

RESEARCH ARTICLE

Tumor Markers and Signatures

Impact of prognostic nutritional index on oncological outcomes and mortality among advanced gastric cancer patients: European GASTRODATA registry analysis

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Abstract

While Prognostic Nutritional Index (PNI) is an established predictor of outcomes in Asian gastric cancer (GC) patients, data among Western populations are limited. This study assessed the predictive value of PNI in European GC patients undergoing multimodal treatment. Data from GASTRODATA, the largest European repository of GC patients undergoing gastrectomy, were collected between 2017 and 2022. The primary outcome was textbook outcome (TO) achievement, and the secondary was 90-day mortality. PNI was calculated one day before surgery, with a cut-off of 45.5 based on ROC analysis. Among 721 patients included 60.7% were men. Most patients had advanced tumors (cT3-4 = 75.2%) and metastatic lymph nodes (57.7%). Neoadjuvant chemotherapy (NAC) was administered to 46.7% of patients, and 32.9% received adjuvant chemotherapy. Median PNI was 49.5 (IQR 45.0–56.4). Low PNI was present among 30% of patients and was associated with decreased odds of TO achievement (OR = 0.57, 95% CI 0.37–0.89), higher 90-day mortality (OR = 4.99, 95% CI 2.32–10.73). NAC administration was associated with lower morbidity risk (OR = 0.56, $p = 0.0408$), and low PNI was a predictor of receiving AC ($p = 0.0005$). PNI was a valuable predictor for oncological outcomes and morbidity among European GC patients undergoing multimodal.

Abbreviations: AC, Adjuvant Chemotherapy; AJCC, American Joint Cancer Committee; ASA, American Society of Anesthesiologists; ASPEN, American Society for Parenteral and Enteral Nutrition; BMI, Body Mass Index; CCI, Comprehensive Complication Index; CDC, Clavien-Dindo Classification; CI, Confidence Interval; DUCA, Dutch Upper Gastrointestinal Cancer Audit; EGCA, European Gastric Cancer Association; ESPEN, European Society for Clinical Nutrition and Metabolism; GC, Gastric Cancer; GLIM, Global Leadership Initiative on Malnutrition; HIPEC, Hyperthermic Intraperitoneal Chemotherapy; ICU, Intensive Care Unit; IQR, Interquartile Range; LN, Lymph Node; LOS, Length of Hospital Stay; NAC, Neoadjuvant Chemotherapy; OR, Odds Ratio; OS, Overall Survival; PNI, Prognostic Nutritional Index; ROC, Receiver Operating Characteristic; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology; TO, Textbook Outcome.

For affiliations refer to page 9

While low PNI was associated with decreased odds of TO achievement and increased risk of 90-day mortality, further prospective and nutritional intervention studies are warranted to standardize the PNI threshold and improve its clinical applicability.

KEYWORDS

biomarker, gastric cancer, multimodal treatment, prognostic nutritional index, textbook outcome

What's New?

Prognostic nutritional index (PNI), which relies on peripheral lymphocyte counts and serum albumin levels, is a validated marker of nutritional and inflammatory status. However, while an established predictor of morbidity following gastrectomy, the relevance of PNI in predicting gastric cancer outcome and mortality remains unknown. The present study evaluated PNI in European patients with advanced gastric cancer who underwent multimodal treatment. Low PNI was found to be strongly associated with increased 90-day mortality and adverse postoperative outcomes. The findings warrant further investigation of PNI for identifying gastric cancer patients who may benefit from individualized preoperative nutritional interventions.

1 | INTRODUCTION

Despite a substantial decrease in gastric cancer (GC) incidence, the global estimate for new cases in 2020 exceeded one million.¹ Despite advancements in disease control, the International Cancer Benchmarking Project highlighted the need for timely treatment and assessment of comorbidities to enhance prognosis and treatment outcomes among GC patients.² In the locally advanced setting (cT2-4N0-3M0), the gold standard of GC treatment is multimodal therapy, which includes perioperative chemotherapy and gastrectomy with adequate lymphadenectomy.^{3,4} While the introduction of systemic treatment has improved survival, surgery remains the mainstay of curative-intent treatment.³⁻⁵

To assess the quality of gastrectomy among GC patients in Europe, the GASTRODATA project was initiated by experts from the European Gastric Cancer Association (EGCA). As the most extensive data repository of GC patient morbidity in Europe, the initiative developed a classification of intra- and post-operative complications.^{6,7} To provide an overall reflection of surgical quality, the composite metrics are increasingly implemented in multimodal cancer care.⁸ Recently, Textbook Neoadjuvant Outcome (TNO) was introduced to evaluate preoperative care.⁹ By integrating multidisciplinary components, such as laboratory tests and nutrition, TNO provides a holistic benchmark to predict postoperative outcomes and optimize patients before surgery. Building upon the concept of comprehensive evaluation, Textbook Outcome (TO) has been widely adopted to assess the quality of surgical outcomes in the postoperative phase.¹⁰ Initially introduced in colorectal cancer surgery, TO has been increasingly adopted across various surgical disciplines to provide a comprehensive assessment of surgical quality.⁸ In GC surgery, achieving TO—which encompasses factors such as the absence of postoperative complications and no mortality—has been associated with improved overall survival (OS).^{11,12} TO enables benchmarking of surgical performance and identification of areas for quality improvement.¹⁰ Given the granularity of the GASTRODATA database, there is increased interest

in assessing TO among locally advanced GC patients undergoing multimodal treatment.¹²

The European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines underscore the importance of routine pre-treatment nutritional assessments, emphasizing the need for complementary diagnostic tools.^{13,14} Four decades ago, Prognostic Nutritional Index (PNI) was proposed, comprising peripheral lymphocyte counts and serum albumin levels to reflect both nutritional and inflammatory status.^{13,14} PNI improves individual risk stratification and is an established predictor of morbidity following gastrectomy.¹⁵⁻¹⁷

Although PNI cut-offs vary between studies, patients with low PNI exhibit a poorer postoperative course and decreased long-term treatment outcomes.^{18,19} However, validation of PNI has been predominantly focused on Asian populations, with a notable absence of multi-institutional reports from European centers.²⁰ The gap in data on the applicability and impact of PNI across diverse ethnic groups and geographical regions has limited the broader utility of PNI in a global context.

Therefore, the objective of the current study was to explore the predictive role of nutritional status assessment among European GC patients undergoing multimodal treatment based on the GASTRODATA registry. Secondly, we sought to evaluate the association between PNI and TO achievement after curative-intent surgery.

2 | METHODS

2.1 | Study participants, outcomes and definitions

An observational retrospective cohort study was conducted based on the GASTRODATA registry analysis. The dataset was originally designed to collect data on complications from referral centers in 11 European countries between 2017 and 2022.⁶ The study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.²¹

The study enrolled cT2-4N0-3M0 GC patients according to the 8th edition of the American Joint Cancer Committee (AJCC) staging system.²² All included patients underwent curative-intent surgical treatment. Exclusion criteria comprised individuals with non-adenocarcinoma neoplasm, individuals with incomplete clinical or pathological data on staging, TO features, NAC administration, and PNI, as well as patients who underwent HIPEC.

The primary outcome of the study was TO achievement, defined according to the proposition of Dutch Upper Gastrointestinal Cancer Audit (DUCA)^{23,24} as a composite of 10 features: (1) curative-intent resection, (2) absence of intraoperative complications, (3) microscopically radical resection, (4) retrieval and examination of at least 15 LNs, (5) no severe postoperative complications, (6) no reintervention within the 30-day post-surgery, (7) no readmission to Intensive Care Unit (ICU) within 30 days after surgery, (8) length of hospital stay (LOS) not exceeding 21 days, (9) no mortality within 30 days post-surgery, and (10) no hospital readmission within 30 days after discharge.

Postoperative complications were assessed relative to occurrence and severity using the Clavien-Dindo classification (CDC) (severe complications defined as > grade II) and the Comprehensive Complication Index (CCI, severe complications defined as >30).²⁵⁻²⁷ Complications were defined according to Incidence and Grading of Complications After Gastrectomy for Cancer, which encompasses 27 complications categorized into three intraoperative, 14 general and 10 surgical postoperative groups.^{6,7} The secondary outcome was 90-day mortality, defined as death within 90 days after surgery, whether as inpatient or outpatient.

2.2 | Data Collection and PNI Assessment

Data were collected on patient characteristics (age, gender), body mass index (BMI), tumor location and size, clinical and pathological stage of the disease based on the 8th AJCC Manual,²² CCI, and CDC classifications, receipt of neoadjuvant and adjuvant chemotherapy, American Society of Anesthesiologists (ASA) classification, type of gastrectomy, surgical approach, resection margin status, number of harvested LNs, and LOS. Preoperative laboratory measurements and blood samples were collected after the patient's admission to the hospital, 1–2 days prior to the date of surgery.

PNI was calculated as the product of “ $10 \times \text{albumin [g/dL]} + 0.005 \times \text{total lymphocyte [count/mm}^3\text{]}^2$ ” multiplication.¹⁵ PNI was assessed as high and low based on the calculated cut-off value of 45.5 (AUC 0.73) with 72% sensitivity and 74% specificity. The cut-off value of 45.5, determined using receiver operating characteristic (ROC) analysis and the Youden Index, was used to categorize PNI as high or low (AUC 0.73, sensitivity 72%, specificity 74%).

2.3 | Statistical analysis

Statistical analyses were conducted using Stata/BE 18.0. Due to non-normal data distribution (assessed by the D'Agostino-Pearson test),

data were presented using median and interquartile range (IQR) or minimum–maximum range. Categorical or dichotomized variables were presented as numbers and percentages. Mann–Whitney *U* test (for two independent groups) or ANOVA Kruskal–Wallis (for more than two independent groups) was used to compare PNI values based on demographic and clinical variables. Spearman rank correlation test assessed correlation between PNI and other variables.

Univariable analysis of the influence of demographic and clinical variables on the odds of TO achievement, risk of 90-day mortality, and postoperative complications was based on the calculation of odds ratios (OR) and corresponding 95% confidence intervals (CI). On multivariable analysis, the influence of demographic and clinical variables on the odds of TO achievement, risk of 90-day mortality, and postoperative complications was assessed using logistic regression models (including calculation of OR and corresponding 95% CI). The backward elimination method was used to indicate which variables should be included in multivariable analyses. American Society of Anesthesiologists (ASA) physical status, tumor site, pathological tumor (pT) stage, NAC, and PNI were used for adjustment in the multivariable analysis of postoperative complication risk. Age, ASA, tumor site, surgical procedure, lymphadenectomy, and PNI were included in the multivariable analysis assessing achievement of TO. Age, pathological nodal (pN) stage, and PNI were used in the multivariable analysis for the adjustment of the risk of 90-day mortality. Two-sided tests were used for all analyses, and statistical significance was defined as a *p*-value below 0.05.

3 | RESULTS

3.1 | Baseline characteristics of the study group

Among 2558 patients included in the GASTRODATA registry, 721 patients were found eligible for the analysis (detailed inclusion criteria are presented in Figure S1). In the analyzed cohort, 70% of the study group ($n = 510$) had high PNI, with a median of 49.5 (IQR 45.0–56.4). The majority of individuals had advanced tumors (cT3–53.3%; cT4–21.9%), whereas LN involvement was observed among 57.7% of patients. Neoadjuvant chemotherapy (NAC) was administered in 46.7% of cases, while adjuvant chemotherapy was administered to 32.9% of patients. The baseline characteristics of the study group are presented in Table 1.

3.2 | Influence of the selected demographic and clinical variables on the odds of TO achievement

The univariable analysis demonstrated that several factors were significantly associated with lower odds of achieving TO. Elderly patients (OR = 0.62), those with higher ASA (OR = 0.56), tumors located in the lower regions (L, M: OR = 0.43), a higher ypT stage (OR = 0.59), TG (OR = 0.46), and a low PNI ≤ 45.5 (OR = 0.48) were associated with decreased odds of TO achievement. Conversely, factors

TABLE 1 Baseline characteristics of the study group.

Variable	Study group [n = 721]
Gender	
Female	283 (39.3%)
Male	438 (60.7%)
Age [years]	
Median [IQR]	70 [61.0–78.0]
<75	478 (66.3%)
≥75	≥75
BMI	
Median [IQR]	24.8 [22.6–27.4]
Underweight	26 (4%)
Normal weight	306 (46.9%)
Overweight	320 (49.1%)
PNI	
Median [IQR]	49.5 [45.0–56.4]
ASA classification	
1	57 (8.2%)
2	400 (57.3%)
3	227 (32.5%)
4	14 (2%)
cT	
cT2	179 (24.8%)
cT3	384 (53.3%)
cT4	158 (21.9%)
cN	
cNx	46 (6.4%)
cN–	259 (35.9%)
cN+	416 (57.7%)
cM	
cM0	721 (100%)
(y)pT	
pT0	23 (3.22%)
pT1	130 (18%)
pT2	109 (15.1%)
pT3	245 (34%)
pT4	214 (29.6%)
(y)pN	
pN0	287 (39.8%)
pN1	144 (20%)
pN2	116 (16.1%)
pN3	174 (24.1%)
NAC	
Yes	337 (46.7%)
No	384 (53.3%)
AC	
Yes	222 (32.9%)
No	452 (67.1%)

(Continues)

TABLE 1 (Continued)

Variable	Study group [n = 721]
Surgery type	
TG	378 (52.67%)
PG	9 (1.3%)
DG	331 (46.1%)
Surgical approach	
Laparoscopy	164 (22.7%)
Open	548 (76%)
Robotic	9 (1.2%)
Resection margin	
R0	679 (94.2%)
R1	36 (5%)
R2	6 (0.8%)
Lymphadenectomy	
D1	115 (16%)
D2	600 (84%)
CCI	
Median [IQR]	0 [0.0–20.9]
LN removed	
Median [IQR]	35.8 [24.0–47.0]
Hospital LOS [days]	
Median [IQR]	8 [7.0–13.0]
Postoperative complications	
Yes	86 (11.9%)
No	635 (88.1%)
30-day mortality	
Yes	14 (1.9%)
No	707 (98.1%)
90-day mortality	
Yes	23 (3.2%)
No	698 (96.8%)

Abbreviations: AC, adjuvant chemotherapy; ASA, American Society of Anesthesiologists Physical Status; CCI, comprehensive complication index; IQR, interquartile range; LN, lymph nodes; LOS, length of stay; NAC, neoadjuvant chemotherapy; PG, proximal gastrectomy; PNI, prognostic nutritional index; POC, perioperative chemotherapy; DG, distal gastrectomy; TG, total gastrectomy.

associated with higher odds of achieving TO included NAC administration (OR = 1.40, $p = 0.0403$) and the performance of D2 lymphadenectomy (OR = 2.10, $p = 0.0004$).

On the multivariable analysis, factors associated with reduced TO achievement included age ≥ 75 (OR = 0.68), higher ASA (OR = 0.60), lower tumor location (OR = 0.56), TG (OR = 0.56), and low PNI (OR = 0.57). On the other hand, the odds of achieving TO were notably higher in patients who underwent D2 lymphadenectomy (OR = 1.79). Detailed results regarding the influence of selected demographic and clinical variables on the chance of TO achievement are presented in Table 2.

TABLE 2 Influence of the selected demographic and clinical variables on the odds of TO achievement.

Variable	TO		Univariable	Multivariable
	No	Yes	OR [95%CI] <i>p</i>	OR [95%CI] <i>p</i>
Gender				
Male	135 (30.8%)	303 (69.2%)	0.85 [0.61–1.18]	0.90 [0.61–1.31]
Female	78 (27.6%)	205 (72.4%)	0.3490	0.5653
Age				
≥75	88 (36.2%)	155 (63.8%)	0.62 [0.45–0.87]	0.68 [0.45–1.00]
<75	125 (26.2%)	353 (73.8%)	0.0053*	0.0548
BMI				
Underweight	8 (30.8%)	18 (69.2%)	0.94 [0.40–2.19]	1.44 [0.54–3.86]
Normal weight, overweight	184 (29.4%)	442 (70.6%)	0.8801	0.4642
ASA				
3,4	90 (37.3%)	151 (62.7%)	0.56 [0.40–0.78]	0.60 [0.41–0.89]
1,2	114 (24.9%)	343 (75.1%)	0.0007*	0.0101*
Tumor site				
L, M	120 (24.4%)	371 (75.6%)	0.43 [0.30–0.62]	0.56 [0.36–0.88]
U	76 (42.7%)	102 (57.3%)	<0.0001*	0.0114*
ypT				
pT3, pT4	153 (33.3%)	306 (66.7%)	0.59 [0.42–0.84]	0.81 [0.55–1.20]
<pT3	60 (22.9%)	202 (77.1%)	0.0033*	0.2883
ypN				
pN+	136 (31.3%)	298 (68.7%)	0.80 [0.58–1.12]	0.90 [0.62–1.31]
pN–	77 (26.8%)	210 (73.2%)	0.1945	0.5853
NAC				
Yes	87 (25.8%)	250 (74.2%)	1.40 [1.02–1.94]	1.32 [0.86–2.02]
No	126 (32.8%)	258 (67.2%)	0.0403*	0.1979
Surgical approach				
Open	168 (30.7%)	380 (69.3%)	0.80 [0.54–1.69]	1.02 [0.65–1.59]
MIS	45 (26.0%)	128 (74.0%)	0.2436	0.9272
Surgical procedure type				
TG	139 (36.8%)	239 (63.2%)	0.46 [0.33–0.65]	0.56 [0.36–0.86]
DG or PG	72 (21.2%)	268 (78.8%)	<0.0001*	0.0082*
Lymphadenectomy				
D2	161 (26.8%)	439 (73.2%)	2.10 [1.39–3.16]	1.79 [1.11–2.88]
D1	50 (43.5%)	65 (56.5%)	0.0004*	0.0167*
PNI				
Low	86 (40.8%)	125 (59.3%)	0.48 [0.34–0.68]	0.57 [0.39–0.84]
High	127 (24.9%)	383 (75.1%)	<0.0001*	0.0043*

Abbreviations: ASA, American Society of Anesthesiologists; CI, confidence interval; DG, distal gastrectomy; L, lower; M, middle; MIS, minimally invasive; NAC, neoadjuvant chemotherapy; OR, odds ratio; PG, proximal gastrectomy; PNI, prognostic nutritional index; TG, total gastrectomy; TO, textbook outcome; U, upper; *, statistical significance.

3.3 | Diagnostic Usefulness of PNI as Predictor of Textbook Outcome and Mortality

PNI demonstrated a sensitivity of 76% and specificity of 39.9% to predict TO (cut-off point: >45.5; AUC = 0.58, 95%CI: 0.55–0.62;

$p = 0.0005$; Figure 1A) and a sensitivity of 72% and a specificity of 74% to predict 90-day mortality (cut-off point: ≤ 45.5 ; AUC = 0.73, 95% CI: 0.69–0.76; $p = 0.0001$; Figure 1B).

In contrast, low PNI was related to an increased risk of postoperative complications (OR = 1.79), unplanned ICU admissions

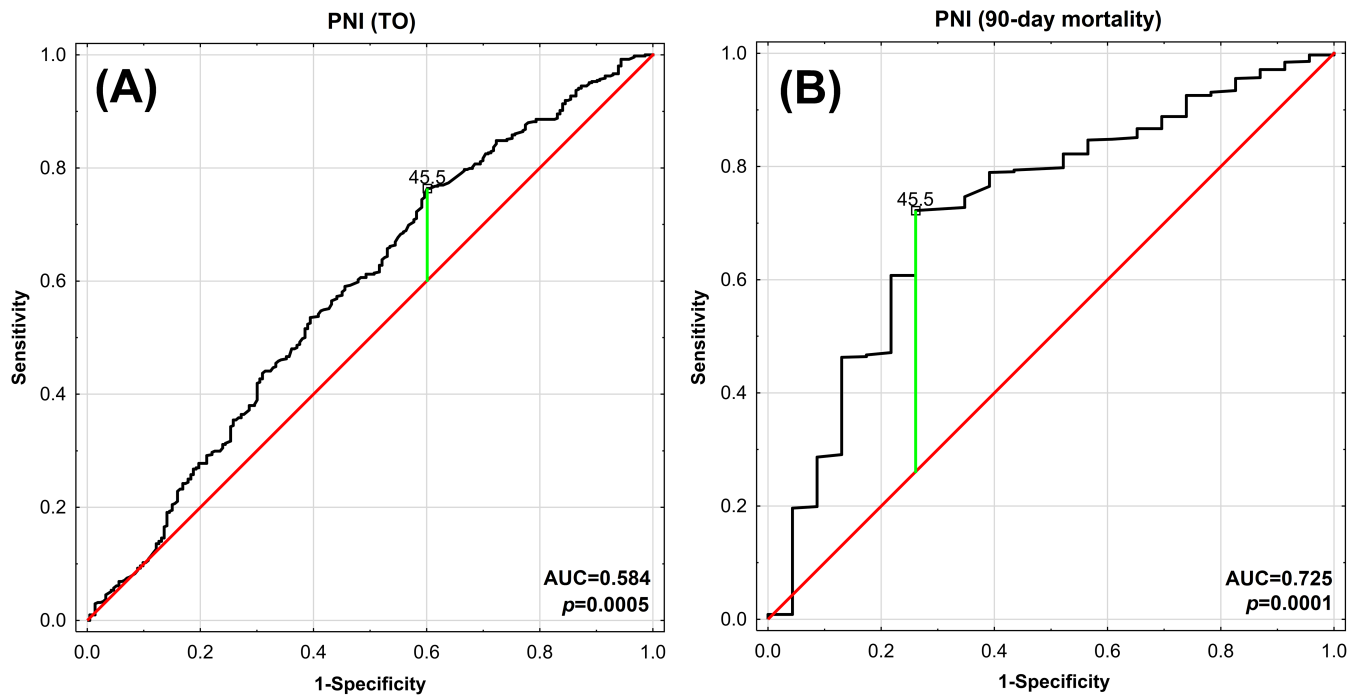


FIGURE 1 ROC curves demonstrating diagnostic usefulness of PNI in predicting TO achievement (A) and 90-day mortality (B). [Color figure can be viewed at wileyonlinelibrary.com]

(OR = 3.44), prolonged LOS (OR = 1.91) and 30-day mortality (OR = 3.31).

On multivariable analysis, low PNI remained associated with a reduced odds of harvesting ≥ 15 LNs (OR = 0.36), an unplanned ICU admission (OR = 3.08), and prolonged hospital LOS (OR = 1.73) (Figure 2). Although low PNI was associated with a higher risk of postoperative complications (OR = 1.71, 95% CI 1.16–2.53), there were no significant differences in the incidence of specific types of postoperative complications based on PNI either in uni- or multivariable analysis. Detailed data were provided in Tables S1 and S2. On multivariable analysis, low PNI was associated with decreased odds of achieving TO (OR = 0.57, 95% CI 0.37–0.89) and an increased risk of 90-day mortality (OR = 4.99, 95% CI 2.32–10.73) (Figure 2).

3.4 | Correlation between PNI and demographic and clinical variables

Among the demographic and clinical variables, the strongest negative correlations were noted between PNI and (y)pN and (y)pT stages ($\rho = -0.189$, $p < 0.0001$ and $\rho = -0.163$, $p < 0.0001$, respectively). Moderately strong correlations were noted between the CCI ($\rho = -0.141$, $p = 0.0001$) and hospital LOS ($\rho = -0.185$, $p < 0.0001$) (Figures 3 and 4). A weak negative correlation was observed between PNI and age ($\rho = -0.132$), ASA ($\rho = -0.125$), and cT stage ($\rho = -0.074$). Notably, a weak positive correlation was observed between PNI and both the extent of lymphadenectomy ($\rho = 0.092$) and the number of resected LN ($\rho = 0.099$). No

significant correlation was noted between PNI and BMI. Detailed data regarding correlations between PNI and demographic and clinical variables are presented in Tables S3 and S4.

4 | DISCUSSION

As the landscape of tailored systemic treatment for GC evolves, the focus on surgical development shifts towards delivering more robust and comprehensive care.^{28,29} Among the crucial factors is nutritional condition, as malnourished GC patients exhibit poorer treatment adherence and decreased tumor response to chemotherapy.³⁰ To support successful multimodal management, ESPEN guidelines highlight the importance of the nutritional status assessment before treatment initiation.¹³ For patients classified as being at severe risk of malnutrition, nutritional intervention is prioritized regardless of possible delay of gastrectomy.¹⁴ In 2019, Global Leadership Initiative on Malnutrition (GLIM) published criteria on malnutrition screening and diagnosis.³¹ Although consensus has been reached, the recommendations highlighted the need for further initiatives evaluating complementary nutritional assessment tools. Preoperative PNI assessment mirrors the immune-nutritional patient's condition, serving as an important marker of inflammation and increased energy requirement.^{32,33} The current study represents the first large European analysis assessing PNI as a predictive marker among locally advanced GC patients. The results demonstrated high PNI among 70% of patients with a median of 49.5. Previous studies showed high PNI was associated with normal nutritional status, while low PNI represented malnutrition.³⁴

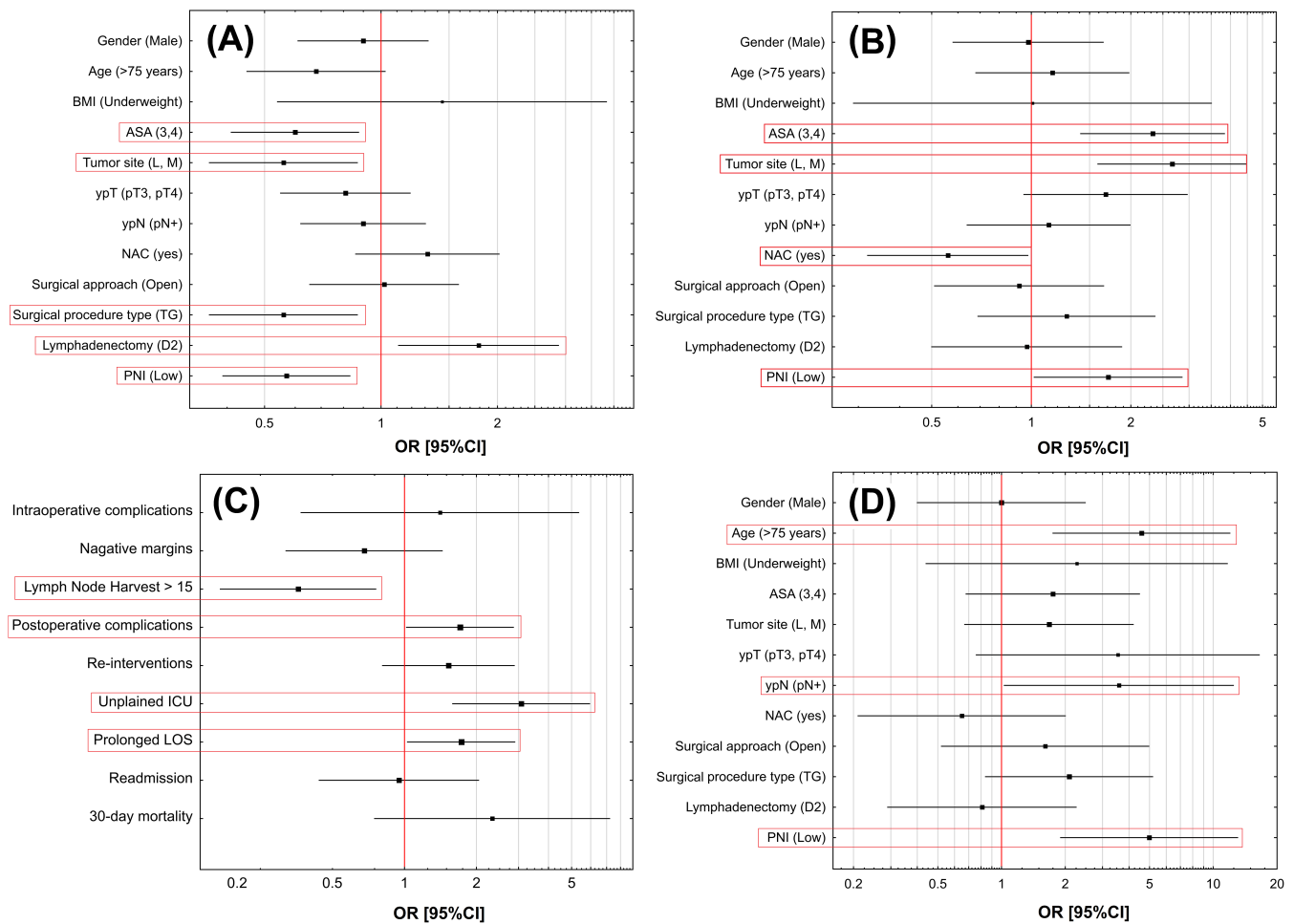


FIGURE 2 Forest plot presenting multivariable analysis of the: Chance of TO achievement (A), risk of postoperative complications (B), and risk of 90-day mortality (D). Association between PNI and chance of achieving selected TO features (C). [Color figure can be viewed at wileyonlinelibrary.com]

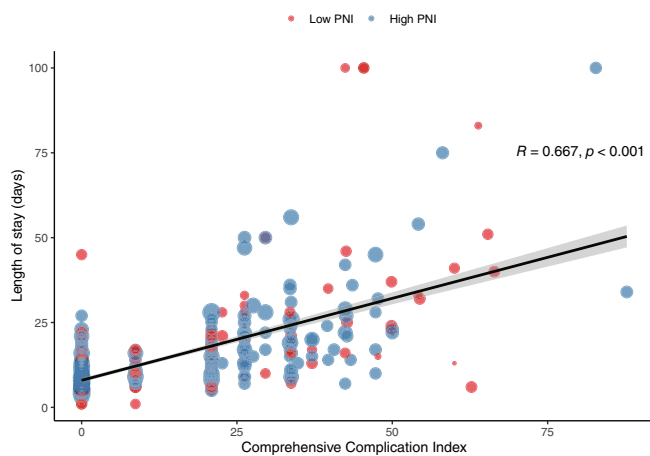


FIGURE 3 Scatter diagram presenting the correlations between CCI and PNI, and LOS and PNI. The figure illustrates the correlation between low PNI and increased morbidity following gastrectomy. The box-and-whisker plots for the CCI indicate that patients with low PNI experienced more severe postoperative complications compared to those with high PNI. Similarly, patients with low PNI had a longer median hospital stay, reflecting a prolonged recovery period. [Color figure can be viewed at wileyonlinelibrary.com]

In the meta-analysis of malnutrition markers among cancer patients, PNI has been highlighted as one of four objective indexes associated with improved OS (HR = 1.89, 95% CI 1.03–3.48).³² However, among 14,403 GC patients evaluated for preoperative PNI as a survival prognosticator and outcomes predictor, only one report came from Europe. This previous investigation aimed to evaluate the role of inflammatory markers to predict long- and short-term outcomes after gastrectomy. However, based on the sample size of 102 patients, it failed to prove PNI was related to OS and disease-free survival (DFS). Although long-term survival was not assessed in this study, our findings demonstrated that low PNI was associated with a higher odd of 30- and 90-day mortality (OR = 3.31 and OR = 4.99, respectively), consistent with reports from high-volume Japanese centers.^{15,16} Nevertheless, prospective validation of PNI utility is essential. The ongoing MOONRISE study (NCT05723718), initiated by the Medical University of Lublin and conducted in a multicenter European setting, is designed to evaluate nutritional status and body composition changes at each stage of multimodal treatment. This study aims to assess the role of nutritional indices, including PNI, in predicting tumor response, treatment toxicity, and survival outcomes to provide robust data to

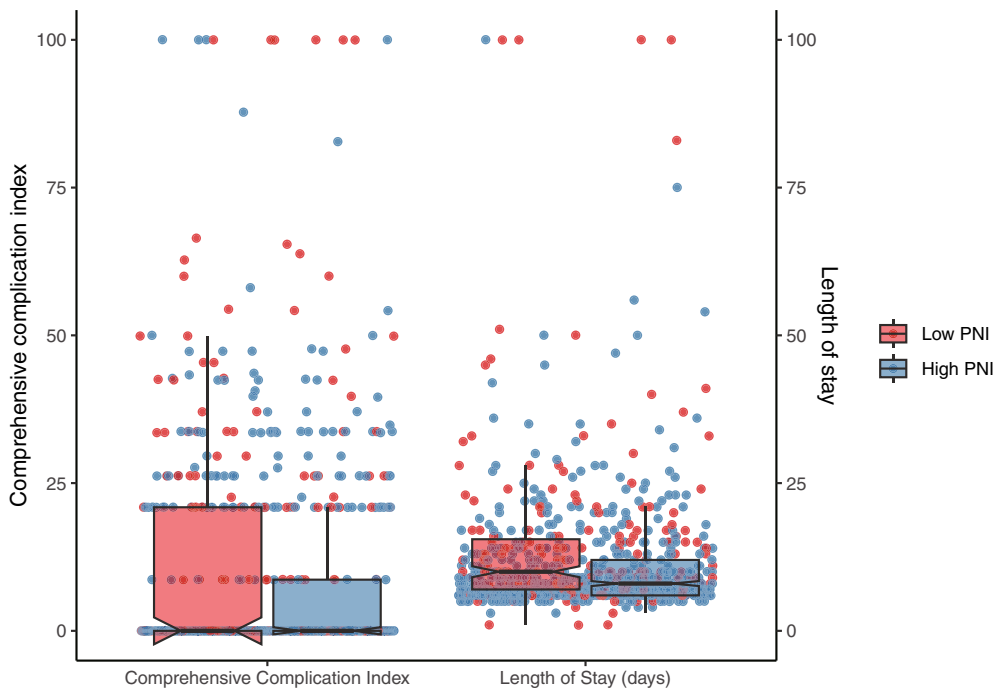


FIGURE 4 Scatter diagram representing a strong positive correlation between increased CCI, prolonged LOS, and PNI. [Color figure can be viewed at wileyonlinelibrary.com]

refine PNI thresholds and support its integration into clinical practice.³³

As a complex procedure, gastrectomy is associated with a significant risk of morbidity, reported to range from 10% to 46%.^{35,36} To identify areas for improvement, surgical composite parameters like TO have been introduced. As an “all-or-none” parameter, its achieving is associated with improved short- and long-term prognosis among GC patients.³⁷ In a European population analysis, 68.5% of individuals achieved TO. Among those who did not, postoperative complications and LOS were the most frequent reasons for noncompliance, occurring in 12.4% and 11.8% of cases, respectively.¹² Implementing PNI could improve surgical risk stratification. This study's findings indicate that a low PNI was significantly associated with a higher likelihood of not achieving TO (OR = 0.57, 95% CI 0.37–0.89), suggesting that patients with low PNI are at higher risk of eventful postoperative courses. Additionally, low PNI was associated with longer hospital stay (OR = 1.91), higher incidence of postoperative complications (OR = 1.71, 95% CI 1.16–2.53), and greater severity of complications ($\rho = -0.141$, $p = 0.0001$), underscoring the predictive value of PNI in postoperative outcomes. Interestingly, while the median of resected LN in the study cohort was 35 (IQR = 24.0–47.0), patients with low PNI had reduced odds of undergoing adequate lymphadenectomy (OR = 0.36), which may impact oncological outcomes. Although this may be related to higher age and increased ASA scores, preoperative PNI evaluation could help identify patients who require additional, individualized dietary support to optimize guideline-adherent treatment.

Designing the most optimal nutritional intervention for GC patients is the subject of many randomized controlled trials^{38–40}

and the recommended approach is yet to be established. The *American Society for Parenteral and Enteral Nutrition* (ASPEN) advocates for preoperative immune-nutrition supplementation⁴¹ while ESPEN does not definitively support their use over standard oral agents.¹⁴ The meta-analysis of immune-modulating supplementation among gastrointestinal cancer patients reported a 5-day preoperative intervention leading to decreased morbidity and LOS.⁴² However, GC patients are especially vulnerable to malnutrition, with almost 30% being diagnosed with sarcopenia before NAC initiation.⁴³ Although perioperative chemotherapy is the gold standard, in the current study, only 46.7% and 32.9% of patients received NAC and AC, respectively.³ To improve execution of the curative-intent treatment plan, dietary intervention before NAC initiation might be necessary.⁴⁴ Evidence suggests that patients who are adequately prepared for preoperative chemotherapy tend to experience improved postoperative outcomes defined by TO achievement¹² and an uneventful postoperative course (OR = 0.56, $p = 0.0408$). However, further research is required to establish the optimal nutritional strategies for GC patients, particularly in the context of multimodal treatment.⁴⁵

Despite PNI being introduced over four decades ago, the heterogeneity of cutoff values remains a matter of debate.^{20,32,46} Initially, thresholds of <40 and <45 were suggested to predict the risk of surgical complications.³² However, a meta-analysis examining the relationship between preoperative PNI and clinicopathological outcomes demonstrated that the cutoff values ranged from 40 to 52.²⁰ Employing various methodologies, 32% of the 25 included studies set the threshold at 45. In the secondary analysis of the rD-FLAP study (outcomes evaluation following proximal gastrectomy with esophagogastrostomy by the double-flap

technique), the cut-off value for PNI was determined to be <45 and ≥ 45 .¹⁵ As this threshold was applied from previous reports, the rD-FLAP results confirmed that preoperative PNI <45 was a poor prognostic factor for overall survival (HR = 3.59, 95% CI: 1.93–6.67). The current study identified a cut-off point of 45.5, determined by the *Youden Index* from the ROC analysis, which demonstrated the predictive power of PNI for TO achievement (AUC = 0.58) and 90-day mortality (AUC = 0.73). However, to translate this finding into routine clinical practice, the proposed cutoff should be validated on a large prospective cohort.

The study has several limitations that need to be considered. First, the retrospective design limited the possibility to reassess the PNI after the surgery to evaluate trends and changes in PNI during multimodal treatment. Nevertheless, the preoperative assessment seems to present higher predictive value compared with postoperative evaluations.¹⁶ Second, the studied cohort might be considered heterogeneous, with half of the study group omitting NAC. While the use of perioperative chemotherapy remains still insufficient, there is an encouraging global trend toward increasing adherence to multimodal treatment.⁴⁷ Third, the PNI cutoff (45.5) determined by ROC analysis showed moderate discriminative ability for predicting TO (AUC = 0.58). While statistically significant, PNI should be interpreted within a broader clinical context rather than as a standalone predictor. Notably, its stronger performance in predicting 90-day mortality (AUC = 0.73) underscores its utility for early postoperative risk assessment. Next, dichotomizing continuous variables like PNI using ROC-derived cutoffs might lead to a loss of statistical power and may not fully account for confounding factors. However, this method is widely accepted in clinical research for its simplicity and practicality in stratifying patient risk groups.⁴⁸ The ancillary nature of the study, the exclusion of cT1 patients due to the lack of perioperative chemotherapy recommendations, and the unavailability of PNI reports from certain institutions may have contributed to the notable number of missing values and the dropout rate. Furthermore, as the GASTRODATA registry was designed primarily to report the morbidity,⁶ missing data were observed for variables such as BMI (9.6%) and ASA classification (3.2%) and there is no assessment of long-term survival. Although the current findings cannot yet be directly translated into clinical practice this study represents the first large-scale evaluation of PNI as a predictive factor among European GC patients.

In conclusion, PNI was a valuable predictor for oncological outcomes and morbidity among European GC patients undergoing multimodal curative-intent treatment. While low PNI was associated with decreased odds of TO achievement and increased risk of 90-day mortality, further prospective large-scale and nutritional intervention studies are warranted to standardize the PNI threshold and improve its clinical applicability as well as surgical outcomes following oncologic surgery.

AUTHOR CONTRIBUTIONS

Zuzanna Pelc: Conceptualization; methodology; writing – review and editing; writing – original draft; investigation. **Katarzyna Sędkak:**

Conceptualization; writing – original draft; methodology; data curation. **Radosław Mlak:** Conceptualization; data curation; methodology; investigation; writing – original draft; visualization. **Yutaka Endo:** Conceptualization; project administration; methodology; writing – review and editing; visualization; formal analysis. **Ines Gockel:** Conceptualization; writing – review and editing; methodology; data curation; supervision. **Johanna van Sandick:** Conceptualization; methodology; writing – review and editing; supervision. **Gian Luca Baiocchi:** Supervision; methodology; conceptualization; data curation; writing – review and editing. **Bas Wijnhoven:** Writing – review and editing; supervision; methodology; conceptualization. **Suzanne Gisbertz:** Conceptualization; methodology; supervision; writing – review and editing. **Manuel Pera:** Supervision; writing – review and editing; methodology; conceptualization. **Paolo Morgagni:** Conceptualization; methodology; supervision; writing – review and editing; software. **Massimo Framarini:** Writing – review and editing; project administration; supervision; conceptualization. **Arnulf Hoelscher:** Conceptualization; writing – review and editing; investigation; supervision. **Stefan Moenig:** Methodology; supervision; writing – review and editing; conceptualization. **Piotr Kołodziejczyk:** Conceptualization; methodology; supervision; writing – review and editing. **Guillaume Piessen:** Writing – review and editing; supervision; methodology; conceptualization. **Clarisse Eveno:** Conceptualization; methodology; supervision; writing – review and editing. **Paulo Matos da Costa:** Methodology; supervision; writing – review and editing; conceptualization. **Cara Baker:** Writing – review and editing; data curation; methodology; investigation; conceptualization; project administration. **Andrew Davies:** Conceptualization; methodology; supervision; writing – review and editing. **William Allum:** Conceptualization; methodology; supervision; writing – review and editing. **Uberto Fumagalli Romario:** Methodology; supervision; writing – review and editing; conceptualization. **Ricardo Rosati:** Conceptualization; methodology; supervision; writing – review and editing. **Daniel Reim:** Writing – review and editing; supervision; conceptualization; data curation. **Lucio Lara Santos:** Conceptualization; data curation; writing – review and editing; supervision; investigation. **Domenico D'ugo:** Investigation; supervision; writing – review and editing; data curation. **Giovanni de Manzoni:** Data curation; methodology; project administration; writing – review and editing; supervision. **Wojciech Kielan:** Writing – review and editing; supervision; methodology; formal analysis. **Paul Schneider:** Methodology; conceptualization; supervision; writing – review and editing. **Timothy M. Pawlik:** Writing – review and editing; supervision; conceptualization; writing – original draft. **Wojciech Polkowski:** Writing – review and editing; writing – original draft; methodology; data curation. **Karol Rawicz-Pruszyński:** Conceptualization; data curation; writing – original draft; writing – review and editing; supervision; methodology; visualization; formal analysis; resources.

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CONFLICT OF INTEREST STATEMENT

Suzanne Gisbertz declares being a consultant for J&J, Medtronic, and Olympus, outside of this study. The other authors do not have a conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the GASTRODATA registry. Access to the dataset can be requested from the corresponding author upon reasonable request and approval from the respective participating institutions.

ETHICS STATEMENT

The study was approved by the GASTRODATA Registry Senior Advisors Board and conducted in accordance with the STROBE guidelines and with the Declaration of Helsinki. Informed consent was obtained from all participants prior to inclusion.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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