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Prognostic Ability of Nutritional Indices for Outcomes of Bladder Cancer: A Systematic Review and Meta-Analysis

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Keywords

Urothelial cancer · Prognostic nutritional index · Controlling nutritional status · Geriatric nutritional risk index · Survival

Abstract

Background: Nutrition has become an important parameter influencing the prognosis of several cancers. However, its impact on outcomes for bladder cancer (BC) is still unclear. This review examines the association between three commonly used nutritional indices, namely, the prognostic nutritional index (PNI), controlling nutritional status (CONUT), and the geriatric nutritional risk index (GNRI) and outcomes of BC. ***Methods:*** PubMed, CENTRAL, Scopus, Web of Science, Embase, and Google Scholar were explored for studies published up to April 13, 2023. Data from studies were pooled to examine the association between PNI, CONUT, or GNRI and overall survival (OS) and recurrence-free survival (RFS). ***Results:*** Thirteen studies were included. Meta-analysis demonstrated significantly poor OS with low PNI versus high PNI in BC patients (hazard ratio [HR]: 1.71; 95% confidence interval [CI]: 1.37, 2.14; I^2 = 0%). This result remained significant in various subgroup analyses. However, no association was noted between PNI and RFS (HR: 1.22; 95% CI: 0.67, 2.24; I^2 = 84%). Meta-analysis showed that patients with high CONUT scores had significantly poor OS (HR: 2.43; 95% CI: 1.82, 3.25; I^2 = 0%) as well as RFS (HR: 2.90; 95% CI: 2.10, 4.01; I^2 = 0%). Data on GNRI were scarce and conflicting. ***Conclusion:*** Limited data show that PNI and CONUT are predictive of outcomes in BC. Low PNI was associated with poor OS, while high CONUT was associated with poor OS and RFS. Data on GNRI are too scarce to obtain conclusions. Further studies are needed to supplement the results.

Introduction

Bladder cancer (BC) continues to be the most common malignancy of the urogenital tract. Estimates suggest that in 2022, 1.6 million individuals were suffering from BC around the world with 80,000 cases and 17,000 cancer-related deaths in the USA alone [1]. Majority of cases are of non-muscle-invasive BC, but around 25% of cases have muscle-invasive or metastatic disease on presentation [2]. Transurethral resection of bladder tumor (TURBT) is the primary therapy for those with non-muscle-invasive BC, but for those with a muscle-invasive disease, neoadjuvant chemotherapy with radical cystectomy and urinary diversion is the mainstay of

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management [3]. Indeed, the invasiveness of cancer affects overall survival (OS) with a 5-year survival of all BC ranging from 60-80% [4], while muscle-invasive disease carries an OS of only 24 months [3]. Given the mortality rates and high prevalence of the disease, there is a need for robust and accurate biomarkers which can predict the outcomes of BC. Prognostic markers have ramifications for surveillance schedules and can alter treatment plans. They can help personalize treatment protocols and recognize individuals who would derive the most benefit [5].

The role of nutrition in the prognosis of cancer patients is being increasingly studied. Evidence shows poor survival, increased complications, and higher healthcare costs among cancer patients suffering from malnutrition [6]. Given that up to 71% of cancer patients may be malnourished before treatment [7], a plethora of research is being conducted to accurately identify malnourished cancer patients so that early interventions can be administered to improve prognosis [8–12]. Nevertheless, there is no clarity on which is the best biomarker for identifying malnutrition and predicting outcomes in cancer patients [13]. Hypoalbuminemia, body mass, psoas muscle measurements, weight loss, and indices like mini-nutritional assessment have all been used but with varied success [14, 15].

Among these markers, prognostic nutritional index (PNI), controlling nutritional status (CONUT), and geriatric nutritional risk index (GNRI) have been identified as independent prognostic indicators in a variety of cancers. Several meta-analysis studies have shown that these three indices can predict OS and recurrence-free survival (RFS) after lung [10], colorectal [16], hepatocellular [17], pancreatic [18], and nasopharyngeal cancer [18]. However, no such review has been conducted to identify their prognostic ability for BC. Given such limitation of the literature, the current review aimed to assess if PNI, CONUT, and GNRI can predict outcomes of BC.

Material and Methods

Search and Inclusion Criteria

The current review protocol was registered on PROSPERO (CRD42023412135). Review reporting was based on the PRISMA statement guidelines [19]. A detailed literature search was carried out by two reviewers independent of one another. PubMed, CENTRAL, Scopus, Web of Science, and Embase were the primary databases searched. An auxiliary distinct search was conducted for gray literature on Google Scholar. All articles available online irrespective of the date of publication, up to April 13, 2023, were eligible for inclusion. We included studies irrespective of the language of publication.

Studies conducted on BC patients were eligible for inclusion. Studies were to assess outcomes (OS or RFS) of BC based on any of the three nutritional indices, i.e., PNI, CONUT, or GNRI. Studies were to compare patients with high or low PNI, CONUT, or GNRI and report outcomes as hazard/risk/odds ratios. Adjusted outcomes were preferred against crude ratios. We did not pre-define the cut-offs for the three indices, and all cut-offs were eligible.

Excluded studies were (1) studies comparing exclusively BC, (2) studies not reporting OS or DFS, and (3) studies with duplicate/overlapping data. If two or more articles used the same dataset from the same period, the study with the highest number of patients was included. Review articles and editorials were not considered for inclusion.

A combination of free-text and MeSH keywords linked with Boolean operators (AND/OR) were used for the literature search. The search terms included "bladder cancer," "bladder carcinoma," "urothelial cancer," "prognostic nutritional index," "controlling nutritional status," "geriatric nutritional risk index," "nutrition," and "survival." Details of the PubMed search strategy are shown in online supplementary Table 1 (for all online suppl. material, see https://doi.org/10.1159/000531884). Identical search threads were utilized for all other databases. Duplicates from the search results were removed, and the remaining records were carefully inquired about based on the eligibility criteria by two reviewers separately. This was done first at the title/abstract level and then at the full-text level. Articles completing all eligibility criteria were included. Any disagreements were solved by consensus. The reference list of eligible articles was hand searched for additional articles.

Data Management and Study Quality

The following particulars were extracted from the studies: author and publication details, study location, type of population included, sample size, age, gender, pathological tumor stage (pT3-T4), high-grade BC, treatment received, type of nutritional index, its cut-off, method to determine cut-off, number of patients malnourished based on the cut-off, follow-up, and outcome data. All data were extracted by two reviewers in duplicate.

Two authors judged the study's quality based on the Newcastle-Ottawa Scale (NOS) [20]. The NOS has three domains: representativeness of the study cohort, comparability, and measurement of outcomes. Points are given based on the preformatted questions. The final score of a study can range from 0 to 9.

Statistical Analysis

We pooled data on different nutritional indices only if at least three studies were available for OS and RFS. If not, a descriptive analysis was done. Outcomes were all reported as hazard ratio (HR) and pooled using "Review Manager" (RevMan, version 5.3; Nordic Cochrane Centre [Cochrane Collaboration], Copenhagen, Denmark; 2014) to generate a combined effect size with 95% confidence intervals (CIs). Considering the variability of included population and treatment provided, a random-effects model was preferred to combine data. Publication bias was not examined as <10 studies were available for each meta-analysis. The I^2 statistic was the tool to determine interstudy heterogeneity. $I^2 < 50\%$ meant low and >50% meant substantial heterogeneity. A leave-one-out analysis was performed to check for any change in the results on the exclusion of any study. If a sufficient number of studies were available for a meta-analysis, we conducted a subgroup analysis based on study location, sample size, treatment given, cut-off determination, and actual cut-off used. p values <0.05 were considered significant.

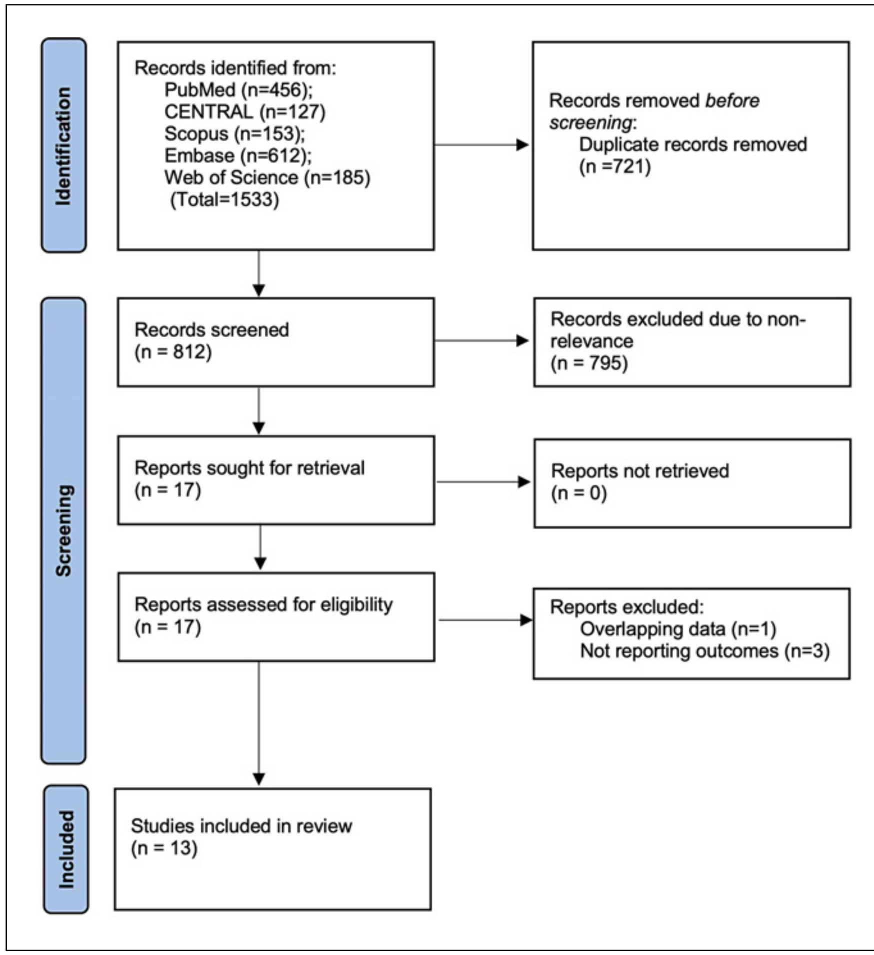

Fig. 1. Study flowchart.

Results

Search

Figure 1 shows the outcomes of the search strategy. Initially, 1,533 studies were found. Duplicates among those were removed, leaving 812 results. After the examination of these articles for primary eligibility, 795 were excluded due to non-relevance. The 17 studies which were selected for full-text analysis underwent detailed examination, and 13 were selected for inclusion [21–33]. The remaining four studies were excluded for reasons mentioned in Figure 1.

Study Details

Details of the studies are shown in Table 1. Seven of the studies were from China, two were from Japan, and one each was from Austria, the USA, Europe, and Turkey. The included studies were published between the years 2017 and 2022. The specific inclusion criteria had some variations among studies with some including only >65-year-old patients while others included only muscle-invasive or invasive BC. One study included patients undergoing robotic surgery, while some included only high-risk BC. The age of the included patients was >60 across all studies. The included cohorts had predominantly male patients. In four studies, pT3-T4 patients were not included, while three did not report such data. The percentage of high-grade BC ranged from 25.8 to 100% among studies. Radical cystectomy was the most common treatment modality. Four studies included patients undergoing TURBT while one included patients treated with radiotherapy only. Six studies reported data on PNI, four on CONUT, and two on GNRI. Both PNI and CONUT were reported in another study. The majority of studies used receiver operating characteristics to determine the cut-off of the nutritional index. Two studies used median values while one used literature data. The number of malnourished based on the study cut-offs was quite variable. The total follow-up ranged from just 1 month to up to 5 years. The NOS score of studies ranged from 6 to 8.

Table 1. Details of included studies

Study	Location	Included patients	Sample size	Age	Male gender, %	pT3-4 stage, %	High grade, %	Treatment	Index	Cut-off	Cut-off determination	Malnourished, %	Follow-up	NOS
Riveros 2022 [23]	USA	>65-year-old patients with BC	1,564	74.5	80.7	NR	NR	Radical cystectomy	GNRI	98	Literature	50	1 month	7
Pan 2022 [24]	China	>65-year-old patients with BC	442	72.1	85	NR	NR	Radical cystectomy	GNRI	100	ROC	42.5	67.5 months (mean)	8
Claps 2022 [22]	Europe	BC patients undergoing RC with PLND and UD	347	72	68.9	54.6	91.1	Radical cystectomy	CONUT	3	ROC	32.3	26 months (median)	8
Zhao 2021 [26]	China	Non-muscle-invasive BC	94	63.2	79.8	0	38.3	TURBT or partial cystectomy	CONUT	1	ROC	47.9	5 years	8
Nemoto 2021 [27]	Japan	Advanced BC without distal organ metastasis	115	69	75.6	NR	83.5	Radical cystectomy	CONUT	3	ROC	19.1	21 months (median)	8
Dan 2021 [25]	China	High-grade T1 stage BC	96	60.7	67.7	0	100	TURBT	CONUT	2	ROC	NR	5 years	6
Yilmaz 2020 [28]	Turkey	Muscle-invasive BC	152	66	87.5	34.9	63.8	Radical cystectomy	PNI	45.9	ROC	NR	16 months (median)	8
Bi 2020[29]	China	High-risk non-muscle-invasive BC	387	69.5	71.6	0	67.9	TURBT	PNI	50.17	ROC	29.9	108 months (median)	8
Zhu 2019 [30]	China	BC patients undergoing robotic surgery	186	65	84.4	11.8	48.4	Radical cystectomy	PNI	50.95	ROC	NR	20.6 months (median)	6
Stangl-Kremser 2018 [31]	Austria	High risk BC	68	82	80.9	8.9	NR	Radiotherapy only	PNI	45.2	Median	NR	13.5 months (median)	7
Peng 2017 [32]	China	BC patients	516	66	84.5	37.4	NR	Radical cystectomy	PNI	46/47	ROC	NR	37 months (median)	8
Miyake 2017 [33]	Japan	Muscle-invasive BC	117	72	78	46	NR	Radical cystectomy	PNI CONUT	50.1	Median	NR	22 months (median)	8
Cui 2017 [34]	China	Non-muscle-invasive BC	329	62.9	79.6	0	25.8	TURBT	PNI	52.57	ROC	51.4	43.9 months (median)	8

BC, bladder cancer; pT3-4, pathological T3 or T4 stage; NOS, Newcastle Ottawa score; NR, not reported; GNRI, geriatric nutritional risk index; ROC, receiver operating characteristics; CONUT, controlling nutritional status; PLND, pelvic lymph-node dissection; UD, urinary diversion; TURBT, transurethral resection of bladder tumor; PNI, prognostic nutritional index.

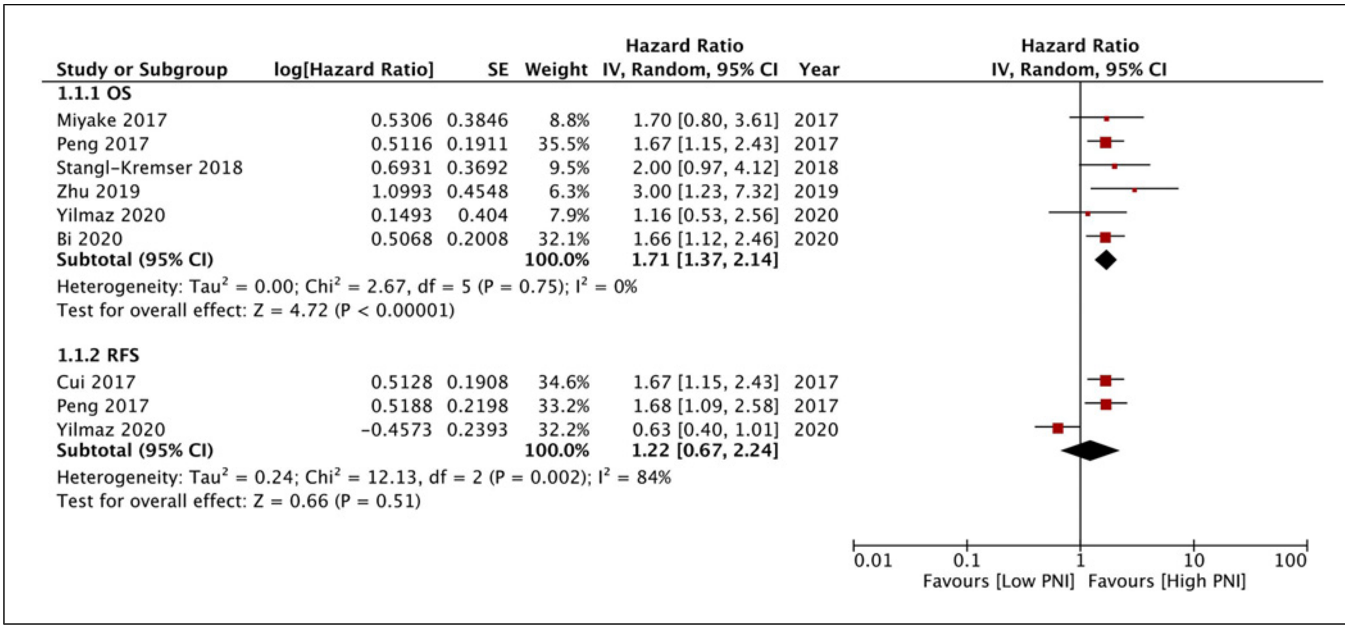

Fig. 2. Meta-analysis of the association between PNI and OS and RFS in BC patients.

Prognostic Nutritional Index

Six studies reported the association between PNI and OS after BC. Meta-analysis demonstrated significantly poor OS with low PNI versus high PNI in BC patients (HR: 1.71; 95% CI: 1.37, 2.14) (Fig. 2). There was no interstudy heterogeneity (I^2 = 0%). The significance of the results did not change on the removal of any study. Details of subgroup analysis for PNI and OS are shown in Table 2. The results were still significant based on study location (Chinese vs. non-Chinese), sample size (>200 vs. < 200), cut-off determination method (median vs. receiver operating characteristics), and cut-off values (≥50 vs. < 50). Based on treatment, the results were significant for studies wherein BC patients were managed by radical cystectomy.

Data on RFS were available only from three studies. Pooled analysis failed to demonstrate a statistically significant association between low PNI and reduced RFS (HR: 1.22; 95% CI: 0.67, 2.24) (Fig. 2). Their interstudy heterogeneity was high (I^2 = 84%). On the exclusion of the study of Yilmaz et al. [30], the results showed poor RFS with low PNI (HR: 1.67; 95% CI: 1.26, 2.22; I^2 = 0%).

Controlling Nutritional Status

Only four studies reported data on the association between CONUT and OS or RFS. Meta-analysis showed that patients with high CONUT scores had significantly poor OS (HR: 2.43; 95% CI: 1.82, 3.25) as well as RFS (HR: 2.90; 95% CI: 2.10, 4.01) (Fig. 3). There was no interstudy heterogeneity (I^2 = 0%) in either analysis. Also, the results remained significant on sensitivity analysis. Further subgroup analysis was not conducted due to limited data.

Geriatric Nutritional Risk Index

Two studies reported the association between GNRI and survival after BC. Riveros et al. [22] demonstrated that per unit decrease in GNRI was associated with a significantly increased risk of 1-month mortality after BC surgery (HR: 1.05; 95% CI: 1.01, 1.05). On the other hand, Pan et al. [26] could not find any significant difference in the risk of OS with low versus high GNRI (HR: 0.783; 95% CI: 0.602, 1.017).

Discussion

Malnutrition is highly prevalent among cancer patients and is an important predictor of prognosis. The European Society for Clinical Nutrition and Metabolism (ESPEN) defines cancer malnutrition as the existence of negative energy balance and skeletal muscle loss due to diminished food intake and metabolic derangements [12]. The presence of malnutrition not only leads to

Table 2. Subgroup analysis of association between PNI and OS

Variable	Groups	Studies	Hazard ratio (95% CIs)
Location	Chinese	3	1.75 (1.35, 2.27)
	Non-Chinese	3	1.61 (1.04, 2.48)
Sample size	>200	2	1.66 (1.27, 2.18)
	<200	4	1.81 (1.23, 2.68)
Treatment	Radical cystectomy	4	1.70 (1.27, 2.27)
	TURBT	1	1.66 (1.12, 2.46)
	Radiotherapy	1	2.00 (0.97, 4.12)
Cut-off determination	Median	2	1.85 (1.10, 3.12)
	ROC	4	1.68 (1.31, 2.15)
Cut-off	≥50	3	1.80 (1.30, 2.50)
	<50	3	1.63 (1.20, 2.22)

ROC, receiver operating characteristics; TURBT, transurethral resection of bladder tumor.

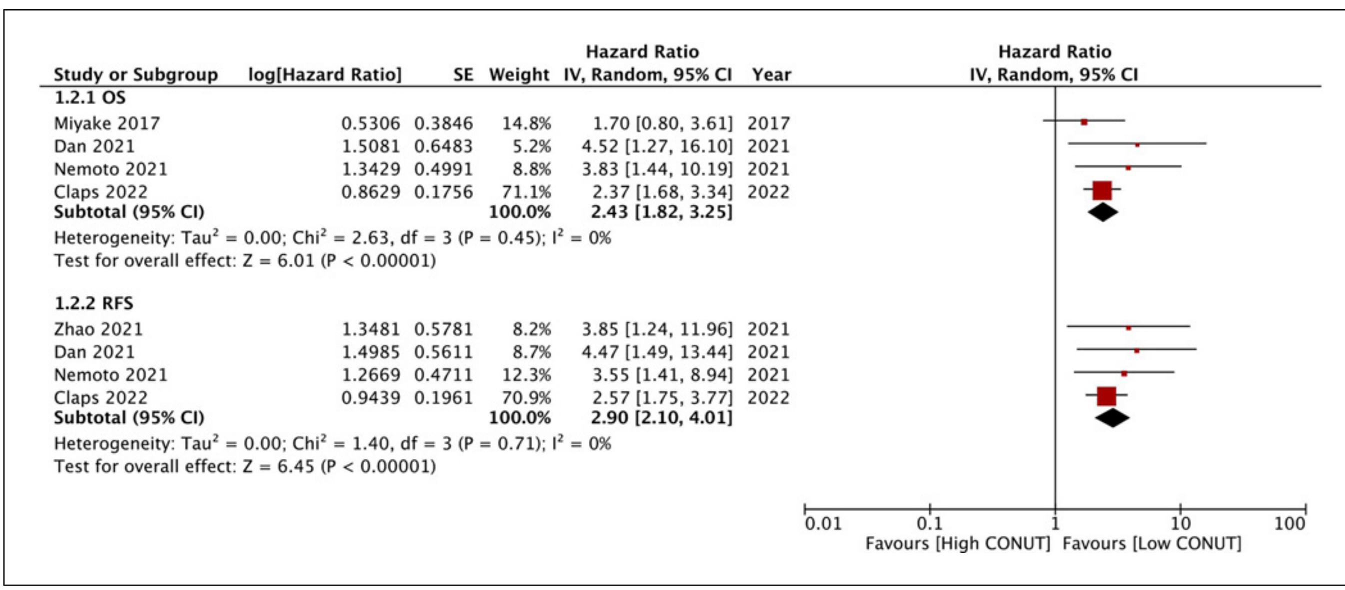

Fig. 3. Meta-analysis of the association between CONUT and OS and RFS in BC patients.

reduced immunity and increased risk of infections but also has an adverse effect on cancer treatment outcomes. Malnutrition in cancer patients has been associated with a higher incidence of treatment-related adverse events, causing a longer length of hospital stay and increased healthcare costs [6]. A large body of evidence also indicates poor survival among malnourished cancer patients [34]. Nevertheless, literature on the prevalence of malnutrition among BC is scarce. A recent review indicates that an estimated 16–33% of BCs were malnourished before starting therapy [7]. Given such high numbers, it is important that accurate pre-treatment nutritional screening is performed for BC patients and at-risk patients are identified for further nutritional therapies. In this context, the role of emerging nutritional biomarkers like PNI, CONUT, and GNRI assumes significance. Surprisingly, while these markers are increasingly being used for other malignancies, evidence on their prognostic ability for BC is still scarce, and no systematic analysis of the evidence has been conducted to date.

In this first review, we demonstrated that PNI and CONUT could be important predictors of the prognosis of

BC patients. The meta-analysis showed a 71% increased risk of poor OS in patients with low PNI versus those with high PNI. Also, high CONUT scores were associated with 2.4 times and 2.9 times increased risk of poor OS and RFS, respectively. The overall interstudy heterogeneity in the meta-analysis was zero and the results remained significant during the sensitivity analysis, thereby increasing the credibility of the outcomes. Furthermore, PNI data were further analyzed via various subgroup analyses which showed that study location, sample size, and cut-offs did not affect the significance of the results. Interestingly, while a strong association between PNI and OS was noted, we failed to find an association between PNI and RFS in BC patients. This could be because only three studies were available. Also, the results were not stable and changed significance with the exclusion of one study [30]. Lastly, insufficient data were available for a pooled analysis of GNRI. While one study [22] noted a significant association between GNRI and mortality, the other [26] failed to show GNRI as an independent predictor of OS. Given the scarce data and variability of outcomes, the results should be interpreted with caution. Only further research can shed light on the prognostic ability of GNRI for BC.

The results of our review are in agreement with other studies evaluating the prognostic ability of PNI and CONUT for cancer patients. While the PNI was initially developed to assess the pre-surgical nutritional status of patients undergoing gastrointestinal intervention, over the years it has become an important tool to predict cancer prognosis [19, 35, 36]. Wang et al. [36] in a review of 21 studies have demonstrated that low PNI is independently associated with poor OS and RFS among lung cancer patients. In a meta-analysis of ten studies, Li et al. [35] have found PNI to be an independent predictor of survival in pancreatic cancer. Another review shows a strong and significant relationship between low PNI and poor OS and RFS in nasopharyngeal carcinoma [18]. Similarly, research also shows CONUT to be an independent predictor of prognosis in cancer patients. Takagi et al. [16] in a pooled analysis of six studies with 2,601 patients noted that high CONUT was associated with poor OS and cancer-specific survival in colorectal cancer. Another meta-analysis has revealed a similar association between CONUT and hepatocellular cancer patients undergoing surgical intervention [17]. Recently, Peng et al. [8] in a review of seven studies have found CONUT to be an independent predictor of OS and RFS in patients with renal cell carcinoma and upper urinary tract urothelial carcinoma. While sufficient research linking GNRI and outcomes of BC is not available in the literature, there have been numerous studies showing GNRI to be an independent prognostic indicator in cancer patients. Reviews have confirmed the prognostic ability of GNRI for non-small cell lung cancer [10], esophageal cancer [37], and colorectal cancer [9].

The PNI, CONUT, and GNRI are all nutritional-based indices but have subtle differences and are calculated using different values. The PNI combines albumin and lymphocyte count, while CONUT is calculated by a combination of albumin, lymphocyte count, and cholesterol levels. On the other hand, GNRI is calculated by combining albumin and adjusted body weight. The common thread in all three factors is albumin, and hypoalbuminemia is reflective of the nutritional status of the patient [38]. Malnutrition can directly influence host immunity and, therefore, cancer outcomes [39]. Individually, hypoalbuminemia alone has been associated with poor prognosis in cancer patients [11]; however, since other confounders and diseases can easily alter albumin levels, it has now been used in combination with other variables. Combination with lymphocytes generates an immune-nutrition marker (PNI) as lymphocyte counts are reflective of cell-mediated immunity and are a vital component of cancer defense. A low lymphocyte count reduces antitumor response and compromises host immunity, causing increased mortality and recurrence [40]. Further addition of cholesterol to PNI generates CONUT. Cholesterol is an important contributor to the cell membrane and immunity which allows immunocompetent cells to initiate an anticancer immune response [41]. Growth of cancer cells requires low-density lipoprotein, which in turn reduces serum cholesterol levels. The reduced cholesterol levels indicate depletion of the reserve calorie stock of the patient and are associated with tumor progression and poor survival [42]. Lastly, GNRI uses adjusted body weight as an additional marker of nutritional status. Calculated as a ratio of current body weight to ideal body weight, it acts as a surrogate marker of body mass index which is also a known factor affecting cancer prognosis [43].

There are numerous strengths in this review. It is the first to quantitatively examine the association between nutritional indices and the prognosis of BC. A detailed literature search was carried out to pool data from all three commonly used indices to present comprehensive evidence. We conducted sensitivity analyses and multiple subgroup analyses (where sufficient data were available) to examine the effects of individual cohorts and study confounders on the results. The low interstudy heterogeneity is an additional dividend in the interpretation of results.

Nevertheless, there are limitations to the study. The number of studies in each meta-analysis was not high. A pooled analysis was not possible for GNRI, and additional subgroup analyses could be conducted only for PNI. Second, despite low interstudy heterogeneity, there were variations among the included studies. The inclusion criteria, stage and grade of tumor, and the treatment provided had certain variations which could impact the outcomes. Third, most of the studies were from China, and only limited data were available from other countries. Therefore, outcomes should be generalized with caution.

Conclusions

Limited data show that PNI and CONUT are predictive of outcomes in BC. Low PNI was associated with poor OS, while high CONUT was associated with poor OS and RFS. Data on GNRI are too scarce to obtain conclusions. Further studies are needed to supplement the results.

Statement of Ethics

An ethics statement is not applicable because this study is based exclusively on published literature.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

H.J., L.W., X.Z., J.W., and T.L. contributed to conception of this study. H.J., L.W., X.Z., and T.L. contributed to performance of work. X.Z. and T.L. contributed to writing of the article. All authors approved this study.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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