meta-analysis methodology ensured the reliability and validity of the results and provided crucial information for comprehensive understanding and informed decision-making in clinical practice. The present study does come with a few limitations. First, there was evidence of high heterogeneity among the included studies, which might have had an impact on the combined results. Although subgroup analysis and sensitivity analyses were used to adjust for heterogeneity, the underlying variability in patient characteristics, treatment provided and cut off used should be taken into account when interpreting the results. All included studies were retrospective in nature, which may add biases and restrict the capacity to demonstrate causation. All included studies were from China and Japan, which may have affected the generalizability of the results. Lastly, the present study included only free full-text English-language articles and did not include grey literature.

The results of the present systematic review and meta-analysis showed that there is inconclusive evidence on the prognostic utility of PNI in determining OS and PFS of patients with cervical cancer. Factors such as the complexity of the tumor microenvironment, the choice of nutritional indicators and the lack of standardized cut-off values may have contributed to these findings. Thus, future prospective studies using PNI cut-off values that are standardised are recommended to increase the clinical efficacy of PNI as a predictive tool.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

DC conceived and designed the study. DC and QD collected the data and performed the literature search. DC was involved in the writing of the manuscript. The two authors have read and approved the final manuscript. DC and QD confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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