

Preoperative CONUT and PNI in Relation to Prognosis after Radical Gastrectomy for Gastric Cancer: A Systematic Review and MetaAnalysis

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ADMINISTRATIVE INFORMATION

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INTRODUCTION

Review question / Objective **R** **question:** ****Review** Among adult patients undergoing radical or potentially curative gastrectomy for gastric cancer, are preoperative Controlling Nutritional Status (CONUT) scores and Prognostic Nutritional Index (PNI) values associated with postoperative survival outcomes?

****Objective:**** This systematic review and meta-analysis aims to evaluate the prognostic associations of preoperative CONUT and PNI with overall survival (OS) after gastrectomy for gastric cancer. Secondary objectives are to examine their associations with disease-free survival (DFS), recurrence-free survival (RFS), progression-free

survival (PFS), cancer-specific survival (CSS), and other reported postoperative outcomes.

****PICOS framework:****

- ****Population (P):**** Adults with histologically confirmed gastric cancer undergoing radical or potentially curative gastrectomy.
- ****Intervention/Exposure (I):**** Preoperative CONUT score or PNI, including measurements obtained before neoadjuvant treatment when clearly specified.
- ****Comparator (C):**** High versus low CONUT, low versus high PNI, or continuous nutritional-index values.

- ****Outcomes (O):**** Primary outcome: OS. Secondary outcomes: DFS, RFS, PFS, CSS, and postoperative clinical outcomes.
- ****Study design (S):**** Prospective or retrospective observational studies reporting interpretable prognostic effect estimates, preferably adjusted hazard ratios with 95% confidence intervals.

The review focuses on prognostic associations rather than causal effects, incremental predictive performance, or the effectiveness of nutritional interventions.

Condition being studied Gastric cancer is a major gastrointestinal malignancy and an important cause of cancer-related morbidity and mortality worldwide. Radical gastrectomy remains a cornerstone of potentially curative treatment for patients with resectable gastric cancer. However, postoperative survival varies considerably, even among patients with similar tumour stages, reflecting differences in nutritional status, systemic inflammation, immune function, comorbidities, and treatment-related factors.

Malnutrition and systemic inflammation are common in patients with gastric cancer and may be associated with impaired postoperative recovery and poorer long-term outcomes. The Controlling Nutritional Status (CONUT) score, calculated using serum albumin, total cholesterol, and peripheral blood lymphocyte count, and the Prognostic Nutritional Index (PNI), derived from serum albumin and lymphocyte count, are readily available nutritional and inflammation-related indices.

This review investigates the associations of preoperative CONUT and PNI with overall survival and other postoperative outcomes in patients undergoing radical or potentially curative gastrectomy for gastric cancer. Particular attention is given to differences in study populations, nutritional-index thresholds, perioperative treatment, and adjustment strategies. The review aims to clarify their potential prognostic relevance while recognising that observational associations do not establish causality or clinical benefit from score-guided interventions.

METHODS

Participant or population The review will include adult patients (aged ≥ 18 years) with histologically confirmed gastric adenocarcinoma who underwent radical or potentially curative gastrectomy. Eligible populations may include patients with different tumour stages, older adults, and those receiving

neoadjuvant or perioperative chemotherapy, provided that the timing of CONUT or PNI assessment is clearly defined and relevant prognostic outcomes are reported.

Studies involving mixed gastric and gastroesophageal junction (GEJ) adenocarcinoma populations will be considered when gastric cancer-specific data or an interpretable eligible subgroup can be identified. Studies involving mixed resection curability will be eligible only when outcomes for patients undergoing potentially curative resection can be identified separately or an appropriate eligible estimate is available.

Studies exclusively involving noncurative or palliative surgery, unrelated malignancies without separable gastric cancer data, or nutritional-index measurements obtained exclusively after surgery will be excluded.

Intervention This review evaluates preoperative nutritional and inflammation-related indices as prognostic exposures rather than therapeutic interventions. The primary exposures are the Controlling Nutritional Status (CONUT) score and the Prognostic Nutritional Index (PNI).

CONUT is calculated using serum albumin concentration, total cholesterol concentration, and peripheral blood lymphocyte count, whereas PNI is derived from serum albumin concentration and peripheral blood lymphocyte count.

Eligible studies must assess CONUT or PNI before gastrectomy or, in neoadjuvant treatment cohorts, before the initiation of systemic therapy when measurement timing is clearly defined. Both categorical and continuous nutritional-index measurements will be considered and analysed separately.

The review aims to evaluate the associations of these indices with postoperative survival outcomes rather than the effectiveness of nutritional interventions. No specific treatment or intervention will be administered as part of this systematic review.

Comparator The comparators will be defined according to the nutritional-index assessment methods used in the included studies. For categorical analyses, patients with high preoperative CONUT scores will be compared with those with low CONUT scores, while patients with low preoperative PNI values will be compared with those with high PNI values. Study-specific cut-off

values will be accepted and recorded, including their derivation methods when available.

For continuous analyses, the prognostic associations will be evaluated per unit change in CONUT or PNI, according to the original study definitions. Effect directions will be standardised so that hazard ratios greater than 1 indicate poorer survival associated with an adverse nutritional profile. Continuous and categorical estimates will be analysed separately. No therapeutic comparator is required because this review evaluates prognostic factors rather than treatment interventions.

Study designs to be included Prospective and retrospective observational cohort studies evaluating the associations of preoperative CONUT or PNI with survival outcomes after radical or potentially curative gastrectomy for gastric cancer will be included. Eligible studies must report hazard ratios with 95% confidence intervals or sufficient data for effect estimation. Reviews, meta-analyses, case reports, editorials, animal studies, and studies without interpretable prognostic data will be excluded.

Eligibility criteria Additional eligibility criteria include clearly defined preoperative CONUT or PNI assessment, identifiable measurement timing, and sufficient information to extract or calculate prognostic effect estimates. Studies reporting multivariable-adjusted hazard ratios with 95% confidence intervals will be prioritised. No restrictions will be imposed on publication year or language.

Studies will be excluded if nutritional indices are measured exclusively after surgery, relevant gastric cancer or curative-resection data cannot be separated from mixed populations, or survival associations are not interpretable. Conference abstracts without sufficient quantitative data, duplicate publications, and reports involving overlapping cohorts without independent eligible estimates will also be excluded. When potentially overlapping cohorts are identified, the most appropriate independent estimates will be selected based on population comparability, adjustment quality, and outcome reporting.

Information sources A comprehensive literature search will be conducted in five electronic databases: PubMed/MEDLINE, Embase, Scopus, Web of Science Core Collection, and the Cochrane Central Register of Controlled Trials (CENTRAL), from database inception to July 31, 2026.

Search strategies will combine controlled vocabulary and free-text terms related to gastric cancer, Controlling Nutritional Status (CONUT), and Prognostic Nutritional Index (PNI). No restrictions will be imposed on publication year or language.

Additional relevant studies will be identified through manual screening of reference lists of included articles and relevant systematic reviews. Forward citation tracking will be performed using Scopus and Web of Science. Retrieved records will be imported into reference-management software, and duplicates will be removed through automated identification followed by manual verification.

The complete database-specific search strategies, search dates, and retrieval counts will be documented to ensure transparency and reproducibility.

Main outcome(s) The primary outcome is **overall survival (OS)**², defined as the time from gastrectomy or the study-defined baseline to death from any cause. The review will evaluate the associations of preoperative Controlling Nutritional Status (CONUT) scores and Prognostic Nutritional Index (PNI) values with OS among patients undergoing radical or potentially curative gastrectomy for gastric cancer.

The principal effect measure will be the hazard ratio (HR) with its corresponding 95% confidence interval (CI), prioritising multivariable-adjusted estimates. For categorical analyses, comparisons will be standardised as high versus low CONUT and low versus high PNI, with HRs greater than 1 indicating poorer survival associated with an adverse nutritional profile. Continuous exposure effects will be analysed separately.

OS will be assessed over the follow-up periods reported by individual studies, without imposing a uniform follow-up duration. Differences in follow-up starting points and lengths will be documented and considered when interpreting the findings.

Quality assessment / Risk of bias analysis The methodological quality and risk of bias of included studies will be assessed independently by two reviewers using the Quality in Prognosis Studies (QUIPS) tool², which is specifically designed for prognostic factor research.

Six domains will be evaluated: (1) study participation, (2) study attrition, (3) prognostic factor measurement, (4) outcome measurement, (5) study confounding, and (6) statistical analysis and

reporting. Each domain will be classified as having a low, moderate, or high risk of bias based on predefined criteria and information reported in the original studies.

Particular attention will be given to the adequacy of adjustment for major prognostic factors, including age, tumour stage, comorbidities, and treatment characteristics. Adjustment for postoperative complications or other post-baseline variables will also be examined because these factors may affect the interpretation of preoperative prognostic associations.

Disagreements between reviewers will be resolved through discussion or consultation with a third reviewer. Domain-specific assessments will be presented graphically and summarised in supplementary tables. Sensitivity analyses will be used to examine the potential influence of studies at high risk of confounding bias on the pooled results. No overall numerical quality score will be calculated from the six QUIPS domains.

Strategy of data synthesis Data will be synthesised separately for the Controlling Nutritional Status (CONUT) score and Prognostic Nutritional Index (PNI), with overall survival (OS) as the primary outcome. Multivariable-adjusted hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) will be prioritised. Effect directions will be standardised so that HRs greater than 1 indicate poorer survival associated with high CONUT or low PNI. Continuous and categorical exposure effects will be analysed separately.

Where at least two clinically comparable studies are available, pooled estimates will be calculated using random-effects meta-analysis with restricted maximum likelihood (REML) estimation and Hartung–Knapp adjustment. Statistical heterogeneity will be assessed using Cochran's Q , I^2 , and τ^2 statistics. Prediction intervals will be calculated where appropriate.

Secondary survival outcomes will be synthesised separately when sufficient comparable data are available. Otherwise, findings will be summarised narratively.

Potential small-study effects will be examined using funnel plots. Egger's regression test will be considered when at least ten independent studies are included in a meta-analysis. Statistical analyses will be conducted using R software.

Subgroup analysis Exploratory subgroup analyses will be considered to investigate potential sources of clinical and methodological heterogeneity in the associations between preoperative CONUT or PNI and survival outcomes.

Prespecified subgroup factors will include geographical region, patient age, tumour stage, nutritional-index cut-off values and their derivation methods, perioperative chemotherapy, nutritional-index measurement timing, and surgical curability. Where sufficient data are available, comparisons may also distinguish gastric cancer-only cohorts from mixed gastric/gastroesophageal junction populations.

Subgroup analyses will be conducted separately for CONUT–OS and PNI–OS, provided that each subgroup contains an adequate number of independent studies with consistently reported characteristics. Differences between subgroups will be evaluated using appropriate statistical tests rather than comparisons of within-subgroup significance alone.

Meta-regression will be considered only when the number of studies and the completeness of moderator information are sufficient. Where quantitative subgroup analyses are not feasible, potential sources of heterogeneity will be discussed descriptively. All subgroup findings will be regarded as exploratory.

Sensitivity analysis Sensitivity analyses will be performed to evaluate the robustness of the primary CONUT–OS and PNI–OS associations.

First, leave-one-out analyses will sequentially exclude individual studies to assess their influence on pooled HRs, 95% CIs, and heterogeneity statistics.

Second, studies classified as having a high risk of bias in the QUIPS study confounding domain will be excluded in separate sensitivity analyses to evaluate the potential influence of inadequate confounding adjustment.

Third, sensitivity analyses will examine the influence of selected prognostic models incorporating postoperative complications, postoperative treatment, or other post-baseline covariates.

Fourth, the potential effects of clinically heterogeneous populations, including mixed gastric/gastroesophageal junction cohorts, elderly or stage-restricted populations, perioperative

chemotherapy cohorts, and studies with uncertain resection curability, will be considered.

Additional influence analyses may examine studies with small sample sizes, unusually large effect estimates, potentially overlapping cohorts, or uncertain effect-estimate precision. Exclusion criteria will be defined independently of the resulting pooled associations.

All quantitative sensitivity analyses will use the same effect-direction standardisation and random-effects framework as the primary analyses. Where reliable quantitative assessment is not possible, the corresponding methodological limitations will be discussed descriptively.

Country(ies) involved China. The study is being conducted by researchers affiliated with academic and clinical institutions in China.

Keywords Gastric cancer; Controlling Nutritional Status; CONUT; Prognostic Nutritional Index; PNI; overall survival; prognosis; systematic review; metaanalysis.

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