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Association between Geriatric Nutritional Risk Index and survival outcomes in patients with urological cancers: an updated meta-analysis

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ABSTRACT

Objectives This meta-analysis aimed to evaluate the association between the Geriatric Nutritional Risk Index (GNRI) and survival outcomes in patients with urological cancer.

Design Systematic review and meta-analysis of observational studies.

Data sources A comprehensive literature search was conducted in Medline, EMBASE, Google Scholar and the Cochrane Library from inception to 7 July 2024.

Eligibility criteria Studies were included if they examined the correlation between the GNRI and long-term survival outcomes in adult patients (≥18 years old) with urological cancers.

Data extraction and synthesis Two researchers independently extracted data and assessed study quality using the Newcastle-Ottawa Scale and certainty of evidence using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) methodology. Publication bias was evaluated using funnel plots and Egger's test for outcomes with more than 10 studies. Pooled HRs and 95% CIs were calculated using a random-effects model. Subgroup analyses, meta-regression and sensitivity analyses were performed.

Results 17 studies involving 8816 patients were included. Study quality assessment showed that 15 studies had a low risk of bias (scores 7–9) and two had a high risk (scores 5–6). Low GNRI was significantly associated with poor overall survival (OS) (HR: 2.6, 95% CI: 2.0 to 3.38, p<0.00001, I^2 = 64%, 13 studies), cancer-specific survival (CSS) (HR: 2.65, 95% CI: 1.76 to 3.98, p<0.00001, I^2 = 75%, 7 studies), recurrence-free survival (RFS) (HR: 1.47, 95% CI: 1.02 to 2.1, p=0.04, I^2 = 58%, four studies) and progression-free survival (PFS) (HR: 1.86, 95% CI: 1.54 to 2.23, p<0.00001, I^2 = 0%, five studies). Funnel plot and Egger's test (p=0.948) indicated a low risk of publication bias for OS. GRADE assessment showed low certainty of evidence for OS and PFS, and very low certainty for CSS and RFS. Meta-regression identified follow-up time and sample size as significant sources of heterogeneity.

Conclusions A low GNRI is significantly associated with poor survival outcomes in patients with urological cancer. The GNRI may serve as a valuable prognostic tool in clinical practice. Further research is needed to validate these findings in diverse populations and to explore the underlying biological mechanisms.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ A comprehensive literature search was conducted across multiple databases without language restrictions to minimise the risk of missing relevant studies.
⇒ The inclusion of 17 studies with a total of 8816 patients provided a robust evidence base for evaluating the association between the Geriatric Nutritional Risk Index and survival outcomes in urological cancers.
⇒ The use of subgroup analyses, meta-regression and sensitivity analyses allowed for a thorough exploration of potential sources of heterogeneity and robustness of the findings.
⇒ The included studies were limited to Asian populations, which may have affected the generalisability of the findings to other geographical regions and healthcare settings.

Prospero registration number CRD42023476678.

INTRODUCTION

Urological cancers encompass a wide range of malignancies, including urothelial carcinoma, renal cell carcinoma, bladder cancer and prostate cancer, each of which contributes to a considerable public health burden.[1] These cancers are particularly impactful in the USA, accounting for approximately 456 860 new cases and 67 290 cancer-related deaths among men in 2023, constituting approximately 18% of all male cancer-related fatalities.[2] Undoubtedly, urological cancers are a major burden on healthcare systems and patients worldwide.[3] Despite the significantly enhanced patient prognosis with advances in immunotherapy, such as therapeutic vaccines and immune checkpoint inhibitors,[4] the recurrence and mortality rates associated with urological cancers remain alarmingly high.[5–8] Traditional prognostic indicators, such as tumour stage, are

not sufficiently comprehensive to assess the overall health status of a patient. Consequently, host-related prognostic factors should be urgently identified to better guide clinical decision-making and improve patient care.

Growing evidence indicates that malnutrition is a prevalent characteristic among patients with cancer, resulting in unintended weight loss attributed to insufficient nutrient intake or absorption.[9] Malnutrition is believed to have detrimental effects on various aspects of cancer management and prognosis. It can diminish the effectiveness of treatments, exacerbate the adverse effects of those treatments, impair the quality of life of patients, and most critically, negatively impact overall survival (OS) rates.[9] Consistently, the nutritional status of patients at pretreatment has been associated with their prognoses.[10] Their nutritional status has been suggested to have a significant impact not only on their tolerance to anticancer therapies[11 12] but also on their response to treatments.[13]

The Geriatric Nutritional Risk Index (GNRI) has been established as a significant prognostic tool for assessing the nutritional status of patients with cancer, providing insights that may influence disease management and outcomes.[14] Previous meta-analyses have established a relationship between GNRI scores and cancer-related outcomes,[15–17] highlighting the index's utility in clinical settings. Notably, a recent meta-analysis of eight observational studies demonstrated that lower GNRI levels were significantly associated with poorer cancer-related outcomes in patients with urological cancers.[18] Despite these advancements, the evidence may not be robust owing to the limited number of studies included in that meta-analysis.[18] Recently, several studies[19–23] have provided new evidence that necessitates an updated meta-analysis. In light of these considerations, the rationale for our meta-analysis is to update the prognostic relevance of the GNRI in light of new evidence and to refine the predictive accuracy of this tool, ultimately helping clinicians tailor nutritional interventions that could improve cancer management and the quality of life of patients.

METHODS

The protocol for this study was registered in advance with PROSPERO under registration number CRD42023476678, and the meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Data sources and search strategies

A systematic and exhaustive literature search was initially conducted across electronic databases, namely Medline, EMBASE, Google Scholar and Cochrane Library, from their inception to 27 October 2023. The most recent search update was performed on 7 July 2024. To ensure a wide coverage, a combination of MeSH terms and keywords was used, including ('geriatric nutritional risk index') AND ('bladder cancer' or 'Urinary Bladder Neoplasm' or 'Bladder Tumor' or 'renal cell cancer' or 'Renal Cell Carcinomas' or 'Renal Adenocarcinoma' or 'Renal Cell Adenocarcinoma' or 'Adenocarcinoma of Kidney' or 'prostate cancer' or 'Prostate Neoplasms' or 'urothelial cancer' or 'Urological Neoplasm' or 'Urinary Tract Neoplasms' or 'Urologic Neoplasm' or 'urological cancer' or 'urinary cancer') and ('overall survival' or 'cancer-specific survival' or 'recurrence-free survival' or 'progression-free survival'). No limitations were imposed based on country or language. Furthermore, the reference lists of the selected articles and previous systematic reviews were manually scanned to ensure that all pertinent studies, even those not indexed, were considered. Online supplemental table 1 provides a detailed summary of the synonyms and controlled vocabulary used for the study search in Medline.

Study selection

All retrieved citations from the database search were imported into reference management software, where duplicates were removed. Titles and abstracts were screened by two independent reviewers against predefined criteria. Full-text articles of potentially relevant studies were assessed for eligibility. Any disagreements between the reviewers were resolved through discussion or consultation with a third reviewer.

Inclusion and exclusion criteria

The inclusion criteria for the meta-analysis were as follows: (1) studies examining the correlation between the GNRI and long-term survival outcomes; (2) the population had to include adult human subjects (≥18 years old) diagnosed with any type of urological cancers, such as bladder, prostate, renal cell carcinoma, upper tract urothelial carcinoma or testicular cancer; (3) eligible studies needed to provide raw or summarised data for calculating HRs and 95% CIs for OS, cancer-specific survival (CSS), progression-free survival (PFS), recurrence-free survival (RFS) or disease-free survival (DFS); and (4) only original research articles from peer-reviewed journals were included.

Studies that met the following criteria were excluded: (a) articles presented as letters, editorials, case reports and reviews; (b) studies that failed to provide adequate data for the meta-analysis or lacked a clear methodological description; (c) studies that only focused on short-term outcomes (eg, postoperative mortality); and (d) articles from platforms known for hosting non-peer-reviewed content, such as preprints on Research Square.

Data collection

A data extraction form pre-tested for consistency was used. Two researchers independently collected the data, and any disagreements were resolved through consensus or consultation with a third reviewer. The variables extracted included countries, sample sizes, demographics (age and sex), urological cancer type and stage, treatment methods, cut-off GNRI values, follow-up periods, and reported outcomes.

Outcome and definition

The primary endpoint was the link between GNRI and OS in patients with urological cancers. The secondary endpoints examined the connection between GNRI and RFS, PFS, and CSS.

Quality assessment of included studies

Two independent reviewers evaluated the quality of the included studies using the Newcastle-Ottawa Scale (NOS). This assessment tool examines three key domains: selection bias, cohort comparability and outcome assessment. Selection bias refers to the appropriateness of the study groups and their selection. Cohort comparability evaluates the extent to which the study controls for confounding variables, and outcome assessment considers the adequacy of outcome measurements and follow-up. Each study was rated on a nine-star scale, with scores of seven or more indicating a high-quality and robust methodology. Any disagreements between the reviewers were resolved through discussion, and a third reviewer was consulted when consensus could not be reached.

Certainty of evidence assessment

To assess the certainty of evidence in this meta-analysis of observational studies, we used the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach, which evaluates the quality of evidence across five domains: risk of bias, inconsistency, indirectness, imprecision and publication bias. Each outcome's overall certainty of evidence was categorised as high, moderate, low or very low, with the initial rating for observational studies starting at low and adjusted based on the domain assessments. Two reviewers independently conducted this evaluation and resolved any disagreements through discussion or by consulting a third reviewer.

Statistical analyses

All statistical analyses were performed using the Cochrane Review Manager (RevMan 5.3; Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2014) and Comprehensive Meta-Analysis (Version 4, Biostat, Englewood, NJ, USA). The association between the GNRI and survival outcomes was evaluated by calculating the pooled HR and 95% CI. For studies reporting both multivariate and univariate HRs, only multivariate results were included to ensure a more robust analysis, adjusting for potential confounders. The I^2 statistic was used to measure the statistical heterogeneity among the studies. Sensitivity analyses were conducted using two approaches: (1) the leave-one-out method to assess the influence of individual studies on the overall effect size, and (2) excluding studies with a high risk of bias (NOS scores ≤6) to evaluate the robustness of our findings. For outcomes with more than 10 studies, funnel plots were created to detect potential publication bias, and Egger's regression test was used to statistically assess asymmetry. Due to the expected heterogeneity among the studies, a random-effects model was applied for the meta-analysis. Subgroup analyses for the primary outcome (ie, OS) were conducted based on factors such as study country, cancer type and treatment. To identify potential sources of heterogeneity, meta-regression analyses were also conducted, considering variables such as sample size, publication year, follow-up duration and percentage of male participants. All statistical tests were two-tailed, with a p value of less than 0.05 considered significant.

RESULTS

Study selection

A total of 235 records were initially identified for potential inclusion in the meta-analysis from the following databases: MEDLINE (n=29), Embase (n=52), Cochrane Library (n=0) and Google Scholar (n=154) (figure 1). After screening, 52 duplicate records were removed, leaving a total of 183. On further assessment of the titles and abstracts, 156 records were excluded, resulting in 27 reports being assessed for eligibility. Of these 27 reports, 10 were subsequently excluded for various reasons: 5 due to data unsuitable for analysis, 2 had no reported outcomes, 2 did not meet the inclusion criteria and 1 was a correspondence or letter-type publication. Consequently, 17 studies published between 2015 and 2024 were included in the final review.[19–35]

Table 1 summarises the characteristics of studies involving a total of 8816 patients. All 17 included studies originated from Asian countries: 10 from Japan,[19–22 24 26 29 30 32 33] two from Taiwan,[23 27] four from China[25 31 34 35] and one from Korea.[28] The sample sizes across these studies varied significantly, ranging from 27 to 4591 participants. The investigated cancer types included renal cell, urothelial, prostate and bladder cancer. The majority of studies (12 of 17) reported a male-dominated participant pool, with >70% male participants.[19–22 24 26–29 32 33 35] Seven studies specifically focused on patients at tumor-node-metastasis stage 4,[21 22 24 26 27 29 31] five addressed stages 1–3[20 23 25 28 30] and five encompassed stages 1–4.[19 32–35] Regarding the use of the GNRI as a prognostic factor, 10 studies established a cut-off value of 92,[19 21 23–29 31] five studies set it at 98,[20 30 32–34] one study at 100[22] and another at 93.82.[35] In terms of survival outcomes, 13 studies reported on OS,[19 20 22–27 29 31–34] 4 on RFS,[25 28 30 35] 5 on PFS,[22 26 27 33 35] 1 on DFS[23] and 7 on CSS.[21 23 28–30 33 34]

Using the NOS to assess study quality (table 1), 15 studies[19 21 23–35] were classified as having a low risk of bias, with NOS scores ranging from 7 to 9. In contrast, two studies[20 22] were identified as having a high risk of bias, with scores of 6 and 5, respectively. A detailed assessment of the NOS for each study is available in online supplemental table 2.

Meta-analysis

Association between GNRI with survival outcomes

Meta-analysis of 13 studies revealed poor OS in patients with low GNRI compared with those with high GNRI (HR, 2.6; 95% CI, 2.0 to 3.38; p<0.00001; I^2=64%)[19 20 22–27 29 31–34]

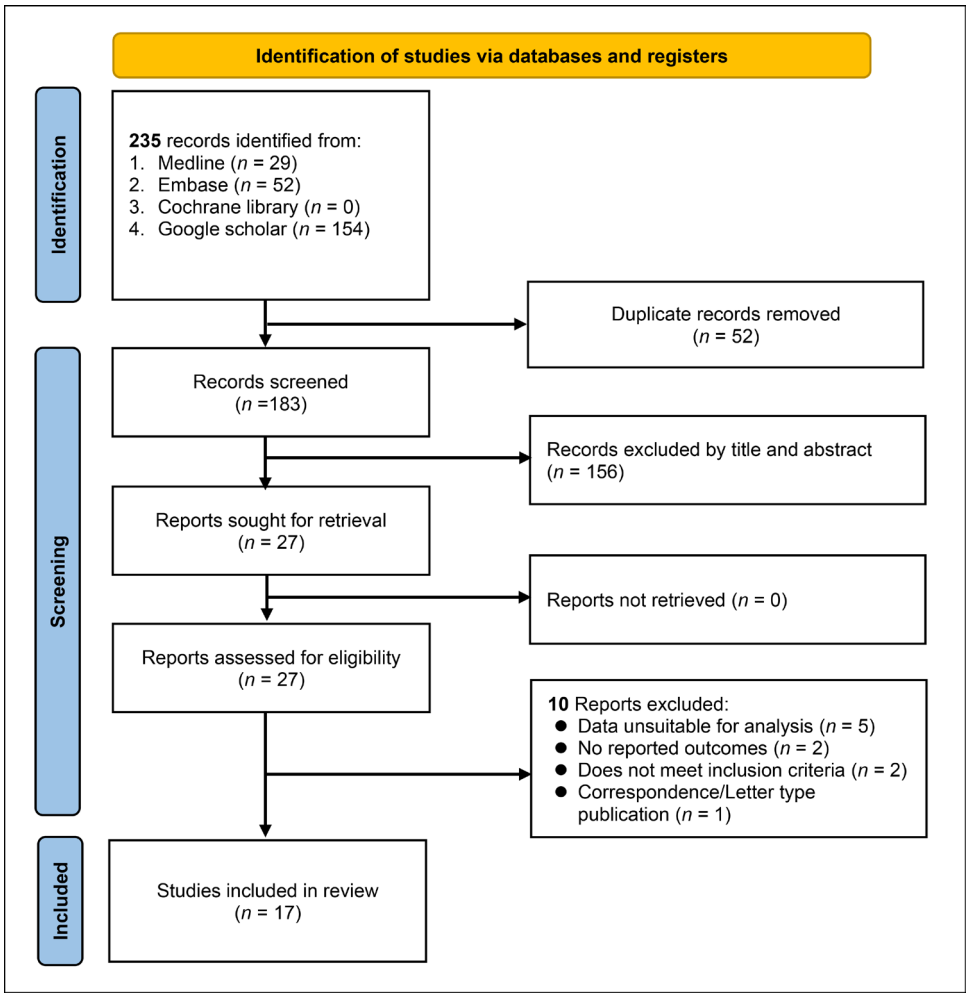

Figure 1 Flowchart of the study selection.

(figure 2). Seven studies provided data to determine the association between GNRI and CSS. Patients with a low GNRI had a poorer CSS than those with a high GNRI (HR, 2.65; 95% CI, 1.76 to 3.98; p<0.00001; I^2=75%) (figure 3).[21 23 28–30 33 34] Pooled results also suggested a significant association between low GNRI and poor RFS (HR, 1.47; 95% CI, 1.02 to 2.1; p=0.04; I^2=58%, four studies) (figure 4a).[25 28 30 35] Similarly, pooled results revealed a significant association between low GNRI and poor PFS (HR, 1.86; 95% CI, 1.54 to 2.23; p<0.00001; I^2=0%, five studies) (figure 4b).[22 26 27 33 35] Sensitivity analyses revealed consistent findings for OS, CSS and PFS; whereas, the results for RFS were unstable. After excluding two studies[20 22] with a high risk of bias (NOS scores ≤6), sensitivity analysis of the remaining 11 studies showed a consistent association between low GNRI and poor OS (HR: 2.62, 95% CI: 1.97 to 3.49, p<0.00001), with heterogeneity remaining substantial (I^2 = 70%) (online supplemental figure 1). The magnitude and direction of the effect were similar to the primary analysis including all studies (HR: 2.6, 95% CI: 2.0 to 3.38).

Meta-regression analysis on the primary outcome

To explore the potential sources of heterogeneity in our pooled results, a meta-regression analysis was performed, focusing on the primary outcome. This analysis revealed that follow-up time (coefficient: −0.02, p=0.0045) (figure 5a) and sample size (coefficient: −0.001, p=0.049) (figure 5b) were significant covariates, indicating their substantial impact on the overall effect size. In contrast, the proportion of male participants (coefficient: 0.004, p=0.65) (figure 5c) and publication year (coefficient: −0.02, p=0.738) (figure 5d) did not show a notable influence on the results. These findings underscore the importance of considering follow-up duration and sample size in future studies to better understand and mitigate heterogeneity.

Subgroup analyses on the primary outcome

Subgroup analyses were conducted to evaluate the influence of factors such as country, type of cancer and type of treatment (ie, medical vs surgical treatment) on the relationship between GNRI and OS. For studies conducted in Japan (n=8), the pooled HR was 2.42 (95% CI: 1.88 to 3.11, I^2=0%) (online supplemental figure 2). In China (n=3), the pooled HR was 1.88 (95% CI: 1.08 to 3.29, I^2=83%), also showing increased risk with low GNRI but with substantial heterogeneity. The two studies from Taiwan had the highest pooled HR of 4.41 (95% CI: 3.27 to 5.96, I^2=0%). The test for subgroup differences

Table 1 Characteristics of the included studies (n=17)

Author year/country	N	Age (year)	Cancer type (TNM stages)	Male (%)	Treatment (follow-up, month)	GNRI cut-off	Analytic type	NOS
Chang 2023 (Taiwan)[23]	488	70.0	UC (1–3)	42	SR (23.2)	92	M	8
Chang 2020 (Taiwan)[27]	170	74	PC (4)	100	Docetaxel (22.5)	92	M	8
Etani 2020 (Japan)[21]	52	71	UC† (4)	83	Pembrolizumab (12.2)	92	M	9
Gu 2015* (China)[31]	300	56.2	RCC (4)	68	Target therapy (30.8)	92	M	9
Isobe 2022 (Japan)[24]	198	68	UC (4)	82	Pembrolizumab (1–35)	92	M	8
Kang 2020 (Korea)[28]	4591	61	RCC (1–3)	73	SR (37)	92	M	7
Makino 2023 (Japan)[20]	213	≥65: 46.9%	RCC (1–3)	73	SR (53.4)	98	OS: U, MFS: M	5
Miyake 2017 (Japan)[30]	432	>70: 62%	RCC (1–3)	64	SR (1–100)	98	U	7
Naiki 2021 (Japan)[26]	68	71	UC (4)	81	Gemcitabine/cisplatin (12.9)	92	M	7
Naiki 2023 (Japan)[32]	175	72–77	PC (1–4)	100	ADT (26.2–33.7)	98	M	7
Okamoto 2019 (Japan)[29]	339	72	PC (4)	100	ADT (26)	92	U	8
Shimizu 2020 (Japan)[22]	27	73	UC (4)	85	Pembrolizumab (7)	100	U	6
Takagi 2023 (Japan)[19]	200	72	Mixed (1–4)	84	SR, medication (22)	92	M	8
Tang 2021 (China)[25]	694	>60: 35.3%	RCC (1–3)	64	SR (60.9)	92	M	8
Watari 2023 (Japan)[33]	119	70	RCC (1–4)	78	ICI (11–14)	98	M	8
Wu 2024 (China)[35]	292	69	BC (1–4)	81	SR (43)	93.82	M	8
Wu 2023 (China)[34]	458	70	UC (1–4)	49	SR (36.8)	98	M	8

*Prospective.
BC, bladder cancer; GNRI, Geriatric Nutritional Risk Index; ICI, immune checkpoint inhibitor; M, multivariate; NOS, Newcastle-Ottawa Scale; OS, overall survival; PC, prostate cancer; RCC, renal cell carcinoma; SR, surgical resection; TNM, tumor-node-metastasis; U, univariate; UC, urothelial cancer.

was significant (p=0.003), indicating that the effect size varied significantly between countries. Overall, the strongest association was seen in Taiwan, followed by Japan and China.

Subgroup analysis of the three types of urological cancer (renal cell carcinoma, urothelial cancer and prostate cancer) indicated that the effect size did not differ significantly between cancer types (online supplemental figure 3). The pooled HR for prostate cancer (3 studies) was 2.81 (95% CI: 1.35 to 5.87, I^2=81%), indicating the strongest association between low GNRI and OS. This was followed by urothelial cancer studies (5 studies) with an HR of 2.69 (95% CI: 1.73 to 4.18, I^2=68%) and renal cell carcinoma (4 studies) with an HR of 2.19 (95% CI: 1.22 to 3.91, I^2=67%).

In addition, a low GNRI was associated with poor OS regardless of treatment type, with a potentially stronger effect in patients receiving medical treatment (HR: 2.94, 95% CI: 2.3 to 3.77, I^2=32%) than in those receiving surgical treatment (HR: 2.06, 95% CI: 1.14 to 3.72, I^2=82%) (online supplemental figure 4). However, this difference was not statistically significant (p=0.27), and substantial heterogeneity was observed, particularly in the surgical treatment subgroup.

Publication bias

For OS (13 studies), the funnel plot was symmetrical, and Egger's test (p=0.948) indicated a low publication bias risk (figure 6). Although formal statistical testing for publication bias was not performed for CSS, RFS and PFS

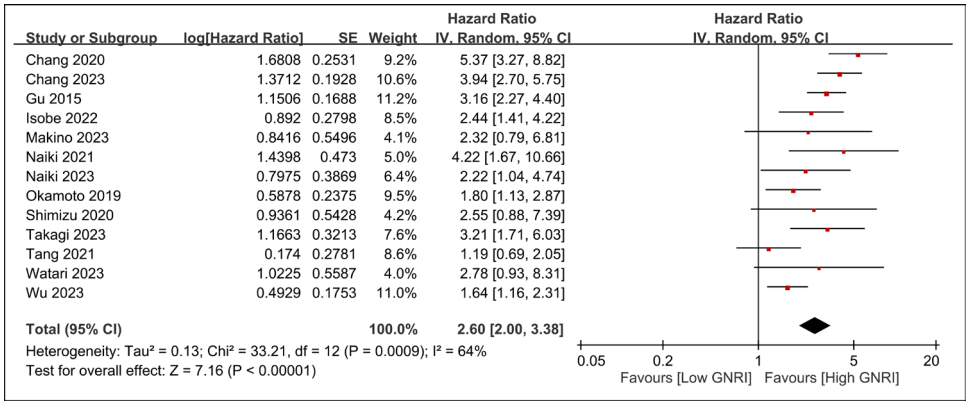

Figure 2 Forest plot showing the association between low Geriatric Nutritional Risk Index (GNRI) and overall survival (OS). IV: invariance.

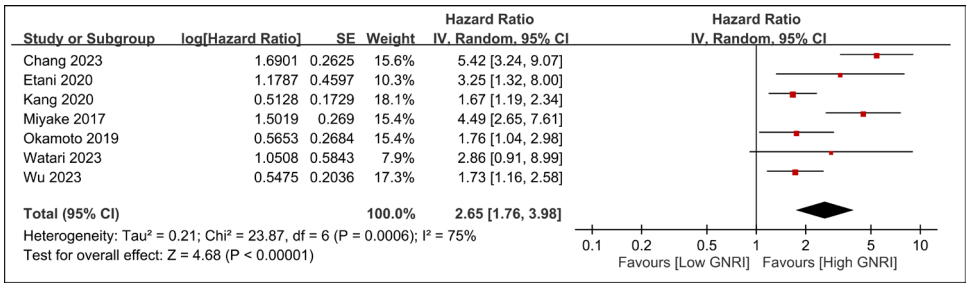

Figure 3 Forest plot showing the association between low Geriatric Nutritional Risk Index (GNRI) and cancer-specific survival (CSS). IV: invariance.

due to limited studies (<10), visual inspection of funnel plots showed relatively symmetric distributions (online supplemental figure 5–7), suggesting no obvious publication bias in these outcomes. However, these visual assessments should be interpreted cautiously, given the small number of studies.

Certainty of evidence

The GRADE approach was employed to assess the certainty of evidence across various outcomes (table 2). Our analysis revealed that the certainty of evidence for OS and PFS was low, suggesting that further research is likely to have an important impact on our confidence in the estimate and may change the estimate. In contrast, the certainty of evidence was very low for CSS and RFS, indicating that any estimate of effect is very uncertain

DISCUSSION

This meta-analysis examined the prognostic value of the GNRI in patients with urological cancers, including 17 studies with 8816 patients. The analysis revealed that low GNRI was significantly associated with poor OS (HR: 2.6, 95% CI: 2.0 to 3.38, p<0.00001), CSS (HR: 2.65, 95% CI: 1.76 to 3.98, p<0.00001), RFS (HR: 1.47, 95% CI: 1.02 to 2.1, p=0.04) and PFS (HR: 1.86, 95% CI: 1.54 to 2.23, p<0.00001). Meta-regression analysis identified follow-up time and sample size as significant sources of heterogeneity. Subgroup analyses showed that the association between the GNRI and OS was consistent across different countries, cancer types and treatment modalities, with potentially stronger effects observed in studies from Taiwan and in patients receiving medical treatment. These findings underscore the potential utility of the GNRI as a prognostic marker in urological cancers, although further research is needed to validate its clinical application.

Higher body weight has been associated with a lower mortality risk in patients with upper tract urothelial carcinoma and renal cell carcinoma.[36 37] Additionally, low serum albumin levels have also negatively affected cancer survival[38] because of its roles in anticancer activity, including transporting anticancer agents, reducing oxidative stress, inhibiting overactivated inflammation and modulating the immune response.[39 40] GNRI, which uses a formula incorporating albumin levels and the ratio of current to the ideal body weight (GNRI=14.89 × albumin [mg/dL] + 41.7 × [current/ideal body weight]), offers a quantitative measure that has been correlated with the prognosis of patients across various cancer types.[15–17 41] The components of the GNRI—serum albumin and body weight—are routinely collected clinical parameters that allow for straightforward implementation in daily

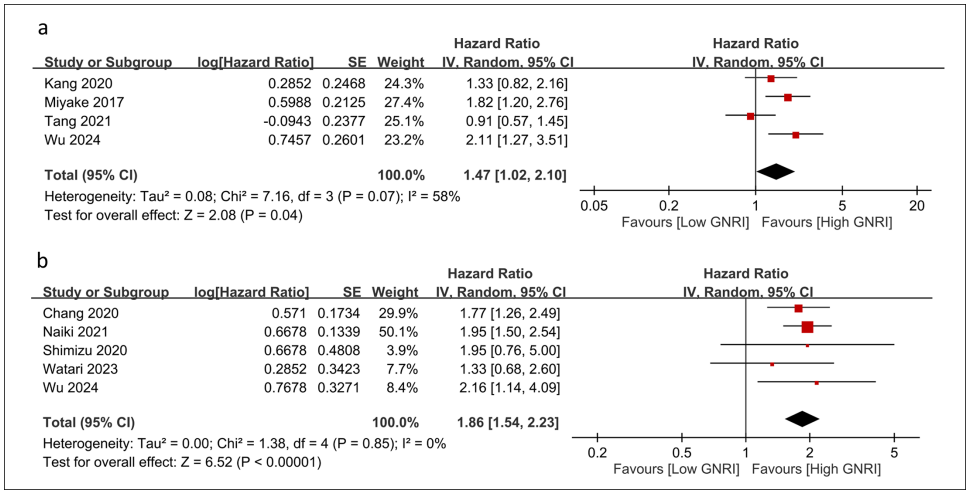

Figure 4 Forest plot showing the association between low Geriatric Nutritional Risk Index (GNRI) and (a) recurrence-free survival (RFS) and (b) progression-free survival (PFS). IV: invariance.

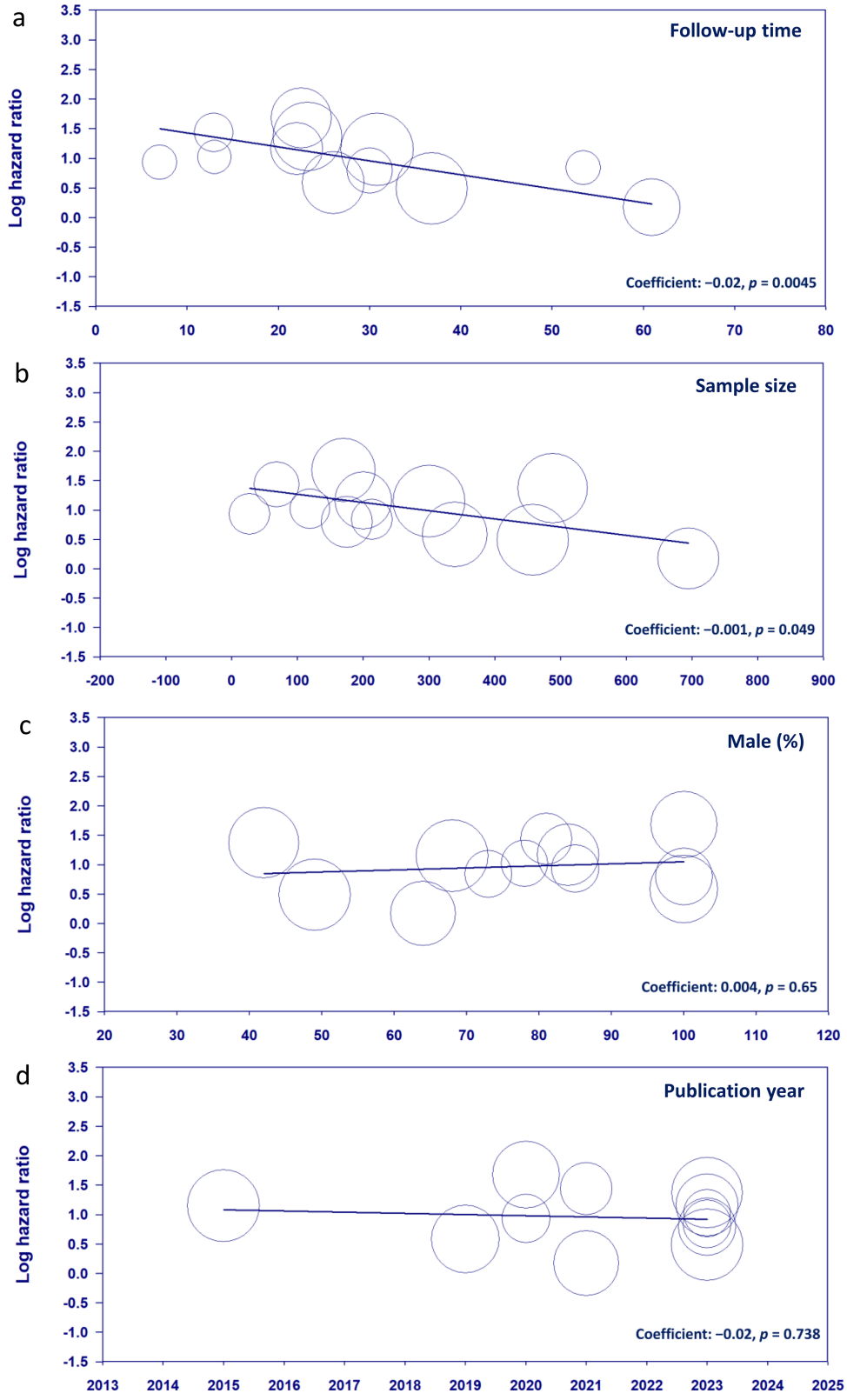

Figure 5 Meta-regression plot analysing the impact of the (a) follow-up time, (b) sample size, (c) male proportion and (d) publication year on the effect size on the association between the Geriatric Nutritional Risk Index (GNRI) and overall survival.

practice without requiring additional specialised training or resources. The GNRI offers a unique advantage over body weight by emphasising serum albumin—a nutritional status marker—over mere body weight, thus, distinguishing between malnourished patients with high weight and well-nourished individuals with low weight.[41] By incorporating serum albumin levels and body weight measurements, the GNRI provides a nuanced assessment

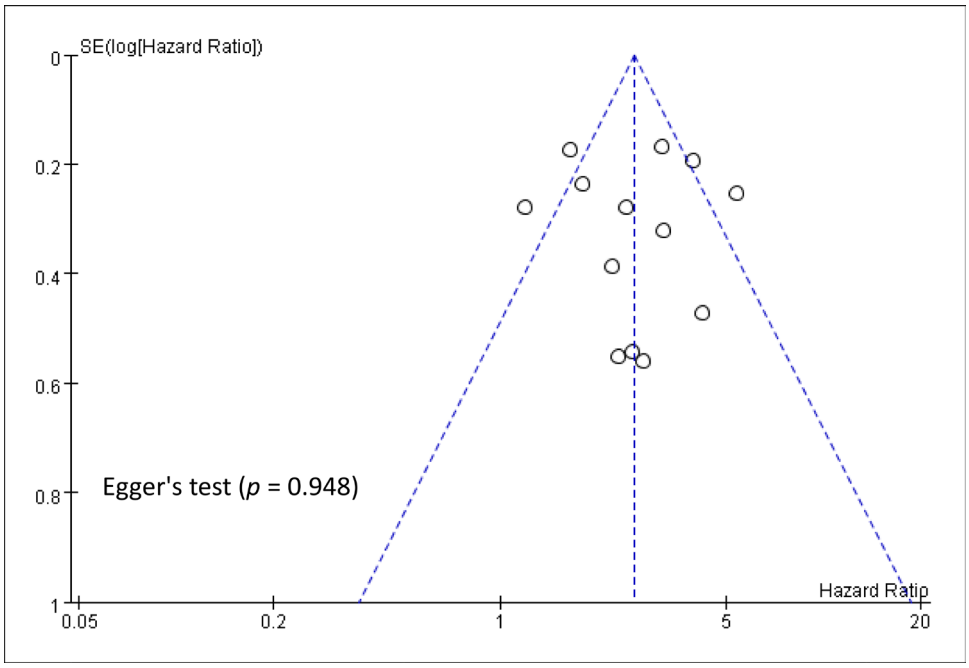

Figure 6 Funnel plot on primary outcome (overall survival) demonstrating symmetry, indicating a relatively low risk of publication bias.

of nutritional status, which is directly linked to patient outcomes. Alternative methods for evaluating nutritional status include the mini-nutritional assessment short-form,[42] subjective global assessment[43] and 2002 nutritional risk screening.[44] However, these assessments depend on patient-reported information, which can be subject to misinterpretation, potentially leading to inconsistencies between different observers.

While our meta-analysis demonstrates the prognostic value of the GNRI, its potential as a predictive biomarker for treatment selection remains largely unexplored. Our subgroup analysis revealed that low GNRI was associated with poorer survival in both the surgical (HR: 2.06) and medical treatment groups (HR: 2.94), with a notably stronger negative impact in the medical treatment group. This suggests that patients with low GNRI might have relatively better outcomes with surgical interventions compared with medical treatments, although all low-GNRI patients still had worse outcomes than their high-GNRI counterparts. The GNRI could be valuable for preoperative risk stratification and identifying patients who might benefit from nutritional optimisation before surgery. However, current evidence primarily focuses on long-term survival rather than treatment-specific outcomes. Future studies should specifically examine whether the GNRI can predict differential treatment effects, postoperative complications and treatment tolerability across various interventions.

Previous studies have shown that a lower GNRI, reflecting albumin levels and nutritional status, correlates with more aggressive cancer invasion.[20 23] This association indicates that the GNRI might function as a surrogate marker for later cancer stages, underscoring its potential utility in forecasting outcomes for patients with

Table 2 Summary of outcomes and certainty of evidence

Outcomes	N	Participants	Certainty assessment (domains) A	B	C	D	E*	Effect size (95% CI)	Certainty
Overall survival	13	3449	+	+	+	+	+	HR 2.60 (2.00, 3.38), p<0.00001	⊕⊕◯◯ Low
Cancer-specific survival	7	6479	+	−	+	+	–	HR 2.65 (1.76, 3.98), p<0.00001	⊕◯◯◯ Very low
Recurrence-free survival	4	6009	+	+	+	−	–	HR 1.47 (1.02, 2.10), p=0.04	⊕◯◯◯ Very low
Progression-free survival	6	676	+	+	+	+	–	HR 1.86 (1.54, 2.23), p<0.00001	⊕⊕◯◯ Low

A: risk of bias; B: inconsistency; C: indirectness; D: imprecision; E: publication bias; green circular icon: not serious; red circular icon: serious.
*Publication bias assessed when more than 10 studies or datasets were available for a given outcome.

cancer. This association can be attributed to two potential mechanisms. First, advanced cancer prompts a systemic inflammatory response, a key factor in reducing albumin synthesis and thus lowering serum albumin levels.[45–47] This response is more pronounced in cases of higher cancer invasion, where inflammation is a major contributor.[48] Such invasiveness can lead to decreased albumin levels, nullifying the anticancer benefits of albumin and perpetuating malignancy. Second, inflammation driven by advanced cancer can increase cytokines such as interleukin-6, contributing to cancer cachexia—severe malnutrition marked by muscle wasting and a decline in physiological function[49]—affecting the majority of patients with cancer, and is responsible for a significant number of cancer-related deaths.[50] Cachexia can also increase toxicity and intolerance to chemotherapy, leading to worse cancer outcomes.[51] These mechanisms provide plausible biological explanations for the observed correlation between lower GNRI and cancer progression.

Our meta-analysis provides an important update to the existing literature on the prognostic value of the GNRI in patients with urological cancers. A previous meta-analysis by Wu *et al* investigated the association between low GNRI and poor OS based on six studies.[18] Our updated analysis builds on previous research by examining 13 studies, including seven additional studies published after Wu *et al*'s work. This expansion strengthened the pooled evidence. The clinical implication of this enhanced analysis is significant, as it provides a more comprehensive understanding of the topic, potentially leading to improved patient care and more informed clinical decisions. In addition, a meta-regression analysis was performed to explore the specific impacts of study variables, such as follow-up time and sample size, on OS. Accordingly, our updated meta-analysis not only confirms the findings of Wu *et al*[18] with a larger patient pool but also meaningfully builds on their work through updated evidence. This provides clinicians and researchers with a comprehensive and current perspective on using the GNRI as a prognostic marker for urological cancers.

Different nutritional indices may vary in their ability to predict cancer-related outcomes. A previous meta-analysis reported that nutritional status, assessed using the Prognostic Nutritional Index (PNI) (calculated based on the serum albumin level and lymphocyte count) and the controlling nutritional status (CONUT) score (calculated based on the serum albumin, lymphocyte count and total cholesterol levels), can effectively predict clinical outcomes in patients with bladder cancer.[52] Data in that meta-analysis were too limited to assess the prognostic ability of the GNRI.[52] The meta-analysis of six studies showed a 71% increased risk of mortality with low PNI (ie, HR, 1.71).[52] However, PNI was not significantly associated with RFS based on limited data from three studies.[52] In contrast, a high CONUT score was significantly associated with poorer OS (ie, HR, 2.43) and RFS (ie, HR, 2.9).[52] These findings imply that different nutritional indices have different predictive abilities. Although the GNRI did not consider immune-nutritional status compared with the PNI and CONUT scores, our results suggest that the GNRI may effectively predict OS, CSS, RFS and PFS. More evidence is required to explore the impact of different nutritional indices on the prognostic outcomes of patients with urological cancers.

Our meta-analysis included studies across different cancer types and stages because of the limited available literature on GNRI in urological cancers (table 1). Among the 17 included studies, seven focused exclusively on stage 4 disease, five examined stages 1–3 and five included stages 1–4. This heterogeneity in disease stages reflects the current state of evidence, where the GNRI has been studied across the disease spectrum. Although combining different stages could introduce clinical heterogeneity, particularly given the vastly different prognoses between localised and metastatic disease, excluding studies based on disease stage would have significantly limited our analysis since only seven studies specifically focused on advanced disease. Future studies should examine the prognostic value of the GNRI within more homogeneous patient populations.

The surprisingly consistent effect of GNRI across different urological cancers (heterogeneity: 64%) suggests that nutritional status may impact cancer outcomes through common biological mechanisms, regardless of cancer type. Rather than directly affecting tumour behaviour, the GNRI likely reflects the patient's overall physiological reserve and ability to tolerate cancer treatments. A low GNRI indicates poor nutritional status, which can compromise immune function, reduce treatment tolerance and impair wound healing, factors that affect survival across all cancer types. Additionally, low albumin levels (a component of the GNRI) are associated with systemic inflammation, which can promote cancer progression through multiple pathways common to different cancers.

In the current meta-analysis, the included studies focused on patients classified into high-GNRI and low-GNRI groups at pretreatment. However, our investigation did not explore the relationship between GNRI changes during follow-up and outcome variations. Notably, Sugiyama's research,[53] which was excluded from our review due to data limitations, demonstrated that unstable GNRI status was a significant independent predictor of poor OS (OR, 2.08). This finding underscores the importance of the GNRI in identifying patients who might benefit from nutritional interventions. The combination of the GNRI with other nutritional risk indicators may enhance its effectiveness in predicting survival outcomes. For example, a previous study by Takagi *et al*[19] found that patients with both low GNRI and CONUT scores had a greater mortality risk than those with only one malnutrition indicator. This finding suggests a compounded risk in the presence of multiple nutritional deficiencies. By integrating multiple nutritional assessments, healthcare providers can obtain a more comprehensive evaluation of a patient's nutritional status. This multidimensional

approach may lead to more accurate prognostic predictions and better-tailored nutritional interventions.

This meta-analysis, while comprehensive, has several important limitations. First, beyond geographical limitations (all studies were from Asian countries) and retrospective study design, this meta-analysis had several methodological constraints. We observed substantial statistical heterogeneity in CSS (I^2 = 75%) and RFS (I^2 = 58%) analyses, varying study quality (two studies with high risk of bias), and GRADE assessment, indicating low to very low certainty of evidence across outcomes. While publication bias was low for OS, it could not be adequately assessed for other outcomes due to the limited number of studies. Second, additional limitations included varying GNRI cut-off values and relatively short follow-up periods in some studies, which may not capture long-term prognostic value of the GNRI. Third, we lack comprehensive analysis of critical mediating and moderating variables that could explain the underlying mechanisms—specifically, the roles of age distribution across different tumour types, smoking status and duration, comorbidities, physical activity levels and performance status could all influence both nutritional status and cancer outcomes but were inconsistently reported across studies, limiting our ability to conduct meaningful subgroup analyses. Fourth, another limitation of our study was the use of binary GNRI cut-offs rather than analysing GNRI as a continuous variable, which may have missed the nuanced relationships between nutritional status and outcomes across different patient subgroups. Future studies should examine the GNRI as a continuous measure while adjusting for important confounders, including age, tumour characteristics, disease stage and comorbidities, to better understand these associations. Finally, the limited number of studies for each specific cancer type may affect the robustness of cancer-specific conclusions.

CONCLUSION

This meta-analysis of 17 studies involving 8816 patients demonstrated that a low GNRI is significantly associated with poor survival outcomes in urological cancers. The consistency of these findings across different cancer types, countries and treatment modalities provides a foundation for future research. However, the low certainty of evidence for OS and PFS, and very low certainty for CSS and RFS indicate that these findings should be interpreted with caution. Large-scale, prospective, multicentre studies with standardised GNRI cut-off values and longer follow-up periods are needed to establish more definitive evidence regarding prognostic value of the GNRI in urological oncology.

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