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## ABOUT COVER

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## AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Oncology* (*WJGO*, *World J Gastrointest Oncol*) is to provide scholars and readers from various fields of gastrointestinal oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

*WJGO* mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc*.

## INDEXING/ABSTRACTING

The *WJGO* is now abstracted and indexed in PubMed, PubMed Central, Science Citation Index Expanded (SCIE, also known as SciSearch®), Journal Citation Reports/Science Edition, Scopus, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2023 edition of Journal Citation Reports® cites the 2022 impact factor (IF) for *WJGO* as 3.0; IF without journal self cites: 2.9; 5-year IF: 3.0; Journal Citation Indicator: 0.49; Ranking: 157 among 241 journals in oncology; Quartile category: Q3; Ranking: 58 among 93 journals in gastroenterology and hepatology; and Quartile category: Q3. The *WJGO*'s CiteScore for 2022 is 4.1 and Scopus CiteScore rank 2022: Gastroenterology is 71/149; Oncology is 197/366.

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SYSTEMATIC REVIEWS

# Prognostic nutritional index in predicting survival of patients with gastric or gastroesophageal junction adenocarcinoma: A systematic review

Stylianos Fiflis, Grigorios Christodoulidis, Menelaos Papakonstantinou, Alexandros Giakoustidis, Stergos Koukias, Paraskevi Roussos, Marina Nektaria Kouliou, Konstantinos Eleftherios Koumarelas, Dimitrios Giakoustidis

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## Abstract

### *BACKGROUND*

Gastric cancer is the third most common cause of cancer related death worldwide. Surgery with or without chemotherapy is the most common approach with curative intent; however, the prognosis is poor as mortality rates remain high. Several indexes have been proposed in the past few years in order to estimate the survival of patients undergoing gastrectomy. The preoperative nutritional status of gastric cancer patients has recently gained attention as a factor that could affect the postoperative course and various indexes have been developed. The aim of this systematic review was to assess the role of the prognostic nutritional index (PNI) in predicting the survival of patients with gastric or gastroesophageal adenocarcinoma who underwent gastrectomy with curative intent.

### *AIM*

To investigate the role of PNI in predicting the survival of patients with gastric or gastroesophageal junction adenocarcinoma.

### *METHODS*

A thorough literature search of PubMed and the Cochrane library was performed for studies comparing the overall survival (OS) of patients with gastric or gastroesophageal cancer after surgical resection depending on the preoperative PNI value. The PRISMA algorithm was used in the screening process and finally 16 studies were included in this systematic review. The review protocol was registered in the International Prospective Register of Systematic Reviews (PRO-

SPERO).

*RESULTS*

Sixteen studies involving 14551 patients with gastric or esophagogastric junction adenocarcinoma undergoing open or laparoscopic or robotic gastrectomy with or without adjuvant chemotherapy were included in this systematic review. The patients were divided into high- and low-PNI groups according to cut-off values that were set according to previous reports or by using receiver operating characteristic curve analysis in each individual study. The 5-year OS of patients in the low-PNI groups ranged between 39% and 70.6%, while in the high-PNI groups, it ranged between 54.9% and 95.8%. In most of the included studies, patients with high preoperative PNI showed statistically significant better OS than the low PNI groups. In multivariate analyses, low PNI was repeatedly recognised as an independent prognostic factor for poor survival.

*CONCLUSION*

According to the present study, low preoperative PNI seems to be an indicator of poor OS of patients undergoing gastrectomy for gastric or gastroesophageal cancer.

**Key Words:** Prognostic nutritional index; Gastric adenocarcinoma; Gastroesophageal junction cancer; Prognosis; Overall survival



**Core Tip:** In the present systematic review, we investigated the role of prognostic nutritional index (PNI) in predicting the survival of patients with gastric or gastroesophageal junction adenocarcinoma that were submitted to surgery with or without chemotherapy. PNI is easy to calculate and provides information about the nutritional status of the patients. Low preoperative PNI seems to be associated with worse survival in patients that will undergo surgery for gastric or gastroesophageal junction adenocarcinoma and therefore could be useful for decision making in clinical practice.

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## INTRODUCTION

Gastric cancer (GC) is one of the most common malignancies and the third most common cause of cancer-related deaths. In 2018, there were approximately 1033701 new cases of GC reported worldwide, resulting in 783000 associated deaths[1-3]. Surgery with or without chemotherapy remains the cornerstone in the management, as it may have curative results. Despite advancements in surgical procedures, chemotherapy, radiotherapy, and targeted treatments, postoperative complications and mortality rates remain high, leading to a poor prognosis for patients[4].

Pathological characteristics such as tumor stage, nodal status, and resection margin are thought to be crucial in determining cancer patient survival[5]. However, it is now obvious that tumor pathology is not the only factor that influences cancer survival; muscle mass, nutritional profile, immunological conditions, and other variables could significantly affect surgical outcomes[6,7]. Malnutrition is particularly common among this group of patients and is attributed to inadequate oral intake, protein-losing gastropathy, ongoing bleeding due to tumors, and ineffective nutritional pathways. Numerous studies have revealed that malnutrition relates to a poor prognosis and multiple postoperative complications in cancer patients, as a result of worsening overall health and increased treatment challenges, emphasizing the need for proper perioperative management to improve the nutritional status of each individual[8-10]. Therefore, early evaluation and management of a patient's nutritional status may enhance the prognosis and outcomes for those undergoing curative surgery for GC[11].

Historically, tumor-node-metastasis (TNM) classification has been the most prevalent and reliable indicator for patient prognosis. However, there is an increasing number of cases where patients classified at the same stage exhibit significantly different prognoses[12,13]. Recent studies have demonstrated that perioperative inflammation-based prognostic scores can predict overall survival (OS) in patients with diverse forms of cancer[14]. Albumin levels are a key indicator of a patient's nutritional status. Several scores based on albumin levels have been developed, such as the nutritional index (NI), Glasgow Prognostic Score, Nutrient Profiling System, and Controlling Nutritional Status score[11,15]. The prognostic NI (PNI) has gained popularity as a means of predicting the surgical risk of patients with GC. It is calculated by multiplying 10 times the serum albumin value (g/dL) plus 0.005 times the lymphocytes count (/mm$^3$). It utilizes nutritional and inflammation status instead of tumor growth, node invasion, and metastasis stage[1,16,17]. PNI has been used as a prognostic tool for patients with solid organ tumors with significant prognostic value regarding

survival and postoperative complications, paving the way for individualized perioperative management[12,17,18]. In this systematic review, we aimed to assess the role of PNI in predicting the survival of patients undergoing curative intent surgery for gastric or gastroesophageal adenocarcinoma.

## MATERIALS AND METHODS

### Study selection

A thorough literature search of PubMed and the Cochrane library was conducted for articles comparing the OS of patients with gastroesophageal cancer after surgical resection depending on their preoperative PNI over the past 10 years. The terms "prognostic nutritional index", "PNI", "gastric cancer", "gastroesophageal cancer", "gastric adenocarcinoma", and "survival" were used in various combinations. The PubMed search yielded 788 results that were scrutinized against the predetermined inclusion and exclusion criteria (Table 1). After title and abstract screening and exclusion of duplicates and irrelevant articles, 71 were eligible for further assessment. After full text screening, finally 16 studies were included in our systematic review. The search and screening processes were completed by two independent reviewers using the PRISMA algorithm and any conflict was resolved through discussion (Figure 1)[19]. The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO ID CRD42023461282).

### Risk of bias and quality assessment

Only cohort studies were included in our systematic review. The risk of bias and the quality of each individual study were assessed using the Cochrane Tool to assess Risk of Bias in Cohort studies and the Newcastle-Ottawa quality assessment scale (NOS), respectively[20]. The Cochrane Tool consists of seven questions and according to the answers a cohort study was categorized as of low or of high risk of bias. The NOS consists of three categories (Selection, Comparability, and Outcome) and eight items. A maximum of one star can be awarded for each item within the selection and outcome categories and a maximum of two stars for the comparability[1,12,13,15,17,21-31] (Table 2). A study with a score of over six stars is considered to be of high quality.

### Data extraction

The following data were extracted: Year of publication, institution, study period, number of participants, patient diagnosis and operation, PNI cut-off value, patient age, sex, body mass index, albumin and lymphocyte count, tumor location and TNM stage, follow-up period, OS, and the univariate and multivariate analysis results. Data extraction was completed by four of the reviewers. Any disagreement during that phase was resolved by consulting a senior reviewer.

## RESULTS

Sixteen studies involving 14551 patients with non-metastatic gastric or gastroesophageal adenocarcinoma who underwent surgery with curative intent between 1997 and 2021 were included in our systematic review. The clinical and pathological characteristics of the patients are shown in Tables 2 and 3.

The PNI cut-off values used in the studies and the survival outcomes are shown in Table 4. PNI was calculated as 10 × albumin (g/dL) + 0.005 × total lymphocyte count (/mm$^3$) and its thresholds ranged between 44.2 and 47 in the majority of the studies; however, three studies used the cut-off values 42.3, 49.2, and 52, respectively. There were 10864 patients in the high PNI group and 3687 in the low PNI group. The patients were submitted to total or partial gastrectomy and lymphadenectomy with or without adjuvant or neoadjuvant chemotherapy. The primary endpoint of our study was OS and the results of univariate and multivariate analyses of the studies that were included are shown in Tables 5 and 6.

### OS

PNI was significantly associated with the OS in all of the studies included except for Toyokawa *et al*[27] enrolled 225 patients with stage III only gastric adenocarcinoma; 184 of them were submitted to adjuvant chemotherapy and PNI was not associated with OS. Hirahara *et al*[22] included 368 patients that were submitted to laparoscopic or laparoscopy assisted gastrectomy and 100 of them were also submitted to adjuvant chemotherapy. The authors demonstrated in univariate analysis that PNI was significantly associated with OS; however, the same result was not reached in multivariate analysis which showed that only carcinoembryonic antigen was significantly associated with OS.

Of 258 patients who underwent curative resection for GC and were included in Ishiguro *et al*[23]'s study, adjuvant chemotherapy was not administered to patients with stage I GC but only to patients with stage II or III. The authors demonstrated that PNI was independently associated with OS.

Lin *et al*[15] included 632 patients with stage I GC, 526 with stage II, and 1024 with stage III who underwent curative gastrectomy; 56% of them received adjuvant chemotherapy. The authors showed that PNI was independently associated with OS. Saito *et al*[24] included 111 GC patients with and 343 without lymphatic invasion; 64 patients received adjuvant and 5 neoadjuvant chemotherapy. The authors demonstrated that high PNI was significantly associated with better OS.

Hashimoto *et al*[21] included only elderly patients between 80 and 94 years of age. Fifty-four of them were submitted to open surgery and fifty-five to laparoscopic surgery; however, it was not stated whether neoadjuvant chemotherapy was administered. The authors demonstrated that PNI was an independent prognostic factor for OS and reported a cumulative 3-year OS rate of 74.7%. Xu *et al*[30] included younger patients (mean age 43.68 ± 4.62) and they also showed

**Table 1 Inclusion and exclusion criteria**

| Inclusion criteria | Exclusion criteria |
|---|---|
| Cohort studies | Metastatic or recurrent disease |
| Studies in English language | Patients receiving palliative care |
| Studies published over the past 10 yr (2013 to 2023) | Cancer other than adenocarcinoma |
| Adult patients (over 18 years old) | Case-control studies |
| Patients with histologically confirmed esophagogastric or gastric adenocarcinoma | Commentaries or letters to the editor |
| Open or laparoscopic gastrectomy | |
| Effect of preoperative PNI on OS as primary outcome | |

PNI: Prognostic nutritional index; OS: Overall survival.

**Table 2 Newcastle-Ottawa scale scores for the included studies**

| Ref. | Selection | | | | Comparability | Outcomes | | | Total |
|---|---|---|---|---|---|---|---|---|---|
| | Representativeness of the exposed cohort | Selection of the non exposed cohort | Ascertainment of exposure | Outcome of interest not present at the start of the study | | Assessment of outcome | Length of follow-up | Adequacy of follow-up | |
| Hashimoto *et al*[21] | * | * | * | * | * | * | | | 6/8 |
| Hirahara *et al*[31] | * | * | * | * | * | * | * | * | 8/8 |
| Hirahara *et al*[22] | * | * | * | * | * | * | | | 6/8 |
| Ishiguro *et al*[23] | * | * | * | * | * | * | | * | 7/8 |
| Kudou *et al*[12] | * | * | * | * | * | * | * | * | 8/8 |
| Lee *et al*[13] | * | * | * | * | * | * | * | * | 8/8 |
| Lin *et al*[15] | * | * | * | * | * | * | * | * | 8/8 |
| Liu *et al*[24] | * | * | * | * | * | * | | * | 7/8 |
| Murakami *et al*[1] | * | * | * | * | * | * | | * | 7/8 |
| Saito *et al*[25] | * | * | * | * | * | * | | * | 7/8 |
| Shen *et al*[26] | * | * | * | * | * | * | * | * | 8/8 |
| Takechi *et al*[17] | * | * | * | * | * | * | | | 6/8 |
| Toyokawa *et al*[27] | * | * | * | * | * | * | * | * | 8/8 |
| Toyokawa *et al*[28] | * | * | * | * | * | * | * | * | 8/8 |
| Wu *et al*[29] | * | * | * | * | * | * | | * | 7/8 |
| Xu *et al*[30] | * | * | * | * | * | * | * | * | 8/8 |

**Table 3 Institute, period, and patient demographics**

| Ref. | Institute | Period | Patients number | Sex | Age (yr) |
|---|---|---|---|---|---|
| Hashimoto *et al*[21] | Sasebo City General Hospital, Japan | 2013-2020 | 109 | 68 M, 41 F | 83 (80-94) |
| Hirahara *et al*[31] | Department of Digestive and General Surgery, Shimane University, Japan | 2009-2016 | 218 | 145 M, 77 F | Low PNI group ($n$ = 109): 78 (46-91). High PNI group ($n$ = 259): 69 (36-89) |
| Hirahara *et al*[22] | Department of Digestive and General Surgery, Shimane University, Japan | 2010-2016 | 368 | 254 M, 114 F | Absent postoperative complications group ($n$ = 265): 70 (36-91). Present postoperative complications group ($n$ = 103): 73 (41-90) |
| Ishiguro *et al*[23] | Department of Surgery in Yokohama City, Japan | 2015-2021 | 258 | 183 M, 75 F | 31-88 |
| Kudou *et al*[12] | Department of Surgery and Science, Kyushu University; Department of Gastroenterological Surgery, National Kyushu Medical Center, Japan | 2005-2016; 2010-2019 (respectively to the 2 institutes) | 206 | 151 M, 55 F | 66.3 (35-92) |
| Lee *et al*[13] | Severance Hospital, South Korea | 2001-2010 | 7781 | 5150 M, 2631 F | 57.1 ± 11.9 |
| Lin *et al*[15] | Fujian Medical University Union Hospital, China | 2009-2014 | 2182 | 1643 M, 539 F | 60.8 (54-68.3) |
| Liu *et al*[24] | Sun Yat-sen University Cancer Center, China | 2000-2012 | 1330 | 905 M, 425 F | 59 (19-89) |
| Murakami *et al*[1] | Tottori University Faculty of Medicine, Japan | 2001-2013 | 254 | 186 M, 68 F | > 70, $n$ = 128; < 70, $n$ = 126 |
| Saito *et al*[25] | Division of Surgical Oncology, Department of Surgery, School of Medicine, Tottori University Faculty of Medicine, Japan | 2005-2013 | 453 | 331 M, 122 F | Low PNI group ($n$ = 188): 73.5. High PNI group ($n$ = 265): 63.5 |
| Shen *et al*[26] | General Surgery Department of the Jinling Hospital, China | 2010-2018 | 525 | 387 M, 138 F | Training set ($n$ = 369): 58.53 ± 10.14. Validation set ($n$ = 156): 57.87 ± 10.28 |
| Takechi *et al*[17] | Onomichi General Hospital, Hiroshima, Japan | 2011-2014 | 182 | 130 M, 52 F | 70 (38-91) |
| Toyokawa *et al*[27] | Osaka City University Hospital, Japan | 1997-2012 | 240 | 168 M, 72 F | 64.5 (58-71.3) |
| Toyokawa *et al*[28] | Osaka City University Hospital, Japan | 1997-2012 | 225 | 147 M, 78 F | 68 (60-75) |
| Wu *et al*[29] | Affiliated Hospital of Jiangnan University, Jiangsu Province, China | 2015-2017 | 77 | 59 M, 18 F | 62.58 ± 8.97 |
| Xu *et al*[30] | Shantou University Medical College's cancer hospital, China | 2016-2020 | 236 | 171 M, 65 F | 43.68 ± 4.62 |

PNI: Prognostic nutritional index; M: Male; F: Female.

that low PNI was significantly associated with lower OS.

Shen *et al*[26] included 525 patients with stages I-III GC in their study who were submitted to robotic gastrectomy, 116 of them to neoadjuvant chemotherapy and 267 of them to adjuvant chemotherapy, and they randomly divided the patients to a training and a validation set. The authors showed that PNI was significantly associated with OS in both sets and that PNI was an independent prognostic factor for OS.

Wu *et al*[29], Liu *et al*[24], and Toyokawa *et al*[27] also showed that PNI was significantly associated with OS. Of note, Wu *et al*[29] included only patients with stage III adenocarcinoma in their study. Toyokawa *et al*[28], who also included only stage III patients, demonstrated that PNI was not significantly associated with OS in those patients. In another study, which included stage II only GC patients, Toyokawa *et al*[27] showed that PNI was an independent prognostic factor for OS. Takechi *et al*[17] confirmed a significant association of PNI and OS only for stage I patients but not for stage II or III patients. Finally, Lee *et al*[13] and Kudou *et al*[12] showed that PNI was significantly associated with OS in stage-stratified analysis for stage I, stage II, and stage III gastric adenocarcinoma patients.

Murakami *et al*[1] reported a 5-year OS rate of 70% and 95.8% in preoperatively low- and high PNI groups, respectively ($P$ < 0.0001). In this study, postoperative PNI values were also recorded at 1 month after surgery. The authors demonstrated that the patients with preoperative and postoperative PNI higher than the threshold had a better 5-year OS (100%) compared to those who had preoperative or postoperative PNI lower than the threshold (5-year OS 83%) and

**Table 4 Patient clinical characteristics**

| Ref. | Tumor location | TNM stage | Operation | Chemotherapy |
|---|---|---|---|---|
| Hashimoto *et al*[21] | NS | I, *n* = 53 (48.6%). II, *n* = 31 (28.4%). III, *n* = 25 (22.9%) | Open surgery 54 (49.5%), laparoscopic 55 (50.5%). Distal/total/proximal gastrectomy: 70/37/2. D2 lymphadenectomy, *n* = 38 (34.9%) | Adjuvant 13 (11.9%). Neoadjuvant NS |
| Hirahara *et al*[31] | EGJ, *n* = 6. Upper, *n* = 41. Middle, *n* = 91. Lower, *n* = 80 | Ia-Ib, *n* = 92, IIa-IIb, *n* = 51, IIIa-IIIc, *n* = 75. T1/2/3/4: 80/27/45/66. N0/1/2/3: 120/30/33/35 | Laparoscopic total/laparoscopic partial/laparoscopy assisted distal gastrectomy: 60/14/144 | Adjuvant: Yes *n* = 79, no *n* = 139. Neoadjuvant chemotherapy in the exclusion criteria |
| Hirahara *et al*[22] | EGJ, *n* = 11. U, *n* = 70. M, *n* = 162. L, *n* = 125 | IA-IB, *n* = 217. IIA-IIB, *n* = 65. IIIC-IIIC, *n* = 86. T1/2/3/4: 192/48/54/74. N0/1/2/3: 244/40/42/42 | Laparoscopic total/laparoscopic partial/laparoscopy assisted distal gastrectomy: 82/37/249 | Adjuvant: Yes *n* = 100, no *n* = 268 |
| Ishiguro *et al*[23] | Upper, *n* = 63 (24.4%). Middle, *n* = 113 (43.8%). Lower, *n* = 82 (31.8%) | T1, *n* = 138 (53.5%). T2 or T3, *n* = 120 (46.5%). Lymphatic invasion positive/negative: 90 (34.9%)/168 (65.1%) | Total/distal/partial gastrectomy: 66/180/11. D1+/D2 lymphadenectomy: 139/112 | 77% of the patients in the high PNI group and 47% in the low PNI group (amongst stages II and III patients) |
| Kudou *et al*[12] | EGJ = 96, UGC = 110 | T1 97 (47.1%), T2 25 (12.1%), T3 55 (26.7%), T4 29 (14.1%). N0 136 (66.0%), N1 33 (16.0%), N2 13 (6.3%), N3 24 (11.7%). I/II/III: 113 (54.9%)/52 (25.2%)/41 (19.9%) | Total/proximal gastrectomy: 161/45. D1 lymphadenectomy (for T1 tumors), *n* = 97. D2 lymphadenectomy (for T2-4 tumors), *n* = 64 | Adjuvant: Yes, *n* = 51 (24.8%), no, *n* = 155 (75.2%). Neoadjuvant chemotherapy in the exclusion criteria |
| Lee *et al*[13] | NS | T1 4182 (53.8%), T2 944 (12.1%), T3 913 (11.7%), T4a 1700 (21.9%), T4b 42 (0.5%). N0 4967 (63.8%), N1 941 (12.1%), N2 798 (10.3%), N3 1075 (13.8%). Stage I 4608 (59.2%), II 1286 (16.5%), III 1887 (24.3%) | Subtotal gastrectomy 5895 (75.8%). Total gastrectomy 1886 (24.2%) | Patients with stage II or higher disease were recommended for adjuvant chemotherapy (numbers not mentioned). Neoadjuvant chemotherapy in the exclusion criteria |
| Lin *et al*[15] | Upper 521 (23.9%). Middle 465 (21.3%). Lower 923 (42.3%). Mixed 273 (12.5%) | TNM stage: I 632 (29.0), II 526 (24.1), III 1024 (46.9) | Total gastrectomy 1134 (52.0%). Distal gastrectomy 998 (45.7%). Proximal gastrectomy 50 (2.3%) | 1223 patients (56%): Adjuvant chemotherapy *n* = 1223 (56%). Neoadjuvant chemotherapy NS |
| Liu *et al*[24] | Upper third 511 (38.4%). Middle third 278 (20.9%). Lower third 541 (40.7%) | I 220 (16.5%). II 334 (25.1%). III 776 (58.3%) | D2 gastrectomy with R0 resection | Adjuvant chemotherapy *n* = 817. Neoadjuvant chemotherapy in the exclusion criteria |
| Murakami *et al*[1] | NS | T1 *n* = 147, T2/3/4 *n* = 107. N0 *n* = 181, N1/2/3 *n* = 73. Stage I *n* = 161, II/III *n* = 93 | Distal/proximal gastrectomy *n* = 181, total gastrectomy *n* = 73. D0/1/1+ lymphadenectomy *n* = 171, D2 lymphadenectomy *n* = 83 | NS |
| Saito *et al*[25] | NS | T1 *n* = 284, T2/3/4 *n* = 169. Lymph node metastasis absent/present: 343/110 | Curative gastrectomy (R0 resection) with regional dissection of lymph nodes. Partial/proximal/total gastrectomy: 311/42/100 | Adjuvant chemotherapy *n* = 64, neoadjuvant chemotherapy *n* = 5, perioperative chemotherapy *n* = 10 |
| Shen *et al*[26] | Upper 158. Middle 202. Lower 165 | Training/validation set: I 138 (37.40%)/64 (41.03%), II 84 (22.76%)/39 (25.00%), III 147 (39.84%)/53 (33.97%) | Robotic gastrectomy proximal/distal/total: 110/272/143 | Neoadjuvant chemotherapy *n* = 116, adjuvant *n* = 267 |
| Takechi *et al*[17] | NS | Stage: I *n* = 114 (62.6%), II *n* = 38 (20.9%), III *n* = 30 (16.5%) | Distal/total/proximal gastrectomy: 124 (68.1%)/51 (28%)/7 (3.8%). D1/D1+/D2 lymphadenectomy: 32 (17.6%)/74 (40.7%)/76 (41.8%) | Postoperative patients with stages II and III GC *n* = 33 (18.1%). Neoadjuvant NS |
| Toyokawa *et al*[27] | Upper *n* = 57 (23.8%). Middle *n* = 98 (40.8%). Lower *n* = 83 (34.6%). Whole *n* = 2 (0.8%) | Only stage II patients: IIA *n* = 111 (46.3%), IIB *n* = 129 (53.7%) | Total/proximal/distal gastrectomy: 72/1/167 | Adjuvant chemotherapy: Yes 62/no 178. Neoadjuvant in the exclusion criteria |
| Toyokawa *et al*[28] | Upper/middle/lower *n* = 209 (92.9%). Whole 16 (7.1%) | IIIA 80 (35.6%), IIIB 72 (32.0%), IIIC 73 (32.4%) | Total/distal gastrectomy: 108 (48%)/117 (52%) | Adjuvant chemotherapy: Yes 41 (18.2%)/no 184 (81.8%) |
| Wu *et al*[29] | NS | Only stage III: *n* = 77 (100%) | Partial gastrectomy (*n* = 15), total gastrectomy (*n* = 62) | The average number of chemotherapy cycles was 6.77 ± 4.14, and all patients completed > 2 chemotherapy cycles. Neoadjuvant chemotherapy in the exclusion criteria |

| | | | | |
|---|---|---|---|---|
| Xu *et al*[30] | EGJ | I 48 (20.3%), II 53 (22.4%), III 135 (57.2%) | Curative gastro-esophageal resection with R0 resection | NS |

NS: Not stated; TNM: Tumor-node-metastasis; EGJ: Esophagogastric junction; U: Upper; M: Middle; L: Lower; UGC: Upper gastric cancer; GC: Gastric cancer.

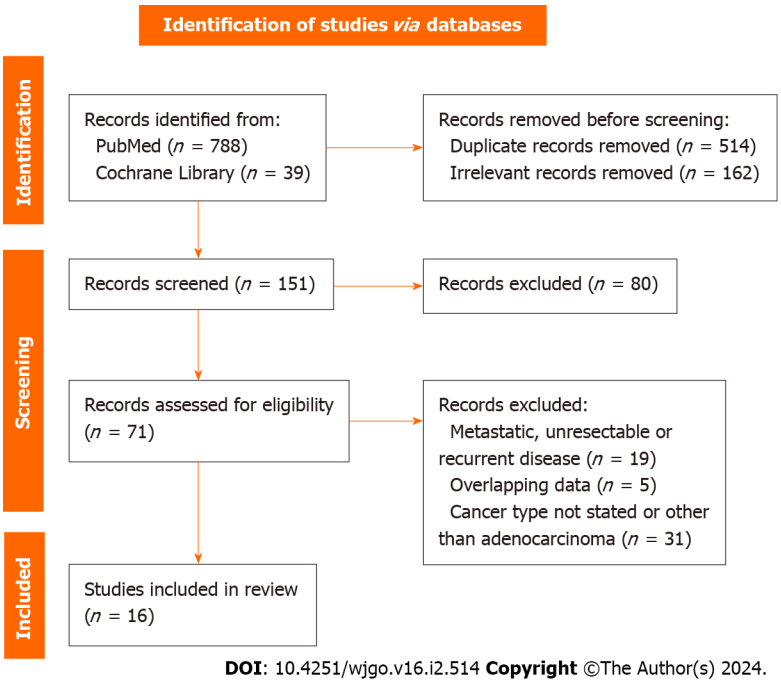


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**Figure 1 PRISMA flowchart.**

compared to the patients with preoperative and postoperative low PNI (5-year OS 67.1%). The authors also compared the 5-year OS rates of these groups in elderly (age over 70 years old) and non-elderly patients (age under 70 years old) and they reported lower OS rates for elderly patients (100% *vs* 75.1% *vs* 59% for elderly patients and 100% *vs* 92.4% *vs* 78.3% for non-elderly patients). Hirahara *et al*[31] also examined the 5-year OS in low- and high-PNI groups in elderly and non-elderly patients. A greater difference in 5-year OS was reported between the low- and high-PNI groups in elderly patients (52.5% *vs* 82.5%) compared to non-elderly patients (46.6% *vs* 54.7%).

## DISCUSSION

In the present study, we assessed the role of PNI in the prognosis of patients with gastric or gastroesophageal junction cancer. However, there are discrepancies in the literature depending on cancer stage. For instance, according to Migita *et al*[32], a low PNI is a significant predictor of poor OS in patients with GC at stages I and III, but not at stages II and IV. In the study of Sakurai *et al*[33], a low PNI was found to be a negative prognostic factor in stages I and II, but not in stage III. This disparity could be explained by the fact that, in addition to cancer stage, other clinicopathological factors, including but not limited to patient's age, nutritional status, or lymphatic or vessel invasion, could influence the survival of patients with different stages of GC[34-36]. Of note, the data are still not conclusive as to whether PNI has better prognostic value in early or advanced GC stage[36-38].

Undoubtedly, there is a link between the nutritional status and the prognosis of patients with GC. Many studies have shown that malnutrition has a negative impact on the prognosis of cancer patients due to its effects on the immune system function resulting in impaired general health and increased treatment complications[9,36]. PNI is a systemic inflammatory marker that has been shown to be useful in cancer prognosis. However, there has been little research into the impact of inflammation on the tumor microenvironment[15]. It is unclear whether a low preoperative PNI is a cause or a result of tumor progression. A low preoperative PNI, according to a meta-analysis of Li *et al*[39], was significantly associated with poor OS, as well as increased postoperative mortality. Therefore, assessing nutritional status is critical because it allows for the identification of malnourished patients at high risk and the implementation of appropriate nutritional interventions that could possibly improve prognosis and reduce complications. However, Migita *et al*[40] showed that preoperative oral nutritional supplementation did not improve low preoperative PNI, therefore more research needs to be done regarding the optimal means of preoperative nutritional support.

**Table 5 Prognostic nutritional index cut-off value calculation method, threshold value and range, follow-up, and survival of the patients**

| Ref. | PNI calculation | PNI cut-off value and groups | PNI range | Follow up (months) | Outcome |
|---|---|---|---|---|---|
| Hashimoto *et al*[21] | ROC curve analysis | 44.2. PNI > 44.2 ($n$ = 72), PNI < 44.2 ($n$ = 37) | NS | 23.9 (0.4-81.9) | The 30-d, 180-d, 1-yr, and 3-yr cumulative OS rates were 100%, 97.0%, 91.6%, and 74.7%, respectively |
| Hirahara *et al*[31] | ROC curve analysis | 44.3. PNI < 44.3 ($n$ = 109), PNI > 44.3, $n$ = 109 | NS | Observation period from date of surgery till day of death | 5-yr OS: Low PNI, 50.9%; high PNI, 73.6% ($P$ < 0.001). In elderly patients (age > 70) 5-yr OS: Low PNI 52.5%, high PNI 82.5%. Non elderly patients (age < 70), 5-yr OS: Low PNI 46.6%, high PNI 54.7% |
| Hirahara *et al*[22] | ROC curve analysis | 44.5. PNI < 44.5 $n$ = 114, PNI > 44.5, $n$ = 254 | NS | NS | NS |
| Ishiguro *et al*[23] | Set according to previous reports | 47. PNI < 47 ($n$ = 75), PNI > 47 ($n$ = 183) | NS | NS | 5-yr OS: A: 44.7%; B: 77.2% ($P$ < 0.001) |
| Kudou *et al*[12] | ROC curve analysis | 44.7. PNI < 44.7 ($n$ = 167, 81.1%), PNI > 44.7 ($n$ = 39, 18.9%) | NS | 60 | Worse 5-year OS rates were associated with PNI < 44.7 (*vs* > 44.7) (OS: 41.7% *vs* 84.5%, HR = 5.460, $P$ < 0.0001). In subgroup analysis PNI < 44.7 (*vs* > 44.7) was significantly associated with poor prognosis in patients with stages II and III disease |
| Lee *et al*[13] | ROC curve analysis | 46.7. PNI < 46,7 ($n$ = 779), PNI > 46,7, $n$ = 7002 | 54.2 ± 5.9 | 60 | The low PNI group had a poor prognosis for all stages of disease (for all stages and stages I, II, and III: $P$ < 0.001) |
| Lin *et al*[15] | Set according to previous reports | 46. PNI ≤ 46 ($n$ = 1348, (61.8%), PNI > 46 ($n$ = 834, 38.2%) | NS | 52 (1-118) | Low PNI 5-yr OS = 55.5%, high PNI 5-yr OS = 75.4% |
| Liu *et al*[24] | Set according to previous reports | 45. Low PNI group PNI < 45. Number of patients NS | | 35 (range 1-179). Final follow-up June 2015, 806 patients were alive by then | NS |
| Murakami *et al*[1] | ROC curve analysis | Preoperative PNI of ≥ 52 (pre-$PNI_{high}$) $n$ = 82, preoperative PNI < 52 (pre-$PNI_{low}$) $n$ = 172, postoperative PNI ≥ 49 (post-$PNI_{high}$) $n$ = 95, postoperative PNI < 49 (pre-$PNI_{low}$) $n$ = 159. Group A, patients with pre-$PNI_{high}$ and post-$PNI_{high}$; group B, patients with either pre-$PNI_{high}$ and post-$PNI_{low}$ or pre-$PNI_{low}$ and post-$PNI_{high}$; group C, patients with pre-$PNI_{low}$ and post-$PNI_{low}$ | Preoperative PNI range 30.6-63.6. Postoperative range 24.2-61.7 | NS | 5-yr OS pre$PNI_{high}$ 95.8%, pre$PNI_{low}$ 70% ($P$ < 0.0001). 5-yr OS post$PNI_{high}$ 91.4%, post$PNI_{low}$ 70.1% ($P$ < 0.0001). 5-yr OS pre$PNI_{low}$ and post$PNI_{high}$ 80.1%, pre$PNI_{low}$ and post$PNI_{low}$ 67.1% ($P$ = 0.031). 5-yr OS pre$PNI_{high}$ and post$PNI_{high}$ 100%, pre$PNI_{high}$ and post$PNI_{low}$ 83.4% ($P$ = 0.0021) |
| Saito *et al*[25] | ROC curve analysis | 46.7. PNI ≥ 46.7 ($n$ = 265, 58.5%) and PNI < 46.7 ($PNI_{low}$, $n$ = 188, 41.5%) | Range 27.7-63.6 | NS | 5-yr OS $PNI_{low}$ 59.5%, $PNI_{high}$ 88.2% ($P$ < 0.0001) |
| Shen *et al*[26] | X-tile 3.6.1 software[1] (Yale University, New Haven, CT, United States) | 45.39. Training set low PNI $n$ = 48 (13.01%), high PNI 321 (86.99%), validation set low PNI $n$ = 29 (18.59%), high PNI $n$ = 127 (81.41%). Patients were randomly divided into the training set and the validation set at a 7:3 ratio | NS | 41 (range 2-102) training set and 38 (range 1-101) validation set | 3-yr and 5-yr OS rates were 80.9% and 74.8% in the training set, and 81.6% and 73.5% in the validation set |
| Takechi *et al*[17] | Set according to previous reports | 45. PNI < 45 ($n$ = 97), PNI ≥ 45 ($n$ = 85) | NS | 39 (range, 1-72) | NS |
| Toyokawa *et al*[27] | ROC curve analysis | 49.2. PNI ≤ 49.2 ($n$ = 136), PNI > 49.2) ($n$ = 104) | NS | 100.5 (70.0-136.8) | The 5-yr OS rate for the entire study population was 78.8% |
| Toyokawa *et al*[28] | ROC curve analysis | 45.6. PNI ≤ 45.6 ($n$ = 90, 40%), PNI > 45.6 ($n$ = 135, 60%) | 46.8 (IQR: 42.5-49.9) | Median 80 (69-124) | The 5-yr OS rate for the entire study population was 48.7%. |
| Wu *et al*[29] | ROC curve analysis | 42.3. Low PNI group PNI < 42.3. Number of patients NS | NS | Shortest 30, longest 64 | 3-yr OS low PNI group < 40%, high PNI group > 60%. Exact number NS (only survival curves available) |
| Xu *et al*[30] | ROC curve | 45.6. Propensity matching patients. PNI < | NS | Every 3 months first | Low PNI group had a 5-yr OS rate |

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|---|---|---|---|---|
| | analysis | 45.6 ($n$ = 58), PNI > 45.6 ($n$ = 85) | 2 yr, every 12 months for 3rd-5th yr, once per year after that. Final follow-up December 2022 | of 46.9%, high PNI group had a 5-yr OS rate of 71.30% |

[1]A bioinformatics tool for biomarker assessment and outcome-based cut-point optimization designed by Yale University.
PNI: Prognostic nutritional index; OS: Overall survival; ROC: Receiver operating characteristic; NS: Not stated; IQR: Interquartile range; HR: Hazard ratio.

**Table 6 Univariate and multivariate analysis results**

| Ref. | Univariate analysis | Multivariate analysis |
|---|---|---|
| Hashimoto *et al*[21] | Low PNI associated with poor OS ($P$ = 0.049) | Low PNI was an independent prognostic factor for poor OS ($P$ = 0.044) |
| Hirahara *et al*[31] | Low PNI value was a significant risk factor for shorter OS ($P$ < 0.001) | PNI was confirmed as an independent prognostic factor for OS ($P$ < 0.001) |
| Hirahara *et al*[22] | PNI was significantly associated with OS (HR = 3.316, 95%CI: 2.133-5.196, $P$ < 0.001) | In patients with high PNI, only CEA was was independently associated with OS ($P$ = 0.002) |
| Ishiguro *et al*[23] | PNI was significantly associated with OS ($P$ < 0.001) | PNI was an independent predictor of OS (HR = 3.452, 95%CI: 2.042-5.836, $P$ = 0.007) |
| Kudou *et al*[12] | PNI < 44.7 (*vs* > 44.7) was associated with worse OS ($P$ < 0.0001) | PNI ($P$ < 0.0001, HR = 8.946) was independently associated with OS |
| Lee *et al*[13] | Low PNI was significantly associated with worse OS (HR = 2.864, 95%CI: 2.544-3.223, $P$ < 0.001) | Low PNI was independently associated with OS (HR = 1.383, 95%CI: 1.221-1.568, $P$ < 0.001) |
| Lin *et al*[15] | PNI was significantly associated with OS ($P$ < 0.001) | PNI was independently associated with OS ($P$ = 0.004) and the 5-yr OS rate in the low PNI group was significantly lower than that in the normal PNI group (55.5% *vs* 75.4%, $P$ < 0.05) |
| Liu *et al*[24] | PNI was associated with OS (HR = 1.627, 95%CI: 1.274-2.078, $P$ < 0.001) | PNI (HR = 1.356, 95%CI: 1.051-1.748, $P$ = 0.019) was independently associated with OS. In stage stratified analysis PNI was not significantly associated with OS |
| Murakami *et al*[1] | 5-yr survival rates were 100.0, 83.0, and 67.1% for groups A, B, and C, respectively | 5-yr OS 100%, 92.4%, and 78.3% for groups A, B, and C, respectively, in non-elderly patients (age < 70) ($P$ = 0.017). 5-yr OS 100%, 75.1%, and 59% for groups A, B, and C, respectively, for elderly patients (age > 70) ($P$ = 0.0029). Group stratification mentioned in Table 4 |
| Saito *et al*[25] | NS | 5-yr OS PNI low group 59.5%, PNI high group 88.2% ($P$ < 0.0001). Median age of the PNI high group (63.5 yr) was significantly younger than of the PNI low group (73.5 yr) |
| Shen *et al*[26] | PNI was an independent prognostic factor for OS. PNI (≤ 45.39 *vs* > 45.39) (HR = 0.439, 95%CI: 0.236-0.734, $P$ = 0.002) | PNI was an independent prognostic factor for OS. PNI (≤ 45.39 *vs* > 45.39) (HR = 0.553, 95%CI: 0.306-0.993, $P$ = 0.048) |
| Takechi *et al*[17] | Low PNI was significantly associated with worse OS (HR = 4.261, 95%CI: 1.734-10.47, $P$ = 0.002). Stage I GC patients in the high PNI group showed significantly better OS than patients in the low PNI group ($P$ < 0.001). No significant difference in OS between PNI groups in stage II and III GC patients | Only PNI score was an independent prognostic factor for OS (HR = 2.889, 95%CI: 1.104-7.563, $P$ = 0.031) |
| Toyokawa *et al*[27] | PNI was significantly associated with OS (HR = 0.381, 95%CI: 0.219-0.662, $P$ = 0.001) | PNI was an independent prognostic factor for OS (HR = 0.415, 95%CI: 0.234-0.736, $P$ = 0.003) |
| Toyokawa *et al*[28] | PNI was not significantly associated with OS ($P$ = 0.073) | PNI was not significantly associated with OS ($P$ = 0.676) |
| Wu *et al*[29] | - | The group with high pre-chemotherapy PNI values had significantly better overall survival than the group with low pre-chemotherapy PNI values (HR = 0.485, 95%CI: 0.255-0.920; $P$ = 0.027) |
| Xu *et al*[30] | Lower PNI was a significant predictor of shorter OS ($P$ = 0.004) | In comparison to the high PNI group, the hazard of endpoint mortality was 2.442 times greater in the low PNI group ($P$ = 0.003) |

PNI: Prognostic nutritional index; OS: Overall survival; HR: Hazard ratio; CI: Confidence interval; GC: Gastric cancer; CEA: Carcinoembryonic antigen.

The PNI cut-off values varied between the studies that were included in this systematic review and the methods that were used to calculate the PNI cut-off value are mentioned in Table 4. An optimal cut-off value for predicting long-term outcomes has not been established in the literature[36]. Future research should focus on standardizing the PNI thresholds by performing receiver operating characteristic curve analysis in prospective studies that include patients with minimum clinicopathological characteristics heterogeneity in order to identify the PNI cut-off value with the maximum sensitivity and specificity, as a standardized PNI cut-off value may have significant impact in daily clinical practice and decision-making. For instance, in the study of Kosuga *et al*[41], it was shown that preoperative PNI may help clarify the extent of lymphadenectomy in patients undergoing gastrectomy for GC.

In our study, there are some limitations that need to be addressed. First, all of the included studies were retrospective cohort studies, which are prone to selection or recall bias. Furthermore, not all patients included in this study had the same stage of cancer. Also, some of them received neoadjuvant therapy prior to surgery, which possibly affected the overall course of the disease. Patients were not divided according to specific tumor characteristics, such as the TNM stage, the size or depth or the tumor, the Siewert type, or the tumor differentiation, therefore a correlation between the PNI and the survival depending on the multiple tumor characteristics could not be established. It would be of interest if future studies would stratify patients and assess the prognostic significance of the PNI based on those characteristics. Due to high heterogeneity of the recorded data, a meta-analysis could not be performed. Of note, the fact that not all deaths were confirmed cancer-related deaths is something to take into account. Furthermore, the studies that we included in our study were all performed in Eastern Asia countries and there were no studies performed in Western countries that matched our inclusion criteria. This could be attributed to the fact that East Asia has the highest prevalence of GC (20-25 patients per 100000, less than 5 patients per 100000 in Northern America)[42]. Finally, patients underwent operations in different institutions by different surgical teams of variable experience, which may have had an impact on the postoperative events.

## CONCLUSION

In conclusion, all of the studies that we included showed that patients with higher preoperative PNI demonstrate better survival than those with lower PNI after surgery for gastric or gastroesophageal cancer with or without chemotherapy regardless of the tumor stage, patients age, total or partial gastrectomy, and open or laparoscopic gastrectomy, except for one study that included stage III GC patients. Future studies should focus on stratifying patients based on tumor stage, as well as on standardizing the PNI cut-offs. Moreover, more research needs to be done in terms of preoperative nutritional support as it could increase PNI and therefore improve short- and long-term outcomes. Moreover, more studies should be performed in Western countries in order to examine whether the association between PNI and survival persists in those patients who undoubtedly present different genetic factors. Finally, PNI could be a useful clinical tool, as it is easy to calculate with standard everyday labs and may lead to individualized patient care and clinical decisions with optimal results.

## ARTICLE HIGHLIGHTS

### *Research background*

Gastric cancer (GC) is a major health problem worldwide. Patients with GC that are eligible for surgery are submitted to gastrectomy with lymphadenectomy followed or not by adjuvant chemotherapy. It is important to identify prognostic factors that could predict the survival of those patients. The prognostic nutritional index (PNI) is an indicator of the nutritional and immune status of GC patients that could assist in identifying patients that will benefit the most from being submitted to surgery and that will present better survival rates.

### *Research motivation*

GC patients with high preoperative PNI seem to present higher survival rates than those with lower PNI. PNI is easy to calculate and low-cost but in order to be used in everyday clinical practice, future research should be conducted to establish a standardized PNI threshold for GC patients that could be submitted to surgery.

### *Research objectives*

To identify whether the PNI could be used in predicting survival outcomes in patients with GC that are submitted to surgery.

### *Research methods*

We performed a thorough literature search of PubMed, the Cochrane library, and *Reference Citation Analysis* for cohort studies that included patients with gastric adenocarcinoma who were submitted to gastrectomy. The keywords that we used for our search were "Prognostic nutritional index", "survival", and "gastric cancer" in combinations, which lead to the retrieval of 16 studies that matched our inclusion criteria. We performed risk of bias assessment and quality assessment of each individual study and our study was prospectively registered in PROSPERO.

### *Research results*

Our systematic review showed that the PNI could be an important prognostic marker in patients undergoing surgery for gastric adenocarcinoma. All of the studies that we included demonstrated that preoperative PNI is significantly associated with survival in GC patients except for one study which included stage III only gastric adenocarcinoma patients. However, two of the studies that we included showed that PNI is significantly associated with survival in patients with stage III gastric adenocarcinoma. Further studies should aim to identify a standardized PNI threshold for gastric adenocarcinoma patients. Moreover, future studies should analyze the correlation between PNI and the stage of disease and whether PNI is associated with survival regardless of the disease stage.

### *Research conclusions*

PNI could be an important prognostic marker that could assist in predicting the survival of patients submitted to gastrectomy.

### *Research perspectives*

Future research should aim at identifying a standardized PNI cut-off value. Furthermore, the correlation between PNI and tumor stage, Lauren classification, and patients' clinicopathological characteristics should be analyzed.

## FOOTNOTES

**Author contributions:** Fiflis S and Papakonstantinou M contributed equally to this work and wrote most of the manuscript; Fiflis S, Papakonstantinou M, and Giakoustidis A designed the research study, performed the research, and analyzed the data; Christodoulidis G offered guidance and assisted as the corresponding author; Koukias S and Roussos P assisted in writing part of the Results and Discussion sections; Kouliou MN and Koumarelas KE assisted in writing part of the Introduction section; Giakoustidis A and Giakoustidis D offered guidance, assisted in writing part of the Discussion section, and performed manuscript revisions; and all authors have read and approved the final manuscript.

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