Prognostic significance of controlling nutritional status score for patients with gastric cancer: A systematic review and meta-analysis

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Abstract. There is a need to identify potentially useful biomarker(s) for the prediction of prognostic outcomes in patients diagnosed with gastric cancer. This meta-analysis provided updated evidence on the association of controlling nutritional status (CONUT) score with survival and other clinicopathological outcomes in patients with gastric cancer. PubMed and Scopus databases were systematically searched. The review included studies, observational in design, that were conducted among patients with gastric cancer and had documented the association of CONUT score with outcomes of interest. The primary outcomes of interest were overall survival (OS), cancer-specific survival (CSS) and recurrence-free survival (RFS) along with tumour size and extent (T status), nodal status (N status) and tumour staging (TNM staging). STATA was used for statistical analysis. The meta-analysis was conducted with 17 studies. The 5-year OS [hazard ratio (HR), 1.75; 95% confidence interval (CI): 1.55, 1.96], RFS (HR, 1.58; 95% CI: 1.30, 1.91) and CSS (HR, 1.89; 95% CI: 1.01, 3.52) were comparatively poorer in the high CONUT group, than in low CONUT group. High CONUT score was associated with increased risk of having T3/T4 tumour [odds ratio (OR), 1.64; 95% CI: 1.16, 2.34], N2/N3 nodal status (OR, 1.44; 95% CI: 1.17, 1.77) and stage III/IV tumour (OR, 1.64; 95% CI: 1.43, 1.88). The risk of microvascular invasion (OR, 1.46; 95% CI: 1.20, 1.77) and post-operative complications (OR, 1.64; 95% CI: 1.31, 2.06) was higher in those with high CONUT. There were no differences in the risk of poorly differentiated tumour and need for adjuvant chemotherapy between the two groups. Findings suggested that preoperative assessment of CONUT score may be included in the routine assessment of patients with gastric cancer due to its association with survival and other clinical as well as pathological outcomes.

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Introduction

In patients with cancer, malnutrition is a common occurrence, and can adversely affect the prognosis and other clinical outcomes (1,2). The nutritional status has also been shown to influence the post-treatment disease progression and survival (1). Therefore, numerous studies focused on identifying biomarkers that reflect the nutritional status and determining their prognostic role in various cancers. A recent addition to these biomarkers is the controlling nutritional status (CONUT) score that comprises of serum albumin, total cholesterol and total lymphocyte count (3). With the growing body of evidence on the possible role of nutrition in cancer progression and overall survival (OS), there has been an emerging interest in elucidating the predictive ability of CONUT score for clinical and survival outcomes.

There has been some indication from previous studies favoring the role of CONUT score in prediction of survival in patients with gastrointestinal (GI) and urinary tract cancers (4,5). A comprehensive systematic review involving 32 studies noted that the CONUT score provided enhanced indication of prognosis i.e., survival, cancer-specific survival and tumor progression in various types of cancers compared with other potential biomarkers (6). In subjects with high CONUT score, lower OS, cancer-specific survival (CSS), and recurrence-free survival (RFS) rates were reported by >85% of the included studies in cancer patients (6). A prognostic role of the CONUT score for prediction of OS, CSS and RFS was shown by ~92, 91 and 53% of the studies, respectively (6). However, as different cancers have their specific prognoses, it is important to carefully document the prognostic role of CONUT in organ-specific cancers (7).

A review by Takagi *et al* (7) that specifically focused on gastric cancers, pooled findings from 5 retrospective studies and found that in patients undergoing gastrectomy, the OS, rate of postoperative complications, clinical and other pathological parameters could be reliably predicted using preoperatively-assessed CONUT score (7). Several new studies on this issue have been published and the main goal of the current meta-analysis was to update the previous review by summarizing the existing data from studies dealing

with gastric cancer, and to assess and document whether the CONUT score could predict tumor stage, survival and recurrence.

Materials and methods

Strategy for identification and selection of relevant studies. The protocol was registered in PROSPERO (https://www.crd.york.ac.uk/prospero/; CRD42021287305) before starting the meta-analytic work. A systematic search was conducted to identify English language studies published before 1st March 2022. The databases searched were PubMed and Scopus. The search strategy used is presented in the Appendix. The search strategy incorporated the following: i) Controlling nutritional status score or CONUT or immuno-nutritional biomarker or serum albumin or total cholesterol or lymphocyte count and ii) stomach tumor or gastric tumor or gastric neoplasm or gastric malignancy or gastric carcinoma or gastric adenocarcinoma and iii) outcomes or mortality or survival or recurrence or prognosis. The primary outcomes of interest were: OS and RFS, CSS, tumor size and extent (T status), nodal status (N status), and tumor staging (TNM staging). Secondary outcomes of interest were tumor differentiation, need for adjuvant chemotherapy, microvascular invasion, hospital stay duration and postoperative complications. The study processes complied with the guidelines laid down in PRISMA (8).

Studies identified by the literature search were independently reviewed by two investigators after duplicate removal. After title and abstract review, full texts of the relevant studies were reviewed to identify studies that meet eligibility criteria. Any disagreements were resolved by discussion between the study authors. To identify additional studies for inclusion, bibliography sections of the selected studies were also reviewed.

Only studies that were performed on patients with gastric cancer and documented the association of CONUT scores (assessed prior to start of management) with outcomes of interest were considered. Observational studies i.e., case-control and cohort (either prospective or retrospective) and those that were performed using analysis of database or clinical records were considered for inclusion. Case-reports, conference abstracts or review articles were excluded. Studies that did not provide findings based on CONUT scores or did not provide data on the outcomes of interest were excluded. Studies that reported alteration in nutritional status secondary to poor eating as a result of any oral surgery or chronic illness other than gastric cancer were also excluded. There were no exclusions based on the modality of treatment received i.e., surgery only, chemotherapy or radiotherapy or immunotherapy only or a combination thereof.

Data extraction and quality assessment. A pre-tested data extraction sheet was used by two independent authors to extract data from relevant studies. In case of any discrepancy, the two authors discussed the issue at hand and achieved consensus. The adapted Newcastle-Ottawa Quality Assessment Scale (NOS) was used for assessing the quality of the included studies (9).

Statistical analysis. All the analysis was carried out using STATA software (StataCorp. 2017; Stata Statistical Software: Release 15. College Station, TX; StataCorp LP). The pooled findings were presented as hazards ratios (HR) or odds ratios (OR) in case the outcome was categorical and as weighted mean difference (WMD) for non-categorical/continuous outcomes. A 95% confidence interval (CI) was presented along with pooled estimates. Subgroup analyses were conducted for survival outcomes, based on a CONUT cut-off score of >3, study design (retrospective or prospective), and study sample size (>300 subjects). The degree of heterogeneity was assessed using I^2 parameter and random-effects model was used in instances when the I^2 value exceeded 40% (10). Egger's test was used to detect publication bias and a P-value of less than 0.05 for statistical significance (11). Additionally, funnel plots were also created to visually inspect presence or absence of publication bias.

Results

Literature search. A total of 767 unique citations (i.e., after removal of duplicates) were identified by the search (Fig. 1). Through the title and abstract screening, 719 studies were removed and further 31 studies were excluded after review of full text. Finally, 17 studies were found relevant for inclusion in the meta-analysis. (12-28) (Tables I and II). Most included studies (n=14) were retrospective in design and utilized clinical databases or records, while the remaining three studies were prospective. A total of nine studies were performed in China, five in Japan, and individual studies in Turkey, Italy and South Korea. The studies used different cut-off values to categorize high and low CONUT scores. Most of the studies (n=12) had a median follow-up period of >24 months. Table SI presents the findings of the quality assessment and the quality of most studies was judged to be favorable.

CONUT score and survival outcomes. 5-year OS in the group of patients with the high CONUT scores was comparatively lower than in the group with low CONUT scores (HR, 1.75; 95% CI: 1.55, 1.96; n=14; I^2=11.9%) (Fig. 2). Similarly, 5-year RFS (HR, 1.58; 95% CI: 1.30, 1.91; n=7; I^2=17.6%) and 5-year cancer-specific survival (HR, 1.89; 95% CI: 1.01, 3.52; n=4; I^2=73.2%) was lower in the high CONUT group compared with the low CONUT group (Fig. 2). There was no evidence of publication bias on Egger's test and also on visual inspection of the funnel plots (Table SII; Figs. S1-3).

CONUT score and clinicopathological outcomes. High CONUT score was associated with an increased risk of T3 or T4 tumor status (OR, 1.64; 95% CI: 1.16, 2.34; n=8; I^2=67.0%), N2 or N3 nodal status (OR, 1.44; 95% CI: 1.17, 1.77; n=8; I^2=33.4%), and stage III or IV tumor (OR, 1.64; 95% CI: 1.43, 1.88; n=12; I^2=26.8%) (Fig. 3). The pooled risk of microvascular invasion (OR, 1.46; 95% CI: 1.20, 1.77; n=5; I^2=0.0%) and post-operative complications (OR, 1.64; 95% CI: 1.31, 2.06; n=11; I^2=67.6%) was higher in patients with high CONUT scores compared with the low CONUT group (Fig. 4). There were no differences in terms of poorly differentiated tumor risk (OR, 1.15; 95% CI: 0.91, 1.46; n=9; I^2=50.1%) and need for adjuvant chemotherapy (OR, 0.87; 95% CI: 0.60, 1.26; n=5; I^2=69.1%) between the two groups (Fig. 4). Those with high CONUT scores had longer hospital stays (in days) compared with those with low CONUT scores

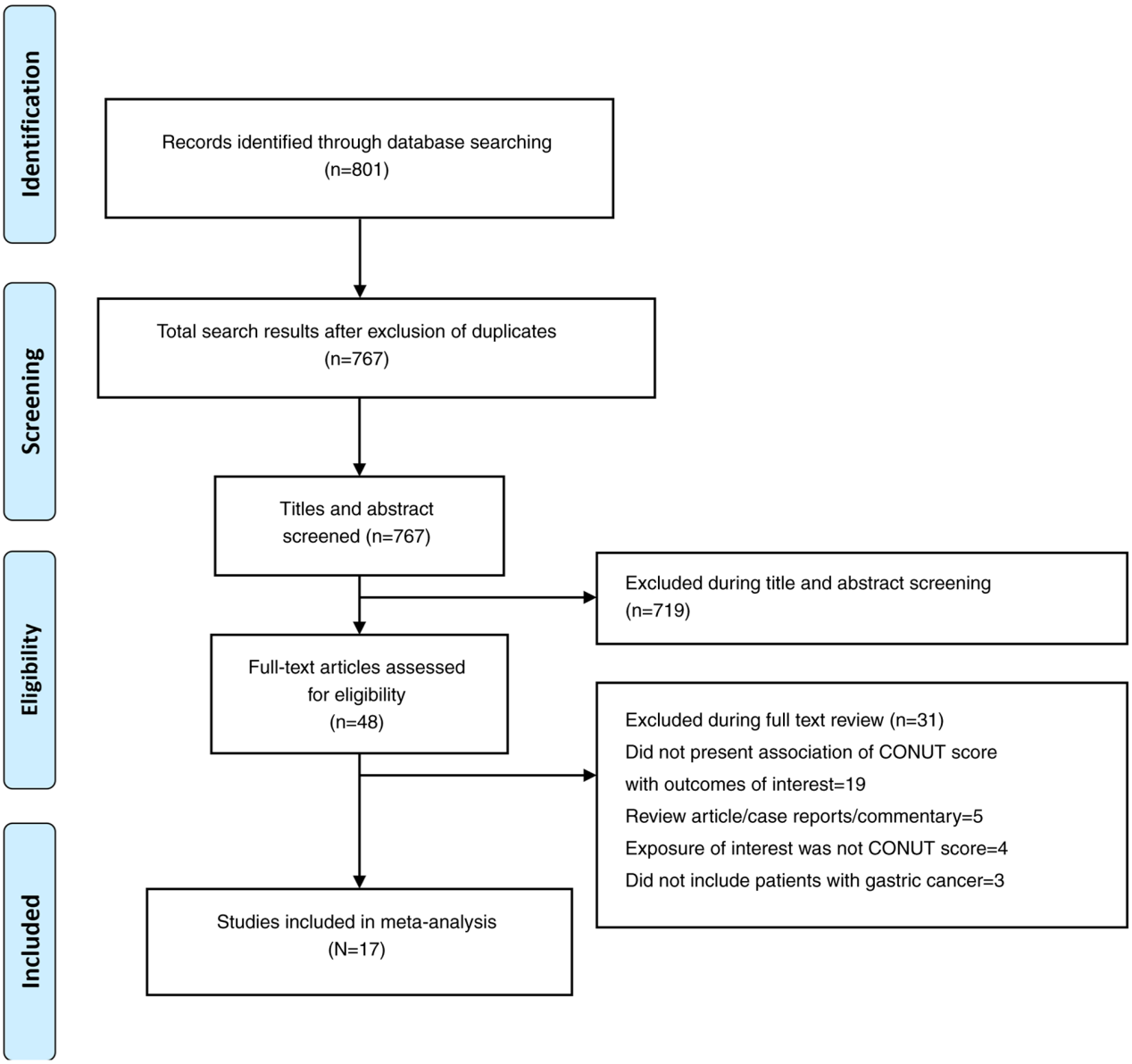

Figure 1. Selection process of the studies included in the review. CONUT, controlling nutritional status.

(WMD, 1.97; 95% CI: 1.17, 2.78; n=6; I^2=88.0%) (Fig. 5). Post-operative complications reported by the studies mainly consisted of surgical site infections, post-operative active haemorrhages, intra-abdominal abscesses, septic shock and organ dysfunction. Egger's test did not indicate presence of publication bias for the outcomes considered, except for risk of post-operative complications (Table SII). The funnel plots for each of the aforementioned outcomes have been presented as Figs. S4-8.

Subgroup analyses. OS and RFS were consistently lower in patients with high CONUT scores compared with the low CONUT group when analyses were restricted to studies with retrospective design, larger sample size (>300), and studies that used a CONUT score cut-off of >3. Due to a limited number of prospective studies, pooled outcomes were only possible for OS. The present results revealed that OS (HR, 1.71; 95% CI: 1.46, 1.99; n=2; I^2=0.0%) was lower in patients with high CONUT scores (Table III).

Discussion

The main goal of this meta-analysis was to update the previous evidence on the predictive value of CONUT scores in estimating tumor stage, survival and recurrence of gastric cancer. Through the inclusion of 17 studies, the review found that the high CONUT score in gastric cancer patients was associated with worse 5-year OS, RFS and cancer-specific survival compared with patients with a low CONUT score. Moreover, a high CONUT score was associated with an increased risk of having T3/T4 tumor status, N2/N3 nodal status and stage III/IV tumor. The pooled risk of microvascular invasion and post-operative complications was higher in patients with the high CONUT group. These findings support the previous review by Takagi *et al* (7) where the authors, using 5 studies, showed that the CONUT score, assessed pre-operatively, was an independent and reliable indicator of OS and postoperative complications as well as stage of tumor and extent of microvascular invasion (7).

Table I. Characteristics of the studies included in the meta-analysis.

First author	Study design	Country	Participant characteristics	CONUT category	Sample size	Quality assessment score (NOS)	(Refs.)
Zhu *et al*	Retrospective data analysis	China	Patients with gastric cancer undergoing total gastrectomy (R0 resection- complete resection with negative margin); male (73%) and <65 years (66%); follow up period ranged from 5-15 years.	High (>3) vs. low (≤3)	245 (high, 141; low, 104)	9	(12)
Galizia *et al*	Retrospective analysis of prospectively maintained database	Italy	Patients with gastric cancer (adenocarcinoma) undergoing total gastrectomy; male (59%) and ≤65years (53%); median follow up period of. 24.7 months	High (>1) vs. low (≤1)	415 (high, 164; low, 251)	9	(13)
Sun *et al*	Prospective follow up	China	Patients with gastric cancer undergoing total gastrectomy (R0 resection); mean age of 60.4 years; male (73%); Mean BMI of 23 kg/m^2; short term follow up of 30 days post-operatively	High (≥2) vs. low (<2)	1479 (high, 852; low, 627)	8	(14)
Qian *et al*	Retrospective analysis of clinical records	China	Patients with gastric cancer undergoing laparoscopic gastrectomy; mean age of 63.4 years; male (73.8%); Mean BMI of 22.8 kg/m2; 38% with hypertension; short term follow up of 30 days post-operatively	High (>2.5) vs. low (<2.5)	309 (high, 95; low, 214)	8	(15)
Jin *et al*	Retrospective analysis of data	China	Patients with gastric adenocarcinoma undergoing gastrectomy (38.6% with total and 48.5% with subtotal gastrectomy) along with neoadjuvant chemotherapy; median age of 61 years; male (74%); BMI of ≥18.5 kg/m2 (86%); median follow up of around 60 months	High (≥4) vs. low (≤3)	267 (high, 85; low, 182)	8	(16)
Akagunduz *et al*	Retrospective review of medical records	Turkey	Patients with gastric carcinoma treated with FLOT (fluorouracil, leucovorin, oxaliplatin or docetaxel) chemotherapy; median age of 58.7 years; male (68.3%); median follow up of 11.2 months	High (>3) vs. low (≤3)	161 (high, 105; low, 56)	7	(17)
Lin *et al*	Prospective follow up	China	Patients with gastric cancer treated with radical gastrectomy; median age of 60.8 years; male (75.3%); median BMI of 22.5 kg/m^2; median follow up of 52 months	High (>2) vs. low (≤2)	2182 (high, 478; low, 1704)	8	(18)
Huang *et al*	Prospective follow up	China	Patients with gastric cancer treated with curative gastrectomy (subtotal gastrectomy in 57%); median age of 73.3 years; male (77%); median BMI of 21.6 kg/m^2; follow up of 12 months	High (≥2) vs. low (<2)	357 (high, 204; low, 153)	9	(19)

Table I. Continued.

First author	Study design	Country	Participant characteristics	CONUT category	Sample size	Quality assessment score (NOS)	(Refs.)
Jeon *et al*	Retrospective review of records	South Korea	Patients who underwent curative gastrectomy; age ≥60 years (51.3%); male (66%); 33% with BMI ≥25 kg/m^2; mean follow-up duration was 59.0 months	High (≥2) vs. low (<2)	1307 (high, 414; low, 893)	8	(20)
Hirahara *et al*	Retrospective review of medical records	Japan	Patients who underwent curative gastrectomy; mean age of 70 years; male (69%); Mean BMI of 22 kg/m^2; median follow-up duration was 35.3 months	High (≥3) vs. low (≤2)	368 (high, 105; low, 263)	8	(21)
Kuroda *et al*	Retrospective review of medical records	Japan	Patients who underwent curative gastrectomy; age≥75 years (32%); male (64%); BMI of ≥18.5 kg/m^2 (90%); median follow-up duration was 61.2 months	High (≥4) vs. low (≤3)	416 (high, 62; low, 354)	9	(22)
Zheng *et al*	Retrospective design	China	Patients who underwent curative gastrectomy; Mean age of 61.1 years; male (75.8%); Mean BMI of 21.9 kg/m^2; median follow-up duration was 60 months	High (≥2) vs. low (<2)	532 (high, 241; low, 291)	9	(23)
Liu *et al*	Retrospective review of medical records	China	Patients who underwent curative gastrectomy followed by adjuvant chemotherapy with 5-fluorouracil based regimen; Age <60 years (59.4%); male (65.6%); median follow-up duration was 36 months	High (≥3) vs. low (≤2)	697 (high, 217; low, 480)	8	(24)
Ryo *et al*	Retrospective review of clinical data	Japan	Patients who underwent curative gastrectomy; Mean age of around 67 years; male (69.4%); mean BMI of around 22 kg/m^2; median follow-up duration was 49.2 months	High (≥2) vs. low (<2)	626 (high, 289; low, 337)	7	(25)
Suzuki *et al*	Retrospective design	Japan	Patients who underwent curative gastrectomy; Mean age of around 80 years; male (67%); mean BMI of around 22.5 kg/m^2; median follow-up duration was 47.0 months	High (≥5) vs. low (<5)	211 (high, 36; low, 175)	9	(26)
Xiao *et al*	Retrospective design	China	Patients undergoing gastric surgery; Median age of 67 years; around 80% males; median follow up of 30 months	High (≥5) vs. low (<5)	106 (high, 63; low, 43)	9	(27)

Table I. Continued.

First author	Study design	Country	Participant characteristics	CONUT category	Sample size	Quality assessment score (NOS)	(Refs.)
Aoyama *et al*	Retrospective design	Japan	Patients with curative surgery and adjuvant treatment; majority aged under 65 years (72%); males (66%)	High (≥2) vs. low (<2)	331 (high, 110; low, 221)	8	(28)

NOS, Newcastle Ottawa Scale score; CONUT, controlling nutritional status; BMI, body mass index.

The inclusion criteria were similar to that of Takagi *et al* (7); however, it was more explicit. For instance, it has been specifically mentioned that the present review would include only observational studies and would not consider case-reports or conference abstracts. It was also mentioned that subjects with evident cause of poor nutrition that is unrelated to gastric cancer would be excluded. Therefore, studies that reported alteration in nutritional status secondary to poor eating as a result of any oral surgery or chronic illness other than gastric cancer were excluded. While the review by Takagi *et al* (7) included studies with gastric cancer subjects undergoing curative resection, the present review did not have exclusions based on the modality of treatment received i.e., surgery only, chemotherapy or radiotherapy or immunotherapy only or a combination thereof. The current meta-analysis was not conducted to challenge the aforementioned review by Takagi *et al* but instead, to update the evidence base through inclusion of more recently published studies on this issue. The fact that the findings of the present study are largely similar to those reported by the previous review provides assurance that these insights could potentially be used to inform the current clinical practice.

Studies have indicated that cancer prognosis and survival rates may be influenced, to a certain extent, by the host's nutritional status as well as the underlying inflammatory status (29). Furthermore, the nutritional status may impact the immune status and metabolic health in patients with cancer (30,31). Particularly, the immune status is known to affect tumor recurrence (32). Therefore, there is a continuous effort to explore biomarkers of nutritional and immune status that could be used as prognostic indicators of various types of malignancies. A commonly utilized marker to reflect nutritional status is the prognostic nutritional index (PI) that is derived from serum albumin values and total lymphocyte count (33). Studies on PNI have shown that it could be a modest predictor of post-operative complications and overall prognosis in various cancers including GI cancers (34,35). In terms of the immune biomarker, other potential candidates have also been explored and tested (36-38). The findings of the current meta-analysis suggest that the CONUT score could be used as a potentially useful biomarker for the prediction of prognostic outcomes in patients diagnosed with gastric cancer. Available evidence suggests that the CONUT score is probably more accurate, compared with other prognostic factors and indicators (39-41). For instance, in a study among subjects with hepatocellular carcinoma undergoing curative hepatectomy, CONUT score exhibited a higher area under the curve value (61.8%), when compared with other immune-nutritional parameters including PNI (59.9%), neutrophil to lymphocyte ratio (57.5%) and platelet to lymphocyte ratio (49.4%) for prediction of OS (39). Similarly, for the prediction of post-operative pulmonary complications in patients with resectable non-small cell lung cancer, the CONUT showed a higher area under curve (64.0%) than other prognostic models such as PNI (61%) and Glasgow prognostic score (57%) (40).

The higher accuracy of the CONUT score, when compared with the other commonly used nutritional marker i.e., PNI could be related to the higher emphasis on peripheral lymphocyte count and additional measurement of total serum cholesterol level. Reduced cholesterol levels (hypocholesterolaemia) may be an indicator of advancing tumour progression (42). There

Table II. Key findings from the studies included in the meta-analysis.

First author	Key outcomes (high vs. low)	(Refs.)
Zhu *et al*	Overall survival (5-year): HR, 2.03; (95% CI: 1.12, 2.95) Disease free survival (5-year): HR, 3.12; (95% CI: 1.24, 4.99) Cancer-specific survival (5-year): HR, 0.89; (95% CI: 0.52, 1.50) Poor differentiation: OR, 1.53; (95% CI: 0.89, 2.64) T3/4: OR, 0.80; (95% CI: 0.48, 1.34) N2/3: OR, 0.83; (95% CI: 0.50, 1.38) Stage III/IV: OR, 2.00; (95% CI: 1.19, 3.36) Need for adjuvant chemotherapy: OR, 0.41; (95% CI: 0.24, 0.68) Microvascular invasion: OR, 1.55; (95% CI: 0.93, 2.58)	(12)
Galizia *et al*	Overall survival (5-year): HR, 1.28; (95% CI: 0.79, 2.05) Disease free survival (5-year): HR, 1.46; (95% CI: 0.68, 3.16)	(13)
Sun *et al*	Post-operative complication: OR, 1.16; (95% CI: 1.08, 1.24) Stage III/IV: OR, 1.51; (95% CI: 1.22, 1.87) Length of hospital stay [mean (sd); days]: 12.3 (6.0); 11.1 (4.6)	(14)
Qian *et al*	Post-operative complication: OR, 2.43; (95% CI: 1.22, 4.86) T3/4: OR, 2.33; (95% CI: 1.38, 3.94) N2/3: OR, 2.07; (95% CI: 1.26, 3.38) Stage III/IV: OR, 2.56; (95% CI: 1.55, 4.24) Length of hospital stay [mean (sd); days]: 14.1 (0.7); 11.6 (0.5)	(15)
Jin *et al*	Overall survival (5-year): HR, 1.62; (95% CI: 1.11, 2.36) Disease free survival (5-year): HR, 1.61; (95% CI: 1.11, 2.34) Poor differentiation: OR, 1.39; (95% CI: 0.74, 2.61) T3/4: OR, 2.02; (95% CI: 1.11, 3.69) N2/3: OR, 1.05; (95% CI: 0.61, 1.80) Stage III: OR, 1.22; (95% CI: 0.73, 2.05) Need for adjuvant chemotherapy: OR, 1.16; (95% CI: 0.51, 2.64) Post-operative complication: OR, 1.08; (95% CI: 0.54, 2.18)	(16)
Akagunduz *et al*	Poor differentiation: OR, 1.91; (95% CI: 0.98, 3.71) T3/4: OR, 0.26; (95% CI: 0.06, 1.21) N2/3: OR, 1.43; (95% CI: 0.72, 2.84) Overall survival (5-year): HR, 2.40; (95% CI: 1.03, 5.54)	(17)
Lin *et al*	Post-operative complications: OR, 1.81; (95% CI: 1.04, 3.18) Overall survival (5-years): HR, 1.69; (95% CI: 1.45, 1.98)	(18)
Huang *et al*	Post-operative complications: OR, 2.69; (95% CI: 1.63, 4.45) Overall survival (1-year): HR, 2.91; (95% CI: 0.91, 9.31) Stage III/IV: OR, 1.51; (95% CI: 0.98, 2.32) Length of hospital stay [mean (sd); days]: 18.7 (10.8); 15.7 (9.1) Microvascular invasion: OR, 1.30; (95% CI: 0.85, 1.98)	(19)
Jeon *et al* (20)	Overall survival (5-year): HR, 2.23; (95% CI: 1.07, 4.66) Stage III: OR, 1.47; (95% CI: 1.05, 2.04)	
Hirahara *et al*	Overall survival (5-year): HR, 2.44; (95% CI: 1.46, 4.07) Poor differentiation: OR, 1.21; (95% CI: 0.77, 1.90) T3/4: OR, 2.70; (95% CI: 1.69, 4.32) N2/3: OR, 1.67; (95% CI: 1.01, 2.78) Stage III: OR, 1.94; (95% CI: 1.17, 3.23) Need for adjuvant chemotherapy: OR, 1.26; (95% CI: 0.76, 2.07) Post-operative complication: OR, 1.73; (95% CI: 1.07, 2.80)	(21)
Kuroda *et al*	Overall survival (5-year): HR, 2.72; (95% CI: 1.74, 4.25) Disease/recurrence-free survival (5-year): HR, 2.63; (95% CI: 1.16, 5.97) Cancer-specific survival (5-year): HR, 4.13; (95% CI: 1.62, 10.54) Poor differentiation: OR, 1.76; (95% CI: 1.01, 3.06)	(22)

Table II. Continued.

First author	Key outcomes (high vs. low)	(Refs.)
	T3/4: OR, 2.33; (95% CI: 1.34, 4.04) N2/3: OR, 2.29; (95% CI: 1.16, 4.52) Stage III: OR, 2.73; (95% CI: 1.44, 5.20) Post-operative complication: OR, 1.54; (95% CI: 0.88, 2.71) Microvascular invasion: OR, 1.90; (95% CI: 1.10, 3.27)	
Zheng *et al*	Overall survival (5-year): HR, 1.36; (95% CI: 0.98, 1.88) Disease/recurrence-free survival (5-year): HR, 1.36; (95% CI: 1.00, 1.88) Poor differentiation: OR, 1.10; (95% CI: 0.76, 1.61) Stage III: OR, 1.66; (95% CI: 1.17, 2.34) Microvascular invasion: OR, 1.51; (95% CI: 1.02, 2.24) Need for adjuvant chemotherapy: OR, 1.12; (95% CI: 0.80, 1.58)	(23)
Liu *et al*	Cancer-specific survival (5-year): HR, 1.55; (95% CI: 1.08, 2.23) Poor differentiation: OR, 0.64; (95% CI: 0.41, 1.01) Stage III: OR, 1.20; (95% CI: 0.83, 1.73) T3/4: OR, 1.62; (95% CI: 0.86, 3.08) N2/3: OR, 1.57 ; (95% CI: 1.11, 2.21) Post-operative complication: OR, 1.30; (95% CI: 0.90, 1.89)	(24)
Ryo *et al*	Overall survival (5-year): HR, 1.74; (95% CI: 1.26, 2.41) Disease/recurrence-free survival (5-year): HR, 1.33; (95% CI: 0.98, 1.81) Poor differentiation: OR, 0.83; (95% CI: 0.60, 1.14) Stage III: OR, 1.55; (95% CI: 1.13, 2.13) T3/4: OR, 1.53 ; (95% CI: 1.01, 2.32) N2/3: OR, 1.33 ; (95% CI: 0.97, 1.82) Microvascular invasion: OR, 1.30; (95% CI: 0.88, 1.94) Post-operative complication: OR, 1.28; (95% CI: 0.91, 1.81) Need for adjuvant chemotherapy: OR, 0.80; (95% CI: 0.58, 1.10) Length of hospital stay [mean (sd); days]: 14.0 (3.9); 13.0 (4.1)	(25)
Suzuki *et al*	Overall survival (5-year): HR, 2.12; (95% CI: 1.18, 3.69) Cancer-specific survival (5-year): HR, 3.75; (95% CI: 1.30, 10.43) Poor differentiation: OR, 1.16; (95% CI: 0.55, 2.43) Stage III: OR, 3.82; (95% CI: 1.57, 9.33) Post-operative complication: OR, 2.22; (95% CI: 1.07, 4.60) Length of hospital stay [mean (sd); days]: 22.0 (2.7); 19.0 (1.5)	(26)
Xiao *et al*	Overall survival (5-year): HR, 1.19; (95% CI: 0.74, 1.92) Post-operative complication: OR, 3.75; (95% CI: 1.72, 8.17) Length of hospital stay [mean (sd); days]: 25.6 (7.5); 24.3 (7.4)	(27)
Aoyama *et al*	Overall survival (5-year): HR, 1.95; (95% CI: 1.10, 3.45) Disease/recurrence-free survival (5-year): HR, 1.71; (95% CI: 1.00, 2.93)	(28)

OR, odds ratio; CI, confidence interval; HR, hazard ratio.

is an increased expression of LDL receptors in tumour cells which leads to increased uptake of circulating LDL cholesterol, thereby leading to hypocholesterolaemia (43). This uptake of LDL cholesterol is required for increased tumour growth (44,45). There is further indication of altered cell membrane fluidity due to hypocholesterolaemia, thereby affecting the mobility of cell surface receptors and their ability to transmit transmembrane signals (46). This leads to a situation wherein even in the presence of adequate number of immunocompetent cells present, the immunological function is compromised (47). Based on these considerations, CONUT is considered to be more sensitive than PNI as a prognostic indicator.

The underlying mechanisms linking CONUT score with prognostic outcomes in gastric cancer patients have not been fully understood. However, previous evidence indicates that there may be a link between individual components of CONUT score and gastric cancer outcomes. For instance,

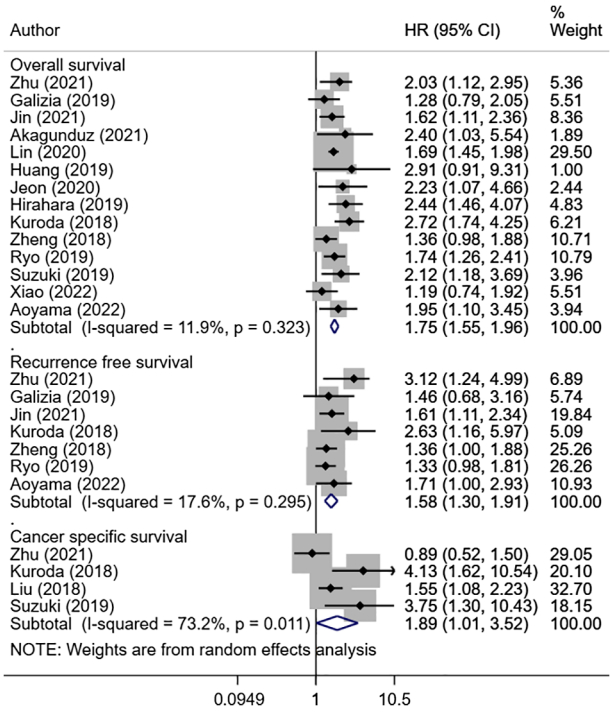

Figure 2. Overall survival, recurrence-free survival and cancer-specific survival in high CONUT score group compared with low CONUT score group. CONUT, controlling nutritional status; HR, hazard ratio; CI, confidence interval.

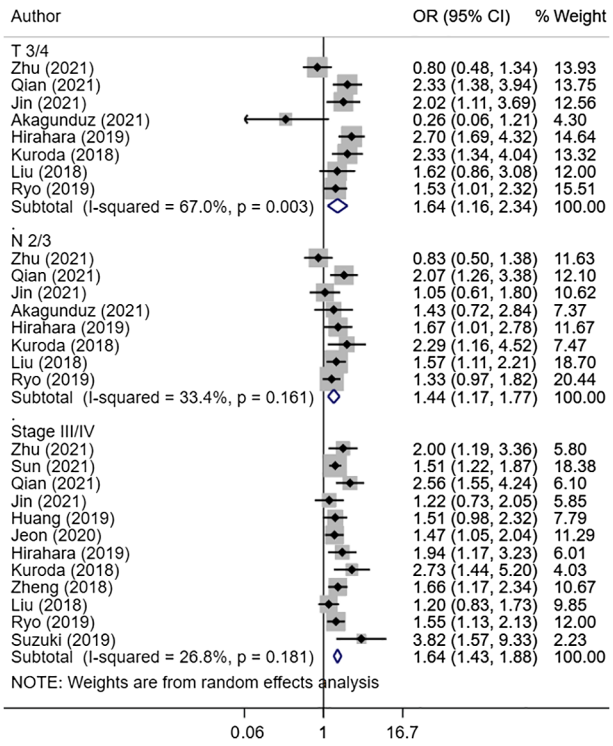

Figure 3. Risk of advanced tumor size and extent (T3/4), nodal metastasis (N2/3) and tumor stage (III/IV) between high and low controlling nutritional status score group. OR, odds ratio; CI, confidence interval.

serum albumin is a prominent indicator of nutritional status and systemic inflammation that is associated with survival in gastric cancer patients (48,49). Numerous studies show that in

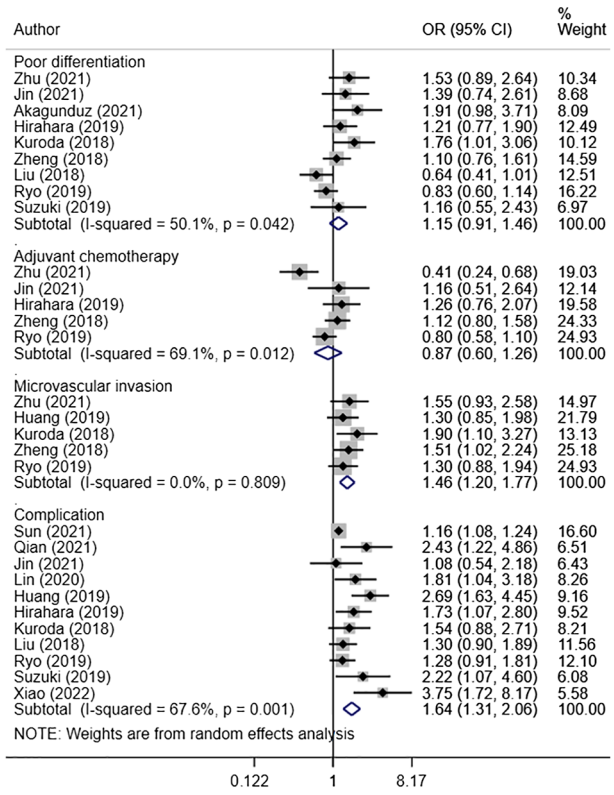

Figure 4. Risk of poor tumor differentiation, need for adjuvant chemotherapy, microvascular invasion and complication between high and low controlling nutritional status score group. OR, odds ratio; CI, confidence interval.

patients with GI cancers serum cholesterol is strongly correlated with tumor progression and survival (50-52). Similarly, total lymphocyte count is related to prognosis in gastric cancer (53). An interesting observation identified by previous studies is that the sensitivity and specificity of the total CONUT score is usually higher than that of each of its three individual components (22,54,55). The present review revealed that the CONUT score was associated with TNM staging as well as tumor size (T) and nodal status (N). However, it remains unclear whether these findings relating to the CONUT score were a cause or a result of the tumor progression.

The present findings support the use of CONUT to assess nutritional status and consider this at the time of planning management for patients with gastric cancer. It will provide an opportunity to improve the nutritional status of those with malnutrition, before starting and/or during treatment, which in turn could considerably maximize the efficacy of the treatment provided, i.e., either surgery and/or a combination of surgery and chemotherapy. The use of CONUT-based nutritional assessment is not meant to alter the standard current management practices for gastric cancer. However, it does help to identify patients that are nutritionally compromised and would therefore need nutritional management in order to improve their OS or reduce the risk of recurrence. Assessment of CONUT score will also help to identify patients at risk of complications and these could be followed up and monitored closely.

There are certain limitations that should be considered while interpreting the findings. The majority of the included studies were retrospective and it is possible that certain

Table III. Subgroup analysis for overall survival, cancer-specific survival and recurrence-free survival.

Parameter	Overall survival	Cancer-specific survival	Recurrence-free survival
High controlling nutritional status score >3	HR, 2.15; (1.74, 2.52); (n=7; I^2=0.0%)[a]	HR, 1.89; (1.01, 3.52); (n=4; I^2=73.2%)[a]	HR, 2.14; (1.37, 3.33); (n=3; I^2=39.0%)[a]
Prospective design	HR 1.71 (1.46, 1.99); (n=2; I^2=0.0%)[a]	-	-
Retrospective design	HR 1.85 (1.57, 2.18); (n=12; I^2=23.0%)[a]	HR 1.89 (1.01, 3.52); (n=4; I^2=73.2%)[a]	HR 1.58 (1.30, 1.91); (n=7; I^2=17.6%)[a]
Sample size >300	HR 1.80 (1.51, 2.13); (n=9; I^2=37.3%)[a]	HR 2.29 (0.89, 5.87); (n=2; I^2=72.7%)	HR 1.40 (1.17, 1.70); (n=5; I^2=0.0%)[a]

[a]P<0.05. HR, hazard ratio. Data is presented as pooled effect size (95% confidence interval); (n=total number of studies; I^2).

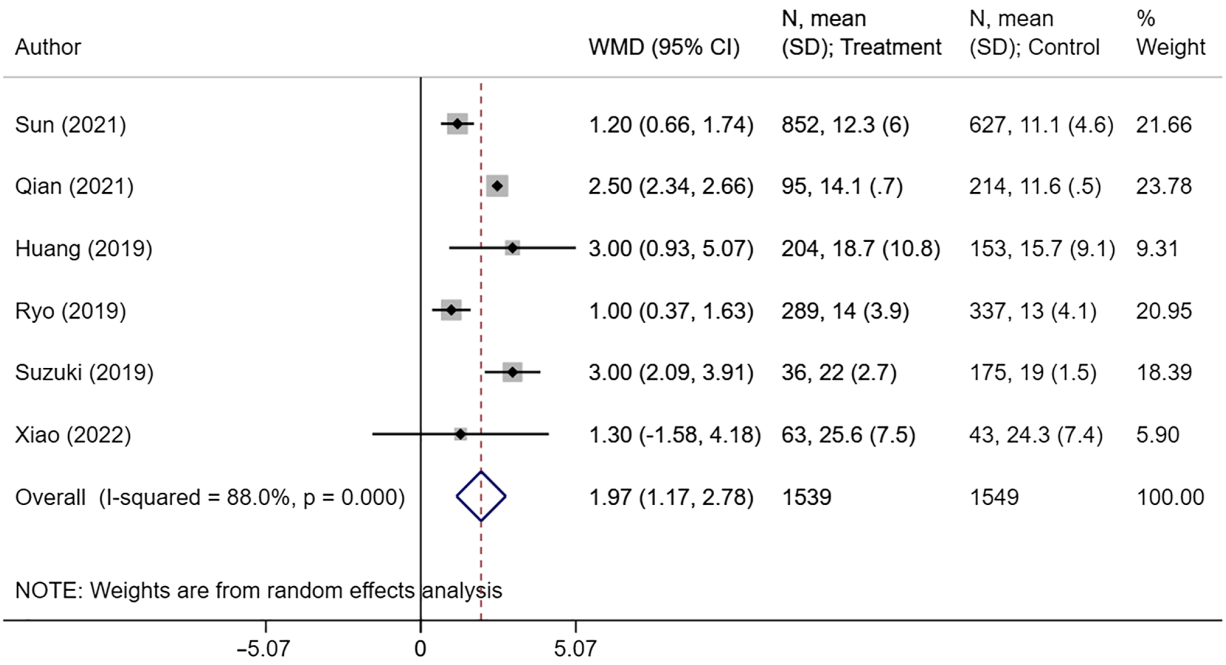

Figure 5. Length of hospital stay (in days) between high and low controlling nutritional status score group. CI, confidence interval; WMD, weighted mean difference.

important variables (possibly certain confounders) may not have been adjusted for in the analysis. Specifically, factors including body mass index and metabolic diseases such as diabetes mellitus have been shown to influence the outcomes in various cancers, including GI cancers (56,57). Additionally, most of the included studies were from Asian countries and consequently, the external validity of the findings remains restricted. This calls for more evidence from developed western settings. Another important limitation is that the studies used different cut-offs to label high and low CONUT scores. This could have led to the heterogeneity noted in certain of the outcomes. Further, large epidemiological studies are needed to carefully define the optimal cut-offs for CONUT scores that effectively predict the prognosis and risk of complication in patients with gastric cancer. Certain studies in the present meta-analysis included patients with gastric adenocarcinoma only, while others had a more heterogeneous population with different histologic types of cancer. Furthermore, the described treatment was also heterogeneous, with patients receiving either total gastrectomy, sub-total/partial gastrectomy, or only chemotherapy. The studies did not provide stratified findings based on these differences i.e., histologic types and treatment offered. This introduced a potential variability in the association of CONUT with prognostic and clinic-pathological outcomes.

In conclusion, the current meta-analysis included a total of 17 studies and reported an increased risk of poor survival outcomes tumor progression, advanced tumor stage, microvascular invasion and post-operative complications in gastric cancer patients with a high CONUT score. The results of the present meta-analysis suggested that in patients diagnosed with gastric cancer, the CONUT score could be an easy-to-use indicator to reflect the nutritional status and may be considered for routine assessment. Additionally, the CONUT score could be helpful as a prognostic biomarker in gastric carcinoma and thereby, aid decision making for appropriate management.

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Availability of data and materials

The datasets generated and/or analyzed during the current study are available in PROSPERO (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021287305), reference no. CRD42021287305.

Authors' contributions

All authors took part in substantial contributions to the study. JY and MW designed the study. JY was the main contributor to the work. JQ and XL participated in the collection and analysis of clinical data. JY was involved in writing the original draft. MW was involved in review and substantial editing of the paper. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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