ABSTRACT

Objectives Previous studies have investigated the prognostic value of the Prognostic Nutritional Index (PNI) in patients with gastrointestinal stromal tumours (GISTs). However, the results have been inconsistent. We performed a meta-analysis to quantitatively determine the prognostic and clinicopathological significance of PNI in GISTs.

Design This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. Pooled HRs and 95% CIs were calculated to estimate the prognostic value of PNI in patients with GISTs. Combined ORs and corresponding 95% CIs were used to evaluate the association between the PNI and clinicopathological characteristics.

Data sources The electronic databases PubMed, Web of Science, Embase and Cochrane Library were thoroughly searched from inception to December 2021.

Eligibility criteria A random-effects model or fixed-effects model was selected based on the level of heterogeneity among the included studies.

Results Eight studies comprising 2307 patients were included in this meta-analysis. A low PNI was significantly associated with worse recurrence-free survival (RFS) (HR 2.02, 95% CI 1.66 to 2.47, p=0.001) and overall survival (OS) (HR 4.35, 95% CI 1.25 to 16.83, p=0.033) in patients with GISTs. In addition, a low PNI was significantly associated with tumour size ≥5 cm (OR 1.65, 95% CI 1.21 to 2.24, p=0.002) and primary tumour site in small intestine/colorectum/extra-GISTs (OR 2.03, 95% CI 1.26 to 3.26, p=0.004).

Conclusions Patients with GISTs and a lower PNI had inferior RFS and OS. Patients with GISTs and a low PNI may have a higher risk of tumour recurrence.

INTRODUCTION

Gastrointestinal stromal tumours (GISTs) account for 0.1%–3% of all gastrointestinal malignant tumours. In Western countries, the incidence of GISTs is estimated to be 10–15 cases per million people per year, whereas in Asia, it is 16–20 cases per million people per year. GISTs are rare, but are the most common mesenchymal tumours of the gastrointestinal tract. Sixty per cent of GISTs are located in the stomach, 30% in the small intestine and others in the duodenum (4%–5%), rectum (4%), oesophagus (<1%) and colon and appendix (1%–2%). The main clinical manifestations of GISTs are haemorrhage, anaemia, indigestion and abdominal pain.

Treatment is based on relapse risk assessment. Surgical resection with or without adjuvant imatinib mesylate (IM) is the standard treatment for patients with localised GISTs. GISTs carry a variable risk of recurrence and metastasis, and the risk stratification models vary depending on the disease stage. For localised GISTs, the prognostic factors are tumour location, size and mitotic rate. Other prognostic factors, such as molecular characteristics, including Kit mutations, also affect GIST survival. Although there are several prognostic parameters for GISTs, the survival rate of GISTs has not been substantially improved over the past decades. The 5-year survival rate of patients with metastatic GISTs is 55%. Therefore, identifying effective and novel prognostic parameters is urgently needed to guide individualised treatment of patients with GISTs.
Recently, the nutritional and immune status of the host was found to affect the survival outcomes of patients with cancer. Many indices derived from blood tests, such as platelet-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio, are associated with prognosis in GISTs. The Prognostic Nutritional Index (PNI) was calculated using the serum albumin levels and total lymphocyte count in the peripheral blood as follows: PNI = 10 × albumin (g/dL) + 0.005 × total number of lymphocytes. PNI is useful for gastrointestinal (GI) surgery to evaluate immune nutritional status. In recent studies, PNI has been reported as an effective prognostic factor for various cancers, including gastric, oesophageal, nasopharyngeal and colorectal cancers. Previous studies have investigated the prognostic role of PNI in patients with GISTs; however, the results have been inconsistent. Some studies have reported that a low PNI was significantly associated with poor survival in GISTs, whereas other researchers could not identify these associations. Therefore, we performed a meta-analysis to explore the prognostic role of pretreatment PNI in GISTs. Moreover, we evaluated the association between PNI and clinicopathological parameters in patients with GISTs.

MATERIALS AND METHODS

Patient and public involvement

There was no patient or public involvement in the development of this research.

Study guideline and ethics

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.

Search strategy

The electronic databases PubMed, Web of Science, Embase and Cochrane Library were thoroughly searched from inception to December 2021. The search terms used were: “prognostic nutritional index,” “PNI,” “gastrointestinal stromal tumors,” “GISTs,” “survival,” “prognosis,” “prognosis” and “recurrence”. The detailed search strategy is presented in online supplemental file. Relevant references were manually searched and retrieved from eligible articles.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) patients with GISTs who were histologically or pathologically diagnosed; (2) studies reporting the prognostic value of PNI for survival outcomes of GISTs; (3) HRs and 95% CIs were reported in the text or could be calculated from the data; (4) the cut-off value of PNI could be extracted from studies; (5) patients with GISTs who received any treatment including but not limited to surgery, chemotherapy and targeted therapy; and (6) studies published in the English language. The exclusion criteria were as follows: (1) reviews, case reports, conference abstracts, letters and comments; (2) studies that did not provide sufficient data on survival outcomes for the meta-analysis and (3) duplicate studies.

Data extraction and quality assessment

Two investigators (NK and HG) independently evaluated the literature and extracted the required information from eligible studies. All discrepancies were resolved through discussion with a third investigator (YN). The following data were extracted from the eligible studies: name of the first author, country, year of publication, sample size, study design, sex, age, study period, cut-off value of PNI, cut-off determination method, follow-up, survival endpoints, survival analysis type, HRs and 95% CIs. All survival outcomes from the eligible studies were extracted. Two independent investigators (XW and SZ) evaluated the quality of each selected study using the Newcastle-Ottawa Scale (NOS). The NOS has three main contents: selection (0–4 stars), group comparability (0–2 stars) and clinical outcome (0–3 stars). Studies with NOS scores ≥6 have been identified as high-quality research.

Statistical analysis

The pooled HRs and 95% CIs were calculated to estimate the prognostic value of the PNI in patients with GISTs. Heterogeneity among studies was evaluated using Cochran’s Q test and Higgins I² statistic. Heterogeneity was considered significant when p<0.1 or I² >50%. A random-effects model was used to pool HRs and 95% CIs; otherwise, a fixed-effects model was used. To detect the source of heterogeneity, subgroup analysis stratified by country, sample size, treatment, cut-off value, cut-off determination and survival analysis types was performed. Combined ORs and corresponding 95% CIs were used to evaluate the association between PNI and clinicopathological characteristics of GISTs. We conducted a sensitivity analysis to determine whether any single study affected the combined HRs. Publication bias was assessed using Begg’s funnel plots and Egger’s tests. All statistical analyses were performed using Stata statistical software (V.12.0; STATA). Statistical significance was set at two-tailed p<0.05.

RESULTS

Search results

An initial literature search identified 45 studies. After excluding 27 duplicates, 18 articles were extracted for further evaluation. Of these, nine studies were removed by reviewing the titles and abstracts. Nine studies were screened by a full-text examination. Subsequently, one study was excluded due to insufficient data. Ultimately, 8 studies comprising 2307 patients were included in this meta-analysis. The process of searching and filtering is illustrated in figure 1.

Characteristics of included studies

The main characteristics of the included studies are summarised in table 1. The included studies were...
published between 2019 and 2021.16–23 Seven studies were conducted in China16 17 19–23 and one study was conducted in Turkey.18 The sample size ranged from 45 to 431, with a median value of 310. All the included studies were retrospective. The cut-off values of PNI for prognostic outcome prediction ranged from 37.5 to 51.3, with a median value of 47.465. Seven studies16–18 20–23 used receiver operating characteristic curves to determine the cut-off value, while one study19 adopted the median value of PNI. All eight studies16–23 reported the prognostic value of low PNI for recurrence-free survival (RFS). One study18 reported a correlation between PNI and overall survival (OS). The NOS scores of the included studies ranged from 7 to 9, indicating that all the included studies were of high quality (table 1).

Prognostic role of PNI for RFS and OS in GISTs

All eight studies with 2307 patients16–23 investigated the prognostic value of the PNI for RFS in GISTs. The fixed-effects model was used because the heterogeneity was not significant (I²=0, Ph=0.881). As shown in figure 2 and table 2, a low PNI was significantly associated with worse RFS in patients with GISTs (HR 2.02, 95% CI 1.66 to 2.47, p<0.001; 2307 patients, 8 studies). Subgroup analysis showed that a low PNI was a significant prognostic factor for poorer RFS, irrespective of country, sample size, treatment, cut-off value, cut-off determination and survival analysis type (table 2). One study18 also reported a correlation between the PNI and OS. The results were as follows: HR 4.35, 95% CI 1.25 to 16.83, p=0.093; 45 patients, 1 study, which demonstrated that a low PNI was significantly associated with inferior OS in patients with GISTs.
The association between PNI and clinicopathological features in GISTs

Two studies with 771 patients reported data regarding the correlation between PNI and clinicopathological factors in GISTs. As shown in table 3 and figure 3, a low PNI was significantly associated with tumour size ≥ 5 cm (OR 1.65, 95% CI 1.21 to 2.24, p=0.002; 771 patients, 2 studies) and primary tumour site in the small intestine/ colorectum/extra-GISTs (OR 2.03, 95% CI 1.26 to 3.26, p=0.004; 771 patients, 2 studies). However, there was no significant correlation between PNI and sex (OR 1.18, 95% CI 0.59 to 2.34, p=0.643; 771 patients, 2 studies) or mitotic index (OR 1.19, 95% CI 0.81 to 1.74, p=0.371; 771 patients, 2 studies).

Sensitivity analysis

A sensitivity analysis was performed by removing one study at a time to evaluate the impact of each study on the overall results. As shown in figure 4, no study significantly affected the pooled HRs of RFS, indicating that the results were reliable.

Publication bias

Begg’s funnel plot and Egger’s test were used to measure publication bias. There was no significant publication bias for RFS (Begg’s p=0.266 and Egger’s p=0.087) (figure 5).

Table 2 Subgroup analysis of prognostic effect of PNI for RFS and OS in patients with GISTs

<table>
<thead>
<tr>
<th>Subgroup variables</th>
<th>No of studies</th>
<th>No of patients</th>
<th>Effects model</th>
<th>HR (95% CI)</th>
<th>P value</th>
<th>Heterogeneity I² (%) Ph</th>
</tr>
</thead>
<tbody>
<tr>
<td>RFS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>8</td>
<td>2307</td>
<td>FEM</td>
<td>2.02 (1.66 to 2.47)</td>
<td>&lt;0.001</td>
<td>0.881</td>
</tr>
<tr>
<td>Country</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>China</td>
<td>7</td>
<td>2262</td>
<td>FEM</td>
<td>2.01 (1.63 to 2.48)</td>
<td>&lt;0.001</td>
<td>0.808</td>
</tr>
<tr>
<td>Turkey</td>
<td>1</td>
<td>45</td>
<td>–</td>
<td>2.14 (1.14 to 4.03)</td>
<td>0.018</td>
<td>–</td>
</tr>
<tr>
<td>Sample size</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤300</td>
<td>4</td>
<td>787</td>
<td>FEM</td>
<td>2.14 (1.64 to 2.79)</td>
<td>&lt;0.001</td>
<td>0.926</td>
</tr>
<tr>
<td>&gt;300</td>
<td>4</td>
<td>1520</td>
<td>FEM</td>
<td>1.88 (1.38 to 2.55)</td>
<td>&lt;0.001</td>
<td>0.537</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical resection</td>
<td>7</td>
<td>2027</td>
<td>FEM</td>
<td>2.16 (1.71 to 2.72)</td>
<td>&lt;0.001</td>
<td>0.926</td>
</tr>
<tr>
<td>Surgical resection+TKIs</td>
<td>1</td>
<td>280</td>
<td>–</td>
<td>1.69 (1.14 to 2.50)</td>
<td>0.009</td>
<td>–</td>
</tr>
<tr>
<td>Cut-off value</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤47.45</td>
<td>4</td>
<td>1096</td>
<td>FEM</td>
<td>1.88 (1.47 to 2.40)</td>
<td>&lt;0.001</td>
<td>0.917</td>
</tr>
<tr>
<td>&gt;47.45</td>
<td>4</td>
<td>1211</td>
<td>FEM</td>
<td>2.35 (1.66 to 3.33)</td>
<td>&lt;0.001</td>
<td>0.696</td>
</tr>
<tr>
<td>Cut-off determination</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ROC curve</td>
<td>7</td>
<td>1950</td>
<td>FEM</td>
<td>1.94 (1.56 to 2.43)</td>
<td>&lt;0.001</td>
<td>0.882</td>
</tr>
<tr>
<td>Median value</td>
<td>1</td>
<td>357</td>
<td>–</td>
<td>2.40 (1.52 to 3.80)</td>
<td>&lt;0.001</td>
<td>–</td>
</tr>
<tr>
<td>Survival analysis type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MVA</td>
<td>7</td>
<td>1950</td>
<td>FEM</td>
<td>1.94 (1.56 to 2.43)</td>
<td>&lt;0.001</td>
<td>0.882</td>
</tr>
<tr>
<td>UVA</td>
<td>1</td>
<td>357</td>
<td>–</td>
<td>2.40 (1.52 to 3.80)</td>
<td>&lt;0.001</td>
<td>–</td>
</tr>
<tr>
<td>Overall survival</td>
<td>1</td>
<td>45</td>
<td>–</td>
<td>4.35 (1.25 to 16.83)</td>
<td>0.033</td>
<td>–</td>
</tr>
</tbody>
</table>

FEM, fixed-effects model; MVA, multivariate analysis; OS, overall survival; PNI, Prognostic Nutritional Index; RFS, recurrence-free survival; ROC, receiver operating characteristic; TKIs, tyrosine kinase inhibitors; UVA, univariate analysis.
DISCUSSION

PNI has been investigated as a prognostic factor for patients with GISTs undergoing surgical resection in previous studies\(^\text{16-23}\), however, the results were inconsistent. In the current meta-analysis, 8 studies with 2307 patients were included, and the results demonstrated that a low PNI was significantly associated with poor RFS and OS in GISTs. The prognostic effect of PNI on RFS was consistent among the various subgroups. However, the association between PNI and clinicopathological features in GISTs was not significant. Sensitivity analysis and publication bias tests confirmed the stability of these results. Taken together, our meta-analysis showed a significant prognostic value of PNI for patients with GISTs, and this index cloud can be used to identify high-risk patients. To the best of our knowledge, this is the first meta-analysis to explore the prognostic and clinicopathological significance of the PNI in patients with GISTs.

PNI was primarily proposed as a nutritional index and surgical risk indicator in 1980.\(^\text{26}\) PNI was calculated using the following formula: 10 × albumin (g/dL) + 0.005 × total number of lymphocytes.\(^\text{12}\) Low PNI could be caused by low albumin levels and/or decreased lymphocyte counts. There are several possible mechanisms to explain the significant prognostic value of the PNI for RFS and OS in GISTs. First, hypoalbuminaemia may be due to malnutrition, since malnourished patients have worse physical condition and may show a worse response to treatments compared with well-nourished patients. Second, lymphocytes play critical roles in the defence against cancer cells. They initiate a cytotoxic immune response and inhibit cancer cell proliferation, invasion and migration in the tumour microenvironment.\(^\text{27}\) Lymphocytopenia is associated with worse clinical outcomes in patients with various cancers.\(^\text{28}\) Taken together, the PNI might predict the survival of patients with GISTs by quantifying

### Table 3  The correlation between PNI and clinical factors in patients with GISTs

<table>
<thead>
<tr>
<th>Clinicopathological factors</th>
<th>No of studies</th>
<th>No of patients</th>
<th>Effects model</th>
<th>OR (95% CI)</th>
<th>P value</th>
<th>Heterogeneity I(^2) (%)</th>
<th>Ph</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male vs female)</td>
<td>2</td>
<td>771</td>
<td>REM</td>
<td>1.18 (0.59 to 2.34)</td>
<td>0.643</td>
<td>80.2</td>
<td>0.025</td>
</tr>
<tr>
<td>Tumour size (≥5 cm vs &lt;5 cm)</td>
<td>2</td>
<td>771</td>
<td>FEM</td>
<td>1.65 (1.21 to 2.24)</td>
<td>0.002</td>
<td>0</td>
<td>0.538</td>
</tr>
<tr>
<td>Primary tumour site (Small intestine/colorectum/E-GIST vs stomach)</td>
<td>2</td>
<td>771</td>
<td>REM</td>
<td>2.03 (1.26 to 3.26)</td>
<td>0.004</td>
<td>56.8</td>
<td>0.128</td>
</tr>
<tr>
<td>Mitotic index, mitoses/50 HPF (&gt;5 vs ≤5)</td>
<td>2</td>
<td>771</td>
<td>FEM</td>
<td>1.19 (0.81 to 1.74)</td>
<td>0.371</td>
<td>0</td>
<td>0.713</td>
</tr>
</tbody>
</table>

E-GIST, extra-gastrointestinal stromal tumour; FEM, fixed-effects model; GISTs, gastrointestinal stromal tumours; HPF, high-power field; PNI, Prognostic Nutritional Index; REM, random-effects model.

Figure 3  Forest plot of studies evaluating the associations between PNI and clinicopathological and prognostic features in GISTs. (A) Sex (male vs female); (B) Tumour size (≥5 cm vs <5 cm); (C) Primary tumour site (Small intestine/colorectum/E-GIST vs stomach); (D) Mitotic index, mitoses/50 HPF (>5 vs ≤5). GISTs, gastrointestinal stromal tumours; PNI, Prognostic Nutritional Index; HPF, high-power field.
the nutritional and immune conditions of individual patients.

In recent years, some studies have also investigated the prognostic value of PNI in diverse types of cancer through meta-analysis.29–32 In a meta-analysis of 12 studies, Xiong et al showed that low pretreatment PNI was significantly correlated with poor survival (eg, OS-specific and cancer-specific survival) in patients with renal cell carcinoma.32 In another meta-analysis of 1608 patients, Lv et al demonstrated that a low PNI was significantly correlated with worse OS in patients with biliary tract cancer.31 A recent meta-analysis of 4511 patients revealed that patients with nasopharyngeal carcinoma who had a low PNI had worse OS, distant metastasis-free survival, PFS and locoregional RFS.32 Hao et al reported that patients with oesophageal cancer patients with a low PNI had worse OS and RFS.34 Our meta-analysis also demonstrated the significant prognostic efficiency of a low PNI for OS and RFS in GISTs, which is in line with findings concerning other cancer types. Therefore, the PNI can be used as a prognostic parameter in clinical practice.

Our meta-analysis showed a significant association between low PNI and tumour size ≥5 cm and non-gastric GIST (table 3). These results suggest that patients with GISTS with larger tumour size and tumour on non-gastric sites should be monitored for nutrient status. Patients with GISTS with low PNI may experience an aggressive tumour burden and poor prognosis. Recent studies have also reported that a variety of biomarkers are associated with a poor prognosis in GISTS. Sarcopenia has been identified as an independent prognostic factor in patients with primary localised GISTS.35 A novel nomogram based on sarcopenia was established to predict the OS of patients with GISTS.35 Programmed cell death-ligand 1 expression is a predictive biomarker for better prognosis of GISTS,36 and the number of tumour-infiltrating CD8+T cells is higher in non-gastric GISTS.36 Moreover, the OS of GIST patients with gastrointestinal bleeding was worse than non-GI bleeding, but had no significant effect on RFS.37

In addition to patients with cancer, there is evidence suggesting that the PNI may be used to predict outcomes in patients with infections, such as COVID-19. A recent meta-analysis including 13 retrospective studies with 4204 patients showed that a per-point increase in PNI was associated with a reduced risk of mortality and disease severity in hospitalised patients with COVID-19.38 In another study using single-centre patient data with systematic review and meta-analysis, Rashedi et al showed the independent predictive value of lower PNI in the prognosis of patients with COVID-19.39 They suggested that it is imperative and necessary to implement a risk stratification index based on PNI values in hospitalised patients with COVID-19.39 The world is still suffering from the pandemic and these studies38 39 contribute pivotal clinical implications for management of patients with COVID-19.

Our meta-analysis had several limitations. First, all the included studies were performed in Asian countries, mainly China. Although we did not restrict the countries and included studies published in English, the eligible studies were conducted in two countries. Therefore, patients of other ethnicities should be included in further studies. Second, our analysis involved a relatively small sample size, including only eight studies. Third, only one study38 provides details on OS. No other studies have presented data on OS, and the prognostic value of PNI for OS in GISTS needs to be consolidated. Therefore,
CONCLUSIONS
In summary, our meta-analysis demonstrated that patients with GISTs with lower PNI had inferior RFS and OS. Due to some limitations, including a small sample size and diverse cut-off values of PNI, further prospective studies are required to validate our results.

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Contributors NK and HG conceived the study and designed the protocol. NK, HG and YN did the literature search, extracted data and quality assessment. XW and SZ analysed the data and created figures. All authors contributed to data analysis and interpretation. NK wrote the first draft of the manuscript; HG and YN participated in the critical revision of the manuscript. XW and SZ were responsible for interpretation of the data and critical revision of the manuscript, and had full access to the pooled data and final responsibility for the decision to submit for publication. YN is responsible for the integrity and accuracy of the data. YN as guarantor is responsible for the overall content. All authors read and approve the final manuscript.

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Competing interests None declared.

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Patient consent for publication Not applicable.

Ethics approval Ethical approval was not provided because all the data analysed in this study were extracted from existing publications.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data sharing not applicable as no datasets generated and/or analysed for this study. Data sharing not applicable as no datasets generated and/or analysed for this study. All data included in this study are available on request by contacting with the corresponding author.

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