BMC Cancer

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Prognostic role of geriatric nutritional risk index (GNRI) and controlling nutritional status (CONUT) on outcomes in patients with head and neck cancer: a systematic review and meta-analysis

Yu-Chieh Huang[1*], Shuo-Wei Chen[2] and Yih-Shien Chiang[3]

Abstract

Background Malnutrition is a common comorbidity in patients with head and neck cancer (HNC), significantly impacting survival rates. The Geriatric Nutritional Risk Index (GNRI) and the Controlling Nutritional Status (CONUT) score are tools used to assess the nutritional status, yet their prognostic value in HNC remains to be fully established.

Methods We performed a systematic review and meta-analysis, adhering to PRISMA guidelines, to evaluate the prognostic significance of GNRI and CONUT on survival outcomes in patients with HNC. Relevant studies up to March 2024 were identified through comprehensive searches of PubMed, EMBASE, and Cochrane CENTRAL databases. The quality of each included study was assessed using the Newcastle-Ottawa Scale.

Results Seventeen studies were included, encompassing a total of 3,816 patients with HNC. Our findings reveal that a lower GNRI is consistently associated with poor overall survival (OS, adjusted hazard ratio [aHR]: 3.9, 95% confidence interval [CI]: 2.47–6.14) and progression-free survival (PFS, aHR: 1.76, 95% CI: 1.41–2.21), demonstrating its utility as a prognostic indicator. However, CONUT scores revealed no significant differences in OS (aHR: 1.65, 95% CI: 0.94–2.91) or PFS (aHR: 1.43, 95% CI: 0.68–3.02).

Conclusion GNRI appears to be a reliable prognostic tool for predicting poorer survival outcomes in HNC patients, underscoring the importance of nutritional assessments in this population. Further research is needed to clarify the prognostic value of the CONUT score, which exhibited less consistent results.

Keywords Geriatric nutritional risk index (GNRI), Controlling Nutritional Status (CONUT) score, Head and neck cancer (HNC), Survival, Meta-analysis, Nutritional assessment, Overall survival (OS), Progression-free survival (PFS), Prognostic biomarkers, Cancer-related malnutrition

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Background

Head and neck cancers (HNCs) consist of a wide variety of malignant tumors that impact the oral cavity, pharynx, larynx, paranasal sinus, nasal cavity, and salivary glands [1]. Worldwide, approximately 878,000 HNC diagnoses and 444,000 deaths occur annually, ranking HNC as the seventh most common and fatal cancer, which imposes a significant burden on global public health [2]. HNC patients often face poor prognosis, with a 50% five-year survival rate [3]. Physicians frequently navigate patients into the palliative phase and, for those with incurable HNC, survival averages around 5 months [4]. Despite the progress made in therapeutic methods, it is essential to continue the search for reliable prognostic indicators to improve patient care and accurately predict outcomes [5].

Malnutrition in cancer arises from a combination of metabolic dysregulation and anorexia, which can be induced by the tumor or its treatment [6]. Severe malnutrition has a negative impact on the postoperative results of cancer patients, leading to increased complications and a deteriorating long-term prognosis [7]. Additionally, malnutrition is associated with reduced survival, and compromised immune response to cancer treatment, and is a common comorbidity in HNC patients [8, 9]. Therefore, it is essential to consider the influence of the nutritional status and its progression during treatment in the provision of patient care.

The Geriatric Nutritional Risk Index (GNRI) is a simple and readily applicable instrument in clinical settings that utilizes measurements of weight, height, and serum albumin levels for assessment [10]. It is a validated tool primarily employed to evaluate the nutritional risk in older patients and has been evident as a potential prognostic indicator in various health settings including cancers [11]. Multiple studies indicate the potential predictive value of GNRI in patients with an advanced HNC [10, 12–18]. Nevertheless, a comprehensive review and meta-analysis are essential to establish the conclusive prognostic significance of GNRI in HNC.

The Controlling Nutritional Status (CONUT) score is a tool used to assess a patient's nutritional status based on three parameters: serum albumin levels, total lymphocyte count, and total cholesterol concentration [19]. It has been utilized in clinical settings to evaluate the nutritional status of patients, particularly those who are hospitalized or undergoing medical treatment. Elevated CONUT levels indicate reduced lymphocyte, albumin, and cholesterol levels, commonly indicative of compromised nutritional and immune health in patients, potentially resulting in poorer survival rates. Recently, CONUT score prognostic value has been documented in urological cancer [20], gastric cancer [21], pancreatic cancer [22], as well as HNC [23]. Also, a systematic review and meta-analysis are essential before reaching a conclusive consensus on its prognostic significance in HNC.

Therefore, this systematic review and meta-analysis aims to review and synthesize the evidence to date regarding whether GNRI and CONUTS serve as reliable prognostic indicators for long-term survival in patients diagnosed with HNC.

Methods

This systematic review and meta-analysis has been registered in PROSPERO (Registration ID: CRD42024611329).

Search strategy

The systematic review and meta-analysis conducted in this study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [24]. We performed an extensive literature search across prominent public databases, including PubMed, EMBASE, and Cochrane CENTRAL. The search employed specific keywords such as "geriatric nutritional risk index," "GNRI," "controlling nutritional status," "CONUT," and "head and neck cancer," combined with Boolean operators. Additionally, Medical Subject-Headings (MeSH) terms were utilized where appropriate. To further expand the search, a manual search of the reference lists of included studies was also conducted to identify additional relevant articles not captured in the initial database search.

The search covered studies published up to March 16, 2024. The exact search strings used for the aforementioned databases were:

1) (geriatric nutritional risk index OR GNRI) AND (head and neck cancer OR oropharyngeal cancer OR laryngeal cancer OR salivary gland cancer OR laryngeal cancer OR hypopharyngeal cancer OR nasopharyngeal cancer OR oral cavity cancer OR paranasal sinus cancer OR nasal cavity cancer);
2) (controlling nutritional status OR CONUT) AND (head and neck cancer OR oropharyngeal cancer OR laryngeal cancer OR salivary gland cancer OR laryngeal cancer OR hypopharyngeal cancer OR nasopharyngeal cancer OR oral cavity cancer OR paranasal sinus cancer OR nasal cavity cancer).

The syntax of the search is detailed in Supplementary Table S1.

Selection criteria

A PECOS framework (Population, Exposure, Comparator, Outcome, and Study design) was used to develop our review question. Eligible studies involved patients with any type of HNC and assessed the associations or prognostic value of the GNRI or CONUT score (P & E & C)

on survival outcomes (O). The inclusion studies covered prospective studies, retrospective studies, case-control studies, and randomized controlled trials (S).

We excluded review articles, letters, commentaries, editorials, proceedings research, meeting abstracts, case reports, and personal communications, as well as studies involving non-human subjects.

Main outcome measures and data extraction

The primary outcome was overall survival (OS) and progression-free survival (PFS). Data extracted from eligible studies included the first author's name, year of publication, number of patients, mean age, male percentage, body mass index (BMI), heavy alcohol use, smoking status, ECOG performance, tumor location, tumor stage, treatment received, cutoff values of GNRI or CONUT score, and median follow-up duration where available.

Ethics statement

This systematic review and meta-analysis solely depended on published studies, without collecting or utilizing raw patient data or private information. Consequently, the hospital's institutional review board (IRB) granted an exemption from protocol approval and informed consent requirements for study subjects.

Quality assessment

We assessed the included studies' quality utilizing the Newcastle-Ottawa Scale (NOS) for cohort studies, as recommended by the Cochrane Non-Randomized Studies Methods Working Group [25]. The NOS assigns a maximum of nine points to each study: four for appropriate participant selection, two for assessing comparability, and three for outcome ascertainment. Two independent reviewers conducted the assessment, resolving uncertainties through consultation with a third reviewer.

Statistical analysis

The study outcomes were analyzed using Cox regression models. The hazard ratios reported in each included study were combined to calculate the effect size. Heterogeneity across the included studies was assessed using the Cochran Q test and the I^2 index. When the p-value less than 0.05 by the Cochran Q test or the I^2 exceeded 50%, it indicated the presence of significant heterogeneity, prompting the use of a random-effects model [26, 27]. Otherwise, a fixed-effects model was employed. A two-sided test with a significance level of $\alpha = 0.05$ was used for statistical analysis. A funnel plot would be generated to assess the publication bias while the study number was over ten [28]. To evaluate the robustness of the results, a sensitivity analysis was considered using the leave-one-out approach. All analyses were conducted using R Studio with the packages "meta", "dmetar", and "metafor."

Results

Study selection process

Figure 1 shows the PRISMA diagram of the study selection process. A total of 22 full-text articles were assessed for eligibility, and 5 were excluded. Finally, 17 studies [10, 12–18, 23, 29–36] with a total of 3,816 patients with HNC were included in the systematic review and meta-analysis. Amongst, 11 studies assessed the prognostic role of GNRI, and 7 studies assessed the CONUT [15, 23, 29, 30, 32, 33, 35] (Pan et al. reported both GNRI and CONUT) (Fig. 1).

Characteristics of the studies included

All of the studies included were of retrospective design. The median age fell from 51 to 79 years, and the proportion of male patients ranged from 61.3 to 95.5%. The most commonly reported GNRI cutoff was 98, while the CONUT cutoff ranged from 2 to 4. More detailed characteristics of the studies included are summarized in Table 1.

Meta-analysis

GNRI on OS

Figure 2 shows the results of the meta-analysis on the association between GNRI and OS. Eight studies [10–12, 14, 15, 18, 34, 36] provided data for crude HR (low vs. high GNRI). According to the high heterogeneity detected ($I^2 = 78\%$, Q test: $p < 0.01$), a random effects model was chosen. Pooled crude HR for OS was 4.08 (95% CI: 2.55–6.54), indicating that patients with a low GNRI had a significantly higher risk for overall mortality.

Eight studies [12, 14–16, 18, 30, 34, 36] provided data of adjusted HR. According to the high heterogeneity detected ($I^2 = 74\%$, Q test: $p < 0.01$), the random effects model was chosen. Pooled adjusted HR was 3.90 (95% CI: 2.47–6.14), indicating patients with a low GNRI had a significantly higher risk for overall mortality (Fig. 2).

GNRI on PFS

Figure 3 shows the results of the meta-analysis on the association between GNRI and PFS. Five studies [10, 12, 13, 17, 34] reported the crude HR. No evidence of heterogeneity was shown ($I^2 = 0\%$, Q test: $p = 0.88$), therefore a fixed effect model was chosen. Pooled crude HR was 1.74 (95% CI: 1.44–2.11), showing that a low GNRI was significantly associated with poor PFS.

Five studies [10, 12, 17, 31, 34] provided adjusted HR. No evidence of heterogeneity was shown ($I^2 = 23\%$, Q test: $p = 0.27$), therefore a fixed effect model was chosen. Pooled adjusted HR for PFS was 1.76 (95% CI: 1.41–2.21), showing that a low GNRI was significantly associated with poor PFS. (Fig. 3)

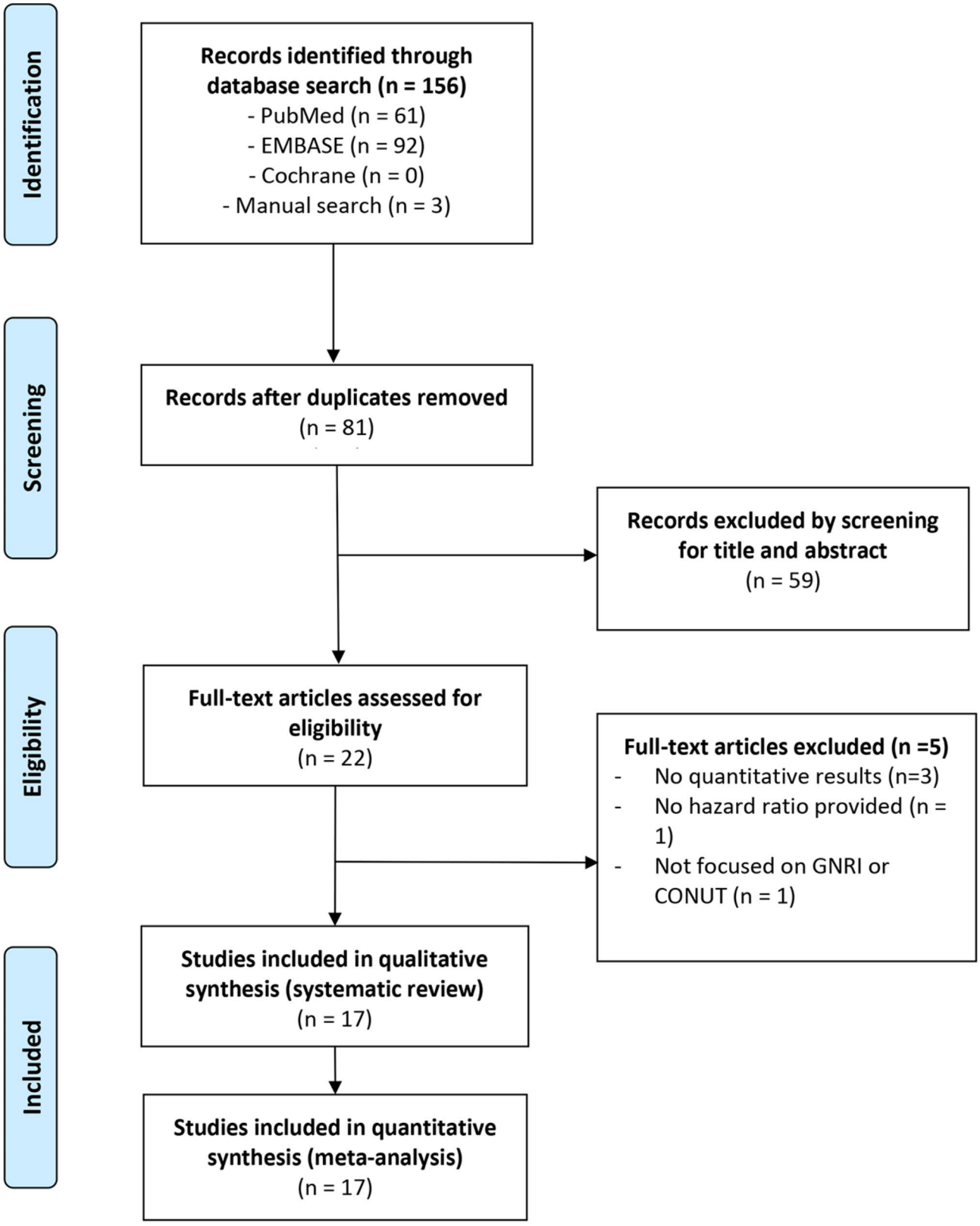

Fig. 1 PRISMA flow diagram of the study selection process

Table 1 Characteristics of the included studies

Study	Number of patients	Age, years	Male (%)	BMI, kg/m^2	Heavy alcohol use (%)	Smoking (%)	ECOG performance, ≥ 1 (%)	Primary site, *n* (%)	Tumor stage, *n* (%)	Treatment received, *n* (%)	Cutoff values of GNRI or CONUT	Median follow-up duration, months
Fujiwara (2023)	111	Median (IQR): 69 (67–71)	79.3%	NA	NA	78.4%	10.8%	Hypopharyngeal: 34 (30.6%) Larynx: 20 (18.0%) Nasopharyngeal: 6 (5.4%) Oral cavity: 1 (0.9%) Oropharyngeal: 45 (40.5%) Sinus: 5 (4.5%)	I/II/III/IV: 30 (27%)/ 31 (27.9%)/ 26 (23.4%)/ 24 (21.6%)	NA	GNRI: 98	60
Haa (2023)	162	Median (range): 65 (28–85)	71.0%	Overweight: 14.8%	29.6%	79.0%	54.9%	Oral cavity: 66 (40.7%) Oropharynx; 33 (20.4%) Hypopharynx: 20 (12.3%) Larynx: 17 (10.5%) Sinonasal: 9 (5.6%) Other: 17 (10.5%)	Locoregional: 75 (46.3%) Distant metastasis: 17 (10.5%) Locoregional + distant metastasis: 70 (43.2%)	Surgery: 26 (16%) Surgery + PORT: 33 (20.4%) Surgery + POCRT/RIT: 13 (8%) RT: 19 (11.7%) CRT/RIT: 58 (35.8%) Palliative only: 13 (8%)	GNRI: 98	42
Ito (2023)	61	Mean: 72.1	70.5%	22.35 ± 3.28	55.7%	49.2%	NA	Maxilla: 9 (14.8%) Buccal: 8 (13.1%) Mandible: 13 (21.3%) Floor of mouth: 5 (8.2%) Tongue: 26 (42.6%)	I/II/III/IV: 18 (29.5%)/ 19 (31.1%)/ 16 (26.2%)/ 8 (13.1%)	NA	GNRI: 93.7	Mean: 48.3
Miyamoto (2023)	106	Median (range): 68 (21–88)	78.3%	Median: 20 (IQR: 17.6–22.9)	NA	NA	53.8%	Oral cavity: 15 (14.2%) Nasopharynx: 15 (14.2%) Hypopharynx: 23 (21.7%) Larynx: 11 (10.4%)	NA	NA	GNRI: 84.2	12
Pan (2023)	398	Median (IQR): 50.9 (44.5-7.0)	73.1%	21.5 ± 3.2	6.0%	14.3%	NA	NA	I/II/III/IV: 5 (1.8%)/ 22 (8.1%)/ 138 (50.7%)/ 107 (39.3%)	RT: 156 (59.8%) Chemotherapy: 231 (83.4%)	GNRI: 98 CONUT: 2	27.6
Shih (2023)	343	Median (range): 54 (30–95)	91.0%	≥ 22: 260 (75.8%)	74.9%	84.5%	20.7%	Tongue: 130 (37.9%) Buccal: 99 (28.9%) Other: 114 (33.2%)	III/IVa/IVb: 92 (26.8%)/ 157 (45.8%)/ 94 (27.4%)	Surgery only: 78 (22.7%) Adjuvant RT: 84 (24.5%) Adjuvant CRT: 181 (52.8%)	GNRI: 97.8	66.5
Fukuda (2021)	86	Median (range): 64 (32–77)	87.2%	NA	59.3%	76.7%	45.4%	Hypopharynx 23 (26.7%) Oral cavity 21 (24.4%) Oropharynx 15 (17.4%) Larynx 12 (13.9%) Nasopharynx 5 (5.8%) Other: 10 (11.6%)	Locoregional recurrence: 15 (17.4%) Metastatic: 71 (82.6%)	Prior surgery 53 (61.6%) Prior RT 50 (58.1%) Prior chemotherapy with cisplatin 22 (25.6%)	GNRI: 98	13.2

Table 1 (continued)

Study	Number of patients	Age, years	Male (%)	BMI, kg/m^2	Heavy alcohol use (%)	Smoking (%)	ECOG performance, ≥ 1 (%)	Primary site, *n* (%)	Tumor stage, *n* (%)	Treatment received, *n* (%)	Cutoff values of GNRI or CONUT	Median follow-up duration, months
Nakayama (2021)	248	Mean: 63.8	85.9%	Mean: 21.6	NA	NA	NA	Larynx: 77 (31.0%) Oropharynx: 82 (33.1%) Hypopharynx: 66 (26.6%) Oral cavity: 23 (9.3%)	III/IV: 56 (22.6%)/ 192 (77.4%)	RT alone: 49 (19.8%) RT + surgery: 23 (9.3%) Radical CRT: 129 (52%) Preoperative CRT + surgery: 47 (19%)	GNRI: 98	NA
Tang (2021)	1065	> 45: 507 (47.6%)	72.4%	> 22.9: 526 (49.4%)	NA	34.7%	NA	NA	I/II/III/IVA/IVB: 3 (0.3%)/ 127 (11.9%)/ 714 (67%)/ 160 (15%)/ 61 (5.7%)	NA	GNRI: 107.7	83
Yamagata (2021)	155	< 70.4: 78 (50.3%)	61.3%	< 18.5: 17 (11.0%)	NA	NA	NA	Tongue: 61 (39.4%) Lower gingiva: 49 (31.6%) Buccal mucosa: 13 (8.4%) Upper gingiva: 12 (7.7%) Floor of mouth: 10 (6.5%) Other: 10 (6.5%)	I/II/III/IVA/IVB: 30 (19.4%)/ 38 (24.5%)/ 25 (16.1%)/ 54 (34.8%)/ 8 (5.2%)	Surgery: 88 (56.8%) CRT: 43 (27.8%) RT: 24 (15.5%)	GNRI: 98	96
Yamahara (2021)	164	Median (range): 72 (41–92)	87.2%	≥ 18.5: 80.5%	NA	NA	NA	Oropharynx: 25 (15.2%) Hypopharynx: 40 (24.4%) Larynx: 76 (46.3%) Oral cavity: 14 (8.5%) Nasal cavity: 9 (5.5%)	I/II/III/IV: 60 (36.6%)/ 54 (32.9%)/ 31 (18.9%)/ 19 (11.6%)	Chemotherapy or radiotherapy: 110 (67.1%) Surgery: 54 (32.9%)	GNRI: 98	53
Ding (2023)	94	≥ 60: 50 (53.2%)	93.6%	≥ 18.5: 82 (87.2%)	NA	NA	NA	Pyriform sinus: 65 (69.1%) Posterior hypopharyngeal wall: 20 (21.3%) Postcricoid area: 9 (9.6%)	I/II: 24 (25.5%) III/IV:70 (74.5%)	NA	CONUT: 4	NA
Lin (2023)	113	CONUT 0–2: 60.21 ± 11.69 CONUT ≥ 3: 59.82 ± 10.21	94.7%	CONUT 0–2: 21.44 ± 2.60 CONUT ≥ 3: 20.42 ± 2.75	59.3%	84.1%	NA	Pyriform sinus: 86 (76.11%) Posterior wall: 17 (15.04%) Postcricoid region: 10 (8.85%)	II/III/IV: 31.9%/ 41.6%/ 26.5%	Radiotherapy: 105 (92.9%) Chemoradiotherapy: 76 (67.3%)	CONUT: 3	60
Sakai (2023)	51	Median (range): 66 (47–83)	94.1%	NA	NA	NA	≥ 2: 2.0%	Oral: 4 (7.8%) Nasopharynx: 1 (2.0%) Oropharynx: 11 (21.6%) Hypopharynx: 24 (47.1%) Larynx: 7 (13.7%) Others: 4 (7.8%)	NA	Immune checkpoint inhibitor and chemotherapy: 100%	CONUT: 4	OS: 10 PFS: 5
Yi (2023)	427	Median (range): 60 (53–67)	95.3%	NA	35.6%	78.0%	NA	Larynx (100%)	I/II: 281 (65.8%) III/IV: 146 (34.2%)	NA	CONUT: 3	67

Table 1 (continued)

Study	Number of patients	Age, years	Male (%)	BMI, kg/m^2	Heavy alcohol use (%)	Smoking (%)	ECOG performance, ≥ 1 (%)	Primary site, *n* (%)	Tumor stage, *n* (%)	Treatment received, *n* (%)	Cutoff values of GNRI or CONUT	Median follow-up duration, months
Lin (2022)	154	CONUT 0–1: 60.90 ± 9.79 CONUT ≥ 2: 59.82 ± 10.21	95.5%	CONUT 0–1: 22.64 ± 3.79 CONUT ≥ 2: 21.30 ± 3.60	44.2%	77.3%	NA	NA	I/II/III/IV: 41 (26.6%)/ 53 (34.4%)/ 34 (22.1%)/ 26 (16.9%)	Surgery: 100% Radiotherapy: 33.1%	CONUT: 2	60
Ishii (2021)	78	Median (range): 79 (70–97)	69.2	NA	NA	NA	71.8%	Oral: 37 (47.4%) Hypopharynx: 9 (11.5%) Oropharynx: 9 (11.5%) Larynx: 7 (9.0%) Sinonasal: 4 (5.1%) Maxillary: 4 (5.1%) Others: 8 (10.3)	I/II/III/IV: 11 (14.1%)/ 17 (21.8%)/ 11 (14.1%)/ 39 (50.0%)	Surgery: 42 (56.8%) Free flap reconstruction: 11 (14.9%) Surgery + PO (C) RT: 7 (9.5%) RT: 11 (14.9%) CRT: 9 (12.2%) Chemotherapy: 2 (2.7%) BSC: 13 (17.6%) Others: 1 (1.4%)	CONUT: 4	23.1

NA, not applicable; ECOG, RT, radiotherapy; CRT, chemoradiotherapy; PORT, postoperative RT; POCRT, postoperative CRT; RIT, radioimmunotherapy; GNRI, Geriatric Nutritional Risk Index; CONUT, Controlling Nutritional Status

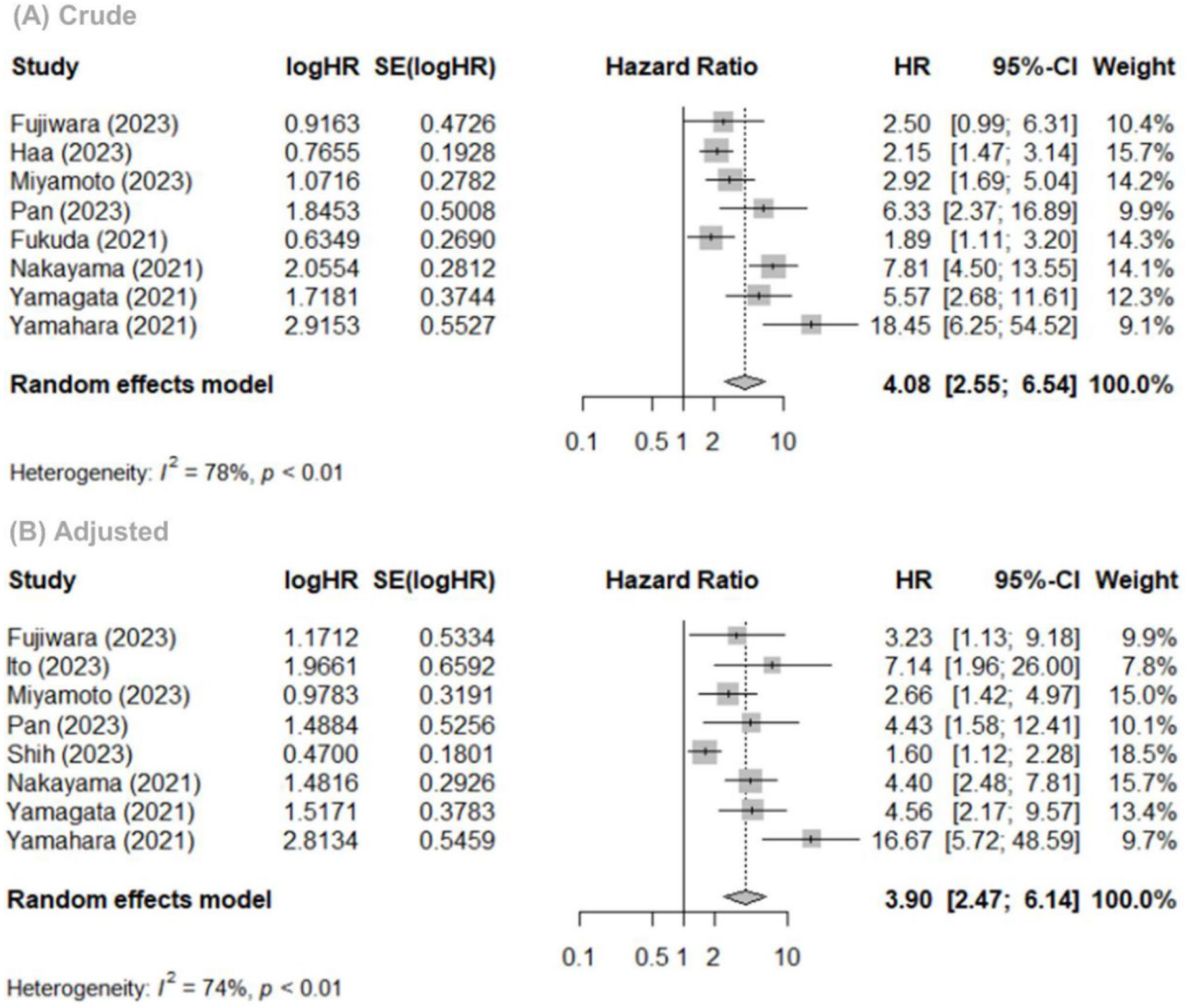

Fig. 2 Meta-analysis for the association between GNRI and OS: (**A**) Crude HR; (**B**) Adjusted HR

CONUT on OS

Figure 4 shows the results of the meta-analysis on the association between CONUT and OS. Seven studies [15, 23, 29, 30, 32, 33, 35] provided data for crude HR (low vs. high CONUT). According to the high heterogeneity detected ($I^2 = 53\%$, Q test: $p = 0.05$), a random effects model was chosen. Pooled crude HR was 2.72 (95% CI: 1.99–3.71), indicating that patients with a high CONUT had a significantly higher risk for overall mortality.

Five studies [15, 23, 29, 32, 33] provided data on adjusted HR. According to the high heterogeneity detected ($I^2 = 83\%$, Q test: $p < 0.01$), the random effects model was chosen. Pooled adjusted HR was 1.65 (95% CI: 0.94–2.91), showing no significant difference between low versus high CONUT in association with OS (Fig. 4).

CONUT on PFS

Figure 5 shows the results of the meta-analysis for the association between CONUT and PFS. Four studies [23, 32, 33, 35] reported the crude HR. No evidence of heterogeneity was shown ($I^2 = 43\%$, Q test: $p = 0.15$), therefore a fixed effect model was chosen. Pooled crude HR was 2.74 (95% CI: 2.11–3.56), showing that a high CONUT was significantly associated with poor PFS.

Three studies [23, 32, 33] provided adjusted HR. According to the high heterogeneity detected ($I^2 = 88\%$, Q test: $p < 0.01$), the random effects model was chosen. Pooled adjusted HR for PFS was 1.43 (95% CI: 0.68–3.02), showing no significant difference between low versus high CONUT regarding PFS. (Fig. 5)

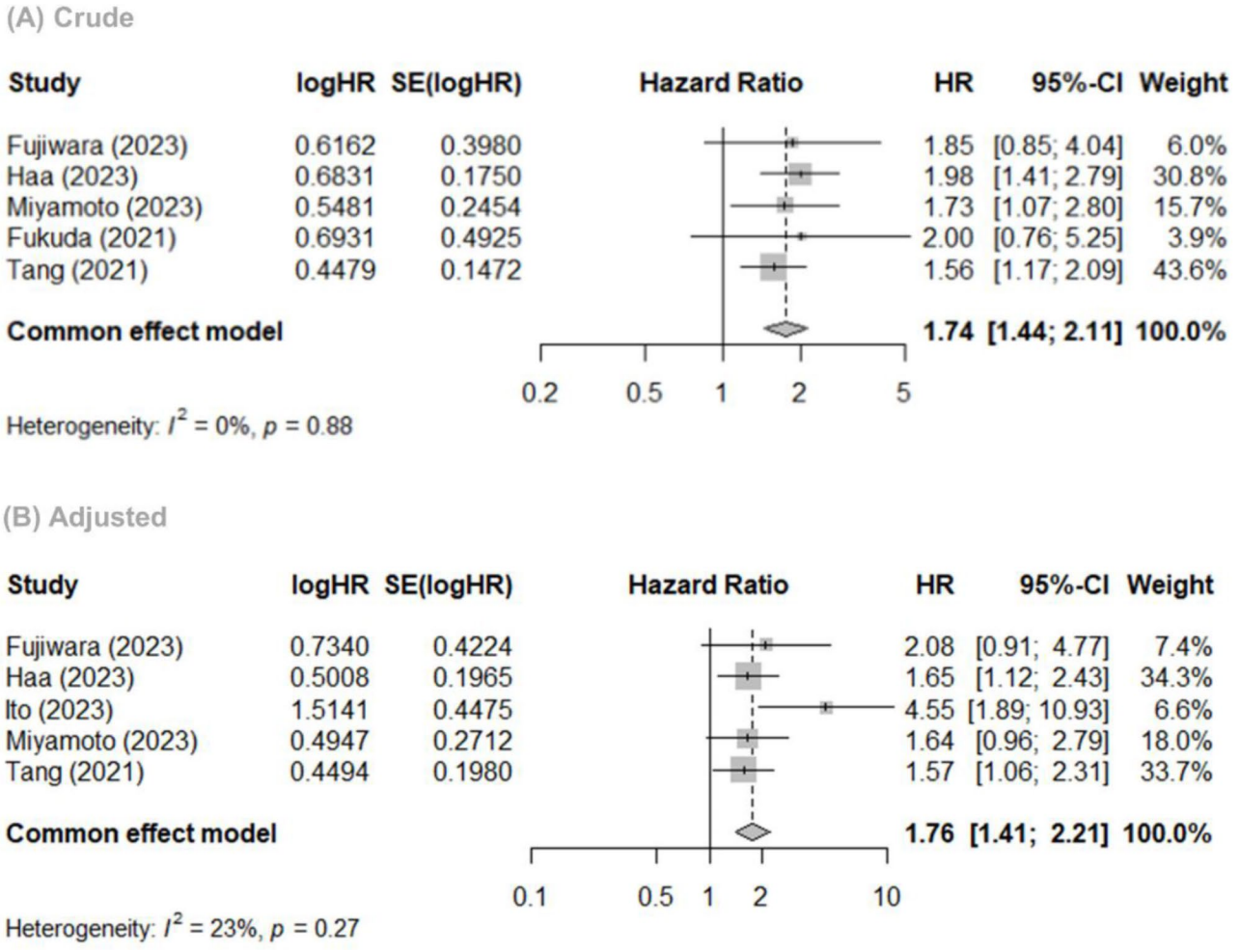

Fig. 3 Meta-analysis for the association between GNRI and PFS: (**A**) Crude HR; (**B**) Adjusted HR

Publication bias

In this meta-analysis, we refrained from generating a funnel plot on publication bias because of the limited number of the included studies (< 10) for each outcome. Specifically, the small study size could potentially result in inadequate statistical power to detect significant patterns, and as a result, the funnel plot might not reliably reflect the presence of publication bias.

Sensitivity analyses

The sensitivity analysis was conducted using a leave-one-out approach for crude HR and the adjusted HR on the association between GNRI and OS. The result revealed that, when excluding individual studies, the pooled adjusted HR did not change a lot, indicating the results of the meta-analysis were robust. (Table 2) Regarding the adjusted HR for the association between GNRI and PFS, excluding the study by Ito (2023) resulted in a decrease in I^2 to 0%, and the pooled HR estimate was 1.65 (95% CI: 1.31–2.08, $p < 0.001$) (Table 3).

Regarding the adjusted HR for the association between the CONUT score and OS, the sensitivity analysis, after excluding the study by Yi (2023), indicated a decrease in heterogeneity (I^2) to 0% for the pooled estimate, with a pooled HR of 2.33 (95% CI: 1.64–3.32, $p < 0.001$), revealing an association between a higher CONUT score and worse OS (Table 4). Similarly, for the adjusted HRs assessing the association between the CONUT score and PFS, excluding Yi (2023) reduced I^2 to 0%, and the pooled adjusted HR became significant (aHR = 2.31, 95% CI: 1.48–3.60, $p < 0.001$). (Table 5).

Risk of bias

The results of the risk of bias assessment for the included studies are presented in Table 6. Across the studies, the NOS scores varied between 6 and 7, suggesting a good overall quality.

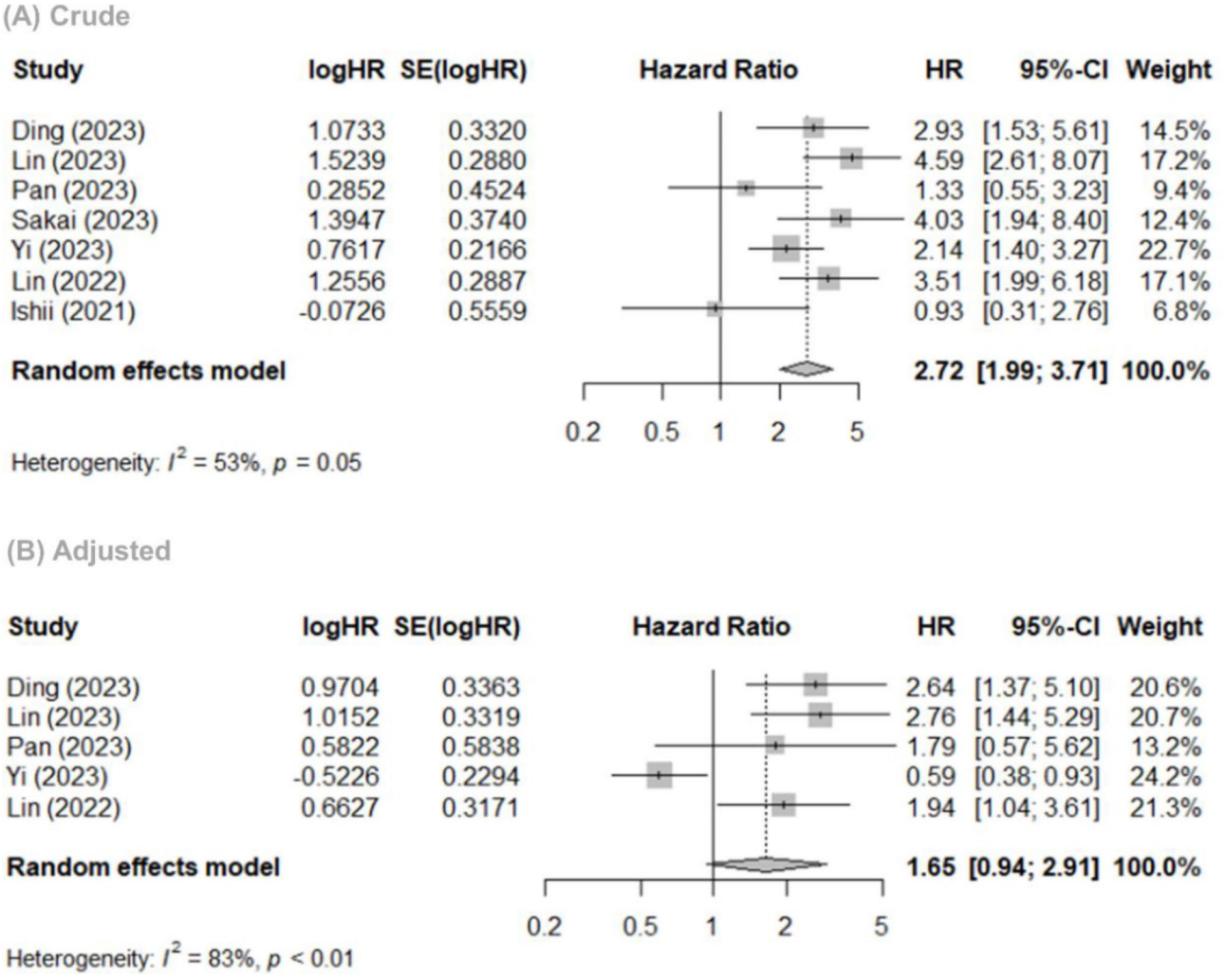

Fig. 4 Meta-analysis for the association between CONUT and OS: (**A**) Crude HR; (**B**) Adjusted HR

Discussion

In patients undergoing surgery for malignancy, severe malnutrition has been reported to increase the incidence of post-operative complications, thus worsening the long-term prognosis [7]. In settings of HNC in particular, malnutrition is a common comorbidity and is known to compromise the immune response, which may contribute to its association with reduced survival and response to cancer treatment in HNC patients [8, 9]. This reality underscores the goals of the present study, which was designed to systemically assess and synthesize the evidence on the prognostic impact on HNC outcomes of the nutritional status, as quantified by the GNRI and CONUT scores. The meta-analytic results have demonstrated a notable correlation between a low GNRI and an unfavorable prognosis, after adjusting for confounders. CONUT is associated with OS and PFS in the univariate analysis (pooled crude HR); however, it appears not significantly associated with either OS or PFS after adjustment for confounders (pooled adjusted HR). These results improve our understanding of the prognostic values of GNRI and CONUT as prognostic indicators for survival outcomes in patients with HNC.

Being a simple and readily applicable instrument in clinical settings, as it utilizes weight, height, and serum albumin levels, GNRI is a validated tool that has been employed to evaluate the nutritional risk in older patients [10] in whom it has been demonstrated to be a potential prognostic indicator in various health settings including malignancies [11]. Scored based on serum albumin levels, total lymphocyte count, and total cholesterol concentration, CONUT also is utilized in clinical settings to evaluate the nutritional status of patients, particularly those who are hospitalized [19]. Commonly, elevated CONUT levels suggest compromised nutritional and immune health in patients, potentially resulting in poorer survival rates.

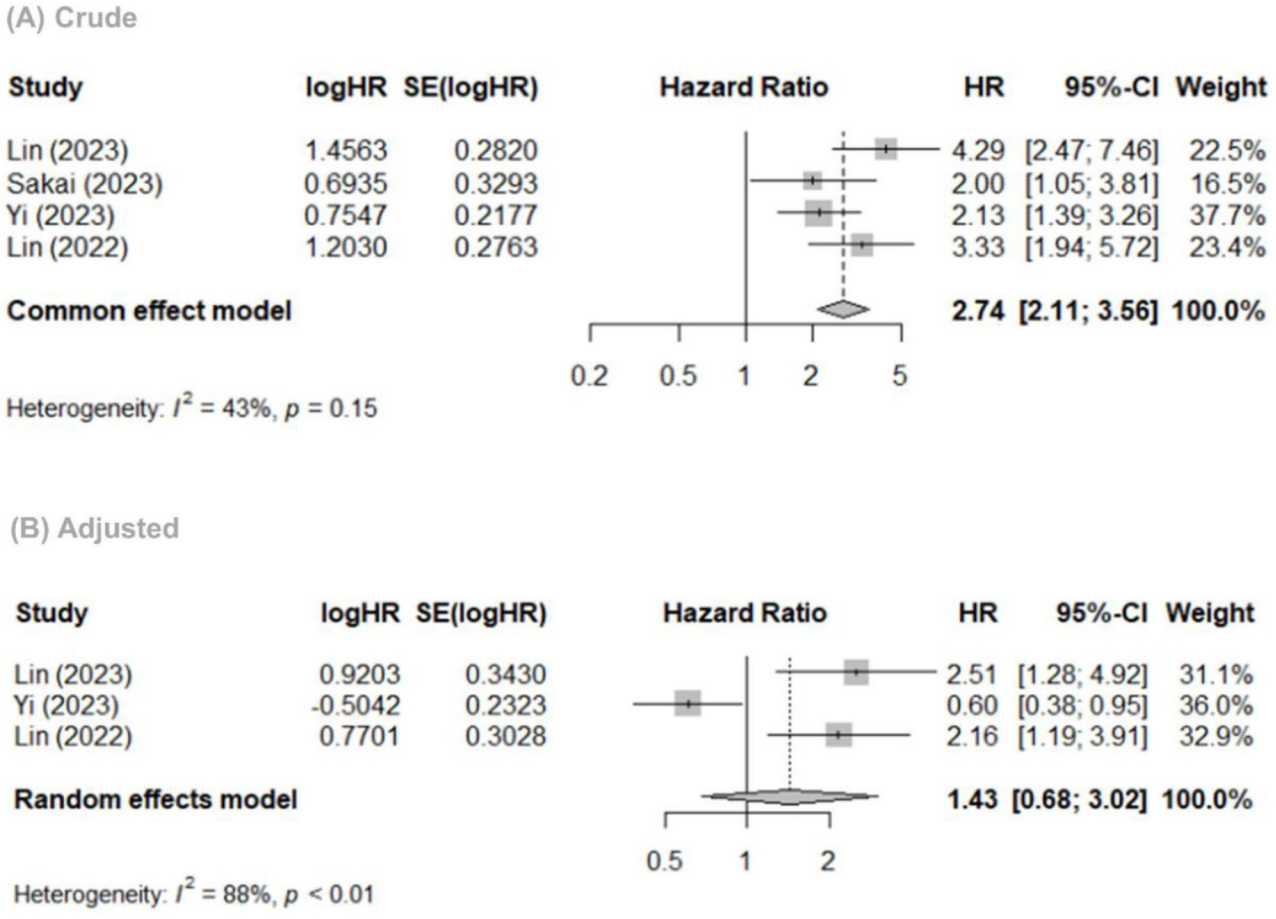

Fig. 5 Meta-analysis for the association between CONUT and PFS: (**A**) Crude HR; (**B**) Adjusted HR. **Abbreviations**: GNRI, Geriatric Nutritional Risk Index; CONUT, Controlling

Table 2 Sensitivity analysis for the association between GNRI and OS

	Pool effect size after each study being left out					
Studies left out	**HR**	**Lower limit**	**Upper limit**	***p*-value**	**tau^2**	**I^2**
Crude HR						
Fujiwara (2023)	4.36	2.59	7.33	< 0.001	0.370	81.30%
Haa (2023)	4.6	2.77	7.63	< 0.001	0.319	76.00%
Miyamoto (2023)	4.36	2.53	7.5	< 0.001	0.394	81.40%
Pan (2023)	3.91	2.34	6.52	< 0.001	0.358	80.50%
Fukuda (2021)	4.62	2.84	7.52	< 0.001	0.293	77.90%
Nakayama (2021)	3.63	2.24	5.89	< 0.001	0.286	72.40%
Yamagata (2021)	3.94	2.32	6.69	< 0.001	0.378	80.30%
Yamahara (2021)	3.46	2.3	5.22	< 0.001	0.196	73.40%
Adjusted HR						
Fujiwara (2023)	4.04	2.43	6.69	< 0.001	0.302	77.90%
Ito (2023)	3.7	2.31	5.95	< 0.001	0.260	76.20%
Miyamoto (2023)	4.23	2.51	7.12	< 0.001	0.306	77.90%
Pan (2023)	3.89	2.35	6.42	< 0.001	0.297	77.30%
Shih (2023)	4.47	3.19	6.27	< 0.001	0.031	35.70%
Nakayama (2021)	3.89	2.29	6.6	< 0.001	0.319	75.60%
Yamagata (2021)	3.86	2.3	6.48	< 0.001	0.307	76.50%
Yamahara (2021)	3.19	2.17	4.71	< 0.001	0.129	63.10%

Table 3 Sensitivity analysis for the association between GNRI and PFS

	Pool effect size after each study being left out					
Studies left out	**HR**	**Lower limit**	**Upper limit**	***p*-value**	**tau^2**	**I^2**
Crude HR						
Fujiwara (2023)	1.74	1.43	2.11	< 0.001	0.000	0.00%
Haa (2023)	1.65	1.31	2.07	< 0.001	0.000	0.00%
Miyamoto (2023)	1.75	1.42	2.15	< 0.001	0.000	0.00%
Fukuda (2021)	1.73	1.43	2.11	< 0.001	0.000	0.00%
Tang (2021)	1.89	1.47	2.44	< 0.001	0.000	0.00%
Adjusted HR						
Fujiwara (2023)	1.74	1.38	2.20	< 0.001	0.000	40.00%
Haa (2023)	1.82	1.38	2.41	< 0.001	0.000	40.00%
Ito (2023)	1.65	1.31	2.08	< 0.001	0.000	0.00%
Miyamoto (2023)	1.79	1.40	2.30	< 0.001	0.000	41.00%
Tang (2021)	1.87	1.42	2.47	< 0.001	0.000	35.40%

Table 4 Sensitivity analysis for the association between CONUT and OS

	Pool effect size after each study being left out					
Studies left out	**HR**	**Lower limit**	**Upper limit**	***p*-value**	**tau^2**	**I^2**
Crude HR						
Ding (2023)	2.65	1.81	3.87	< 0.001	0.326	60.40%
Lin (2023)	2.47	1.88	3.25	< 0.001	0.095	43.50%
Pan (2023)	2.93	2.17	3.95	< 0.001	0.197	49.50%
Sakai (2023)	2.56	1.81	3.61	< 0.001	0.278	56.60%
Yi (2023)	2.90	2.01	4.17	< 0.001	0.274	53.50%
Lin (2022)	2.55	1.76	3.71	< 0.001	0.308	57.70%
Ishii (2021)	2.93	2.20	3.91	< 0.001	0.185	42.40%
Adjusted HR						
Ding (2023)	1.47	0.77	2.80	0.248	0.555	83.80%
Lin (2023)	1.44	0.76	2.73	0.259	0.543	83.00%
Pan (2023)	1.64	0.86	3.13	0.134	0.585	86.80%
Yi (2023)	2.33	1.64	3.32	< 0.001	0.000	0.00%
Lin (2022)	1.60	0.80	3.20	0.188	0.607	86.10%

Table 5 Sensitivity analysis for the association between CONUT and PFS

	Pool effect size after each study being left out					
Studies left out	**HR**	**Lower limit**	**Upper limit**	***p*-value**	**tau^2**	**I^2**
Crude HR						
Lin (2023)	2.40	1.79	3.24	< 0.001	0.000	0.90%
Sakai (2023)	2.91	2.19	3.88	< 0.001	0.029	52.40%
Yi (2023)	3.19	2.29	4.44	< 0.001	0.000	36.20%
Lin (2022)	2.58	1.91	3.48	< 0.001	0.038	56.80%
Adjusted HR						
Lin (2023)	1.11	0.46	2.68	0.818	0.332	91.00%
Yi (2023)	2.31	1.48	3.60	< 0.001	0.000	0.00%
Lin (2022)	1.18	0.44	3.15	0.745	0.420	91.50%

As noted previously, various published studies have pointed to the potential predictive value of GNRI in patients with an advanced HNC [10, 12–18], whereas the prognostic value of CONUT has been documented in HNC settings [23], along with non-HNC malignancies, such as urological cancer [20], gastric cancer [21], and pancreatic cancer [22]. At this point, however, it is appropriate to review additional published studies relevant, both to GNRI and CONUT in connection with HNC and ongoing efforts to identify biomarkers useful in prognosticating outcomes and tailoring and optimizing current and emerging, new therapeutic modalities.

Based on an observational, longitudinal study, one report published in 2021 reported a variety of nutrition-impact symptoms, such as xerostomia, dysphagia, and dysgeusia, occurring in HNC patients [37]. Meanwhile,

Table 6 Quality assessment of included studies based on the NOS

Study	Selection (4)	Comparability (2)	Outcome (3)	Total NOS score
Fujiwara (2023)	★★	★	★★★	6/9
Haa (2023)	★★	★	★★★	6/9
Ito (2023)	★★	★	★★★	6/9
Miyamoto (2023)	★★	★	★★★	6/9
Pan (2023)	★★★	★	★★★	7/9
Shih (2023)	★★	★	★★★	6/9
Fukuda (2021)	★★	★	★★★	6/9
Nakayama (2021)	★★	★	★★★	6/9
Tang (2021)	★★	★	★★★	6/9
Yamagata (2021)	★★	★	★★★	6/9
Yamahara (2021)	★★	★	★★★	6/9
Ding (2023)	★★	★	★★★	6/9
Lin (2023)	★★	★	★★★	6/9
Sakai (2023)	★★	★	★★★	6/9
Yi (2023)	★★	★	★★★	6/9
Lin (2022)	★★	★	★★★	6/9
Ishii (2021)	★★	★	★★★	6/9

NOS, Newcastle-Ottawa Scale (NOS)

A star system was employed to conduct a semi-quantitative evaluation of study quality. Each numbered item within the selection and exposure categories could receive a maximum of one star, while comparability allowed for a maximum of two stars. The scale for the NOS spans from 0 to 9 stars. We categorized studies as high-quality if they attained 7 stars or more, medium-quality if they received 4 to 6 stars, and poor-quality if they garnered fewer than 4 stars

focusing specifically on the GNRI in HNC settings, a recently published meta-analysis encompassing ten studies and 2,793 patients suggests that low pretreatment GNRI predicts poor OS [38]. While this result supports the hypothesis that poor nutritional status should predict worsened outcomes, the present meta-analysis incorporates additional studies published over the past year. This expands the number of included patients to 3,816 and allows for a more comprehensive analysis of both OS and PFS, particularly in terms of adjusted hazard ratios.

No previous systematic review or meta-analysis has specifically synthesized data regarding the value of the CONUT score in the setting of HNC. However, one systematic review and meta-analysis suggest that the CONUT score may be an independent predictor of prognosis in esophageal cancer patients undergoing esophagectomy [39]. Meanwhile, results of a retrospective analysis reveal that CONUT could be useful in identifying gastric cancer patients who are unlikely to benefit from therapy with immune checkpoint inhibitors [21]. The implications are that CONUT should be considered a potential, novel immuno-nutritional biomarker, a useful perspective, especially concerning inflammatory and nutritional contributors to the pathogenesis of cancer.

Also evaluating the CONUT score from the biomarker standpoint, another retrospective analysis suggests that it could be useful as a screening tool for thyroid cancer and as a biomarker for assessing prognosis in thyroid cancer patients receiving treatment with tyrosine kinase inhibitors [40]. Meanwhile, a recent systematic review and meta-analysis evaluating both prognostic nutritional index (PNI) and CONUT score concerning breast cancer found a high CONUT score to be associated with reduced OS [41]. Additionally, a systematic review and meta-analysis revealed that high CONUT predicted inferior OS, cancer-specific survival, disease-free survival, recurrence-free survival, and RFS in patients treated surgically for renal cell cancer and upper urinary tract urothelial cancer [42].

A couple of publications that explore molecular and genetic HNC markers warrant mention, not only for their potential prognostic value but also for implications to personalized cancer therapy. One of these is a letter to the editor in *Clinical and Translational Medicine* discussing the big picture of such research [43]. The other is a systematic review of some fifty published studies on proteomics and genetics of HNC, which identified 242 genes and 44 proteins associated with HNC [44]. Although beyond the scope of this meta-analysis, these two aforementioned publications raise another question that should be open for future research, namely whether any of the various genetic and proteomic markers could be combined with GNRI or CONUT, or possibly worked into upgraded GNRI or CONUT scales, to enhance the accuracy of prognosis and therapeutic personalization.

Of note, heterogeneity has been detected among the studies included in the current meta-analysis. The possible sources of this heterogeneity, although uncertain, could be the different cutoff points of the GNRI or CONUT score chosen across the studies, the varying treatment modalities for HNC, the different cancer stages, and the proportions of different primary tumor sites. However, subgroup analysis could not be performed due to the relatively small number of studies. This issue should be addressed in future research as more studies become available. There is discrepancy between the crude HR and adjusted HR in the results of Yi (2023) for CONUT's impact on survival, which warrants explanations. The discrepancy between the crude and adjusted HR in Yi (2023) may be partly related to the specific variables included in the adjustment model. While that study adjusted for smoking, alcohol use, age, pathological TNM stage, and hypertension, it did not account for other critical factors such as BMI, radiotherapy, chemotherapy, or additional comorbidities—factors that are known to significantly impact survival and were commonly adjusted for in other studies. We conducted a sensitivity analysis using the leave-one-out approach. Excluding Yi et al. from the analysis reduced the I^2 value for the meta-analyses on associations (adjusted HR) between CONUT

and OS or PFS to no heterogeneity. Further, the adjusted HR became statistically significant, demonstrating that a higher CONUT score is associated with poorer OS and PFS (Tables 4 and 5). These observations suggest that Yi et al. is a primary source of heterogeneity in the analysis.

It should be noted that, the receipt of palliative treatment and variations in palliative care protocols, along with the severity of disease progression in advanced cancers, can significantly influence nutritional indices such as GNRI and CONUT, thereby potentially confounding their predictive value for survival outcomes. Palliative care interventions, particularly those addressing malnutrition, such as nutritional support, dietary counseling, or artificial nutrition, can alter these indices by improving nutritional status and mitigating cancer-related cachexia [45]. These variations create heterogeneity that may obscure the true prognostic utility of GNRI and CONUT in survival analyses. For example, improved survival outcomes in patients receiving effective palliative care could reflect the benefits of symptom management and nutritional support rather than the intrinsic predictive value of the indices themselves. As such, accounting for palliative treatment practices is crucial to accurately interpret the relationship between these nutritional indices and survival outcomes. However, data constraints prevented us from conducting a comprehensive subgroup analysis based on cancer stage or the palliative treatments employed. Addressing these factors should be a priority in future efforts to conduct an updated meta-analysis.

Lastly, given that our review included non-elderly age groups, we note that the GNRI, though originally designed for elderly populations, has also been validated across diverse age groups and clinical settings, including relatively younger populations [46, 47]. This broad applicability underscores the versatility of GNRI as a nutritional assessment tool, demonstrating its capacity to provide valuable prognostic information across a wide range of patient demographics and healthcare contexts.

Strength and limitations

This review represents the largest meta-analysis to date on the GNRI in predicting outcomes for patients with HNC. Additionally, this study marks the first systematic review and meta-analysis to investigate the prognostic role of the CONUT score in HNC patients. Furthermore, the inclusion of both crude and adjusted hazard ratios in the pooling of data enhances the robustness and reliability of the findings. This offers a more nuanced understanding of the relationship between nutritional status indicators and patient outcomes in HNC. However, all the studies included in this analysis were retrospective in design, which can introduce biases. While the GNRI cutoffs were generally consistent across studies, there were still a few instances where different cutoff values were used, which could affect the accuracy and comparability of the results. Similarly, the CONUT cutoff values were not the same among the studies, which introduces potential inconsistencies in the interpretation of the data. Additionally, the baseline ECOG scores, cancer stages, and treatment modalities varied across the included studies. These differences in patient characteristics and treatment approaches may influence the analytical outcomes and limit the generalizability of the findings.

Conclusion

A low GNRI in patients with HNC is predictive of worse OS and PFS. CONUT score appears not predictive of OS or PFS after adjustment for confounders. These results fill an important knowledge gap and highlight the potential of GNRI as a reliable prognostic tool for evaluating clinical outcomes in HNC.

Abbreviations

GNRI	Geriatric Nutritional Risk Index
CONUT	Controlling Nutritional Status
HNC	Head and neck cancer
OS	Overall survival
PFS	Progression-free survival

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-13565-7.

Supplementary Material 1

Acknowledgements

None.

Author contributions

Yu-Chieh Huang: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Visualization, Supervision, Writing - original draft, Writing - review & editing. Shuo-Wei Chen: Conceptualization, Data curation, Formal analysis, Project administration, Writing - original draft, Writing - review & editing. Yih-Shien Chiang: Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing. All authors read and approved the final manuscript.

Funding

None.

Data availability

The datasets analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This systematic review and meta-analysis solely depended on published studies, without collecting or utilizing raw patient data or private information. Consequently, the hospital's institutional review board (IRB) granted an exemption from protocol approval and informed consent requirements for study subjects.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 21 August 2024 / Accepted: 20 January 2025
Published online: 11 February 2025

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