

The prognostic significance of prognostic nutritional index in gastrointestinal stromal tumors

A systematic review and meta-analysis

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Abstract

Background: Risk assessment before treatment is important for gastrointestinal stromal tumors (GISTs), which will determine the priority of surgery or preoperative treatment. The prognostic nutritional index (PNI) is an integrated parameter consisting of serum albumin and lymphocyte count. Immunonutritional status defined in this manner is well-known to be closely linked to the prognosis of several other cancers. Nevertheless, the prognostic value of PNI specifically in GISTs has not been well-established. This study aimed to verify the prognostic role of PNI in patients with GISTs.

Methods: A comprehensive literature search was conducted on medical databases up to June, 2022, and the raw data (hazard ratios and 95% confidence intervals [CIs]) focusing on the prognostic value of PNI in patients with GISTs regarding recurrence-free survival were extracted and synthesized adopting the random-effects model. This review was registered in the PROSPERO database (CRD42022345440).

Results: A total of 8 eligible studies including 2627 patients with GISTs was analyzed and the pooled results confirmed that an elevated PNI was associated with a better recurrence-free survival (hazard ratio: 0.52, 95% CI: 0.40–0.68), with a moderate heterogeneity (I-square, 38%). The findings from subgroup analysis were consistent with the overall pooled results, and a sensitivity analysis, not the subgroup analysis, identified the source of heterogeneity.

Conclusion: Elevated pretreatment PNI may be a useful indicator for assessing risk of recurrence in patients from China with GISTs. Studies in other countries and regions are needed to further verify the prognostic value of PNI in GISTs.

Abbreviations: CI = confidence interval, GI = gastrointestinal, GISTs = gastrointestinal stromal tumors, HR = hazard ratio, I² = I-square, NCCN = National Comprehensive Cancer Network, NIH = National Institutes of Health, PNI = prognostic nutritional index, RFS = recurrence-free survival, TIL = tumor-infiltrating lymphocyte, TKIs = tyrosine kinase inhibitors.

Keywords: gastrointestinal stromal tumors (GISTs), prognostic nutritional index (PNI), Recurrence-free survival (RFS)

1. Introduction

Gastrointestinal stromal tumors (GISTs) are the most common gastrointestinal (GI) mesenchymal tumors. They harbor activating somatic mutations involving the tyrosine kinase receptor c-kit (CD117) and platelet-derived growth factor- α , expressed as by the Interstitial Cells of Cajal which control GI track peristalsis.^[1] Tyrosine kinase inhibitors (TKIs), as represented by imatinib, have achieved gratifying therapeutic benefit for the treatment of GISTs.^[2] Complete excision is recommended for primary resectable GISTs without significant risk of recurrence, but otherwise, targeted therapy should be considered as the preferred treatment option based on risk assessment, as

emphasized by the first guidelines separately and specifically for GISTs recently published by the National Comprehensive Cancer Network.^[3] Tumor location, size, mitotic index and tumor rupture are convincingly incorporated into the assessment of potentially malignant biological behavior of GISTs,^[4–6] but nevertheless, it is difficult to accurately assess the risk of recurrence without pathological assessment. Hence, for predicting the likelihood of recurrence, other easily accessible and effective indicators are needed.

Nutritional status is closely connected to both tumor progression and prognosis.^[7] Malnutrition usually indicates a worse clinical outcome of most cancers, and several prognosis-related nutritional parameters have been identified and shown to

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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represent effective predictors of prognosis, such as Nutritional Risk Screening 2002, Patient-Generated Subjective Global Assessment, and the prognostic nutritional index (PNI).^[8–18] The PNI was originally proposed by Buzby in 1980 and applied by Onodera in 1984 to predict the surgical risk in GI malignancy. Due to its convenience and efficiency, the PNI was rapidly tested in other types of cancers as well, including GISTs.^[8,11–22] The population sample size in reports on predicting the recurrence risk of GISTs based on the PNI was usually small, making it difficult to draw convincing conclusions. However, according to the National Comprehensive Cancer Network guidelines, preoperative effective assessment of postoperative recurrence risk is particularly important for GISTs, because it will determine the priority of surgical treatment or preoperative TKI treatment.^[3]

Although other meta-analyses have previously determined the prognostic value of PNI in most tumors,^[21,22] these earlier studies had not clearly differentiated GISTs from GI epithelial cancers by pathology. In fact, unlike GI epithelial cancers, the existing risk assessment criteria and prognostic parameters for GISTs are self-contained and developing.^[6,13] Accordingly, we conducted a meta-analysis to verify the prognostic significance of PNI in GISTs. This is the first meta-analysis in this field.

2. Materials and methods

The present study was carried out based on the published studies. Thus, the approval from an ethics committee or institutional review board was not required.

2.1. Search strategy

Two independent researchers conducted a thorough literature search on the electronic databases PubMed, Embase, and the Cochrane Library from inception up to June 2022. Appropriate search terms included MeSH terms, as well as the free text words “gastrointestinal stromal tumors” or “GISTs,” and “prognostic nutritional index” or “PNI,” and “survival” or “prognosis” or “recurrence” or “clinical outcome.” References cited by the identified documents were screened carefully to avoid missing possible eligible articles. This review proceeded in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses^[23] and was registered in the PROSPERO database, an international register of systematic reviews (register number CRD42022345440).

2.2. Selection criteria

Prespecified acceptance criteria for studies included in the present meta-analysis were discussed by the authors and the final decision was made by the senior author when encountering disagreements, and was then approved by all authors. The inclusion criteria were: studies concerned with GISTs confirmed by pathology; studies provided the prognostic value of the PNI prior to treatment; studies with available hazard ratios (HRs) and 95% confidence intervals (CIs) for survival data of GISTs; availability of the full text published in English. The exclusion criteria were: studies irrelevant to PNI for prognosis of GISTs; duplicated publications; case reports, comments, conference abstracts, and reviews.

2.3. Data extraction and quality assessment

Data extraction was carried out from publications that met the requirements after full-text reading by 2 investigators independently, including the first name of authors, year of publication, region, study type, age, gender, sample size, tumor type, recurrence risk according to the National Institutes of Health (NIH) criteria, treatment, observation period, follow-up, endpoint, cutoff value of PNI, and quality score. The HRs and 95%

CIs for endpoints were extracted directly from multivariate or univariate analyses, as feasible. Because all studies met the inclusion criteria reported just for the recurrence-free survival (RFS), here, we took this parameter as the only endpoint.^[8,11–18] The Newcastle–Ottawa quality assessment scale was utilized to assess the quality of the included studies.^[24]

2.4. Statistical analysis

The original data were synthesized using Review Manager software (version 5.4, Cochrane Collaboration, Copenhagen, Denmark). I-square (I^2) statistical testing and Cochrane (Q) tests were used to investigate the heterogeneity among the eligible studies, with a P value of $< .1$ taken to indicate significant heterogeneity.^[25] This was classified into 3 degrees according to the I^2 results as follows: low ($I^2 < 25\%$), moderate ($I^2, 25–75\%$) and high ($I^2 > 75\%$).^[26] A random effect model was used if heterogeneity was observed. A two-sided P value of $< .05$ was considered statistically significant. Subgroup analysis was conducted to explore the source of heterogeneity subsequently based on the common layering characteristic of the publications. Moreover, sensitivity analysis was executed to further identify the source of heterogeneity and demonstrate the stability of the pooled results by omitting any single study. Results were visualized using Graphpad Prism software (version 7.0, San Diego, California). Finally, publication bias was shown as funnel plots and further validated by Egger’s test and Begg’s test^[27,28] using Stata statistical software (version 12.0, College Station, TX).

3. Results

3.1. Search results

The specific literature search process is shown in the flowchart (Fig. 1). The initial literature search yielded 27 articles, 11 of which were retained for rigorous screening through recognition of titles and abstracts. After reading the full text of these 11 articles, 2 that did not provide enough data and another 2 found to be published by the same center^[11,14] were excluded so that finally 8 retrospective studies including 2627 patients with GISTs that fully met the requirements were adopted for the current meta-analysis.^[8,11–13,15–18]

All of these eligible studies published between 2019 and 2022 evaluated the predictive capacity of PNI for the RFS of GISTs patients from China. The main treatment for GISTs in these studies was surgical resection, with 4 of them reporting primary GISTs treated solely by surgery,^[8,13,16,18] while the other 4 reported the predictive effect of PNI on the prognosis of GISTs treated with surgery and followed by imatinib.^[11,12,15,17] HRs and 95% CIs were extracted directly from the articles, accompanied by the cutoff values of PNI ranging from 40.7 to 51.3. The characteristics of the accepted studies and patients are summarized in Table 1.

3.2. Meta-analysis

Eight studies reported the prognostic value of PNI for RFS of 2627 patients, with a pooled HR of 0.52 (95% CI: 0.40–0.68), indicating that patients with an elevated PNI had a better RFS relative to those with a lower PNI. Heterogeneity analysis revealed an I^2 value of 38%, indicating moderate heterogeneity among the included studies, but this was not statistically significant ($P = .13$, Fig. 2). A random-effects model was used and subgroup analysis was performed to explore the differences between groups with respect to the characteristics of the different studies. Subgroup analysis according to sample size (cutoff point, 300) and treatment (surgery only vs. surgery and imatinib) showed lack of heterogeneity

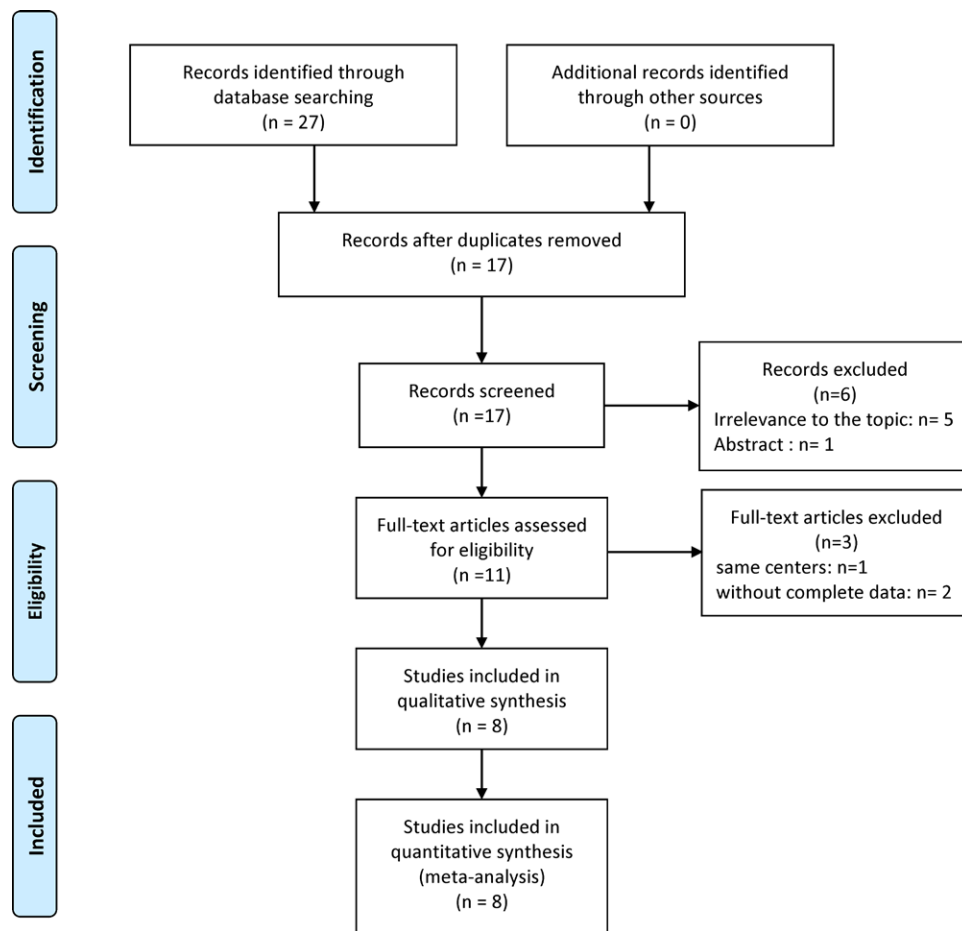


Figure 1. Search flow diagram for studies included in the meta-analysis.

in the subgroup “sample size >300” (I^2 value = 0; HR: 0.46, 95% CI: 0.36–0.58) and in the subgroup “surgery only” (I^2 value = 0; HR: 0.45, 95% CI: 0.33–0.60). In contrast, significant heterogeneity was observed among the subgroup “sample size < 300” (I^2 value = 74%; HR: 0.67, 95% CI: 0.47–0.95) and the subgroup “surgery and imatinib” (I^2 value = 61%; HR: 0.63, 95% CI: 0.39–1.02). However, these results failed to identify the source of the heterogeneity, as subgroup analysis based on the sample size and treatment could not eliminate or even reduce it (Table 2).

To identify the source of heterogeneity, as well as document the stability of our results, a sensitivity analysis was carried out by omitting one study at a time and recalculating the summarized HRs for the remaining studies. The results changed only when the study by Li et al^[12] was excluded (I^2 value = 0; HR: 0.48, 95% CI: 0.39–0.59). In contrast, including that study resulted in an I^2 value ranging from 38% to 47%, with a similar range of HRs (0.51–0.53) and 95% CIs (Fig. 3). The results of this sensitivity analysis thus indicated that the study published by Li et al in 2020^[12] was the sole source of heterogeneity in the current meta-analysis.

4. Publication bias

The shape of the funnel plot showed symmetry of the whole dataset (Fig. 4) and indicated no apparent publication bias among the included studies. Further statistical analysis suggested that publication bias was not significant (Table 3, Begg’s test $P = .711$, Egger’s test $P = .995$). However, it should be noted that although there is no significant publication bias, there is

clearly a geographical bias because all the studies were from China.

5. Discussion

Decisions on treatment strategies for GISTs depend on the assessment of the risk of recurrence.^[3] R0 resection does not usually imply cure for GISTs with a high preoperative and post-operative risk of recurrence. TKIs are recommended for increasing RFS.^[2,3] Even though tumor location, size, mitotic index and tumor rupture have been identified as classic parameters for predicting recurrence of GISTs,^[4–6] accuracy is often limited by the inability to obtain accurate pathological confirmation prior to treatment. Hematological indicators such as neutrophil to lymphocyte ratios had been shown to be useful in assessing the risk of GIST recurrence.^[29] Similarly, recent studies showed that GIST patients with a high PNI tend to have a longer RFS, with HRs ranging from 0.17 to 0.59.^[8,11–18] Moreover, a nomogram including tumor site, tumor size, mitotic index, tumor rupture, and PNI demonstrated better predictive ability than the commonly used risk stratification systems, such as modified NIH criteria and NIH–Miettinen criteria.^[13]

In the current meta-analysis, a total of 8 studies including 2627 patients with GISTs was analyzed regarding the prognostic value of PNI.^[8,11–13,15–18] The pooled results revealed that an elevated PNI prior to treatment was related to a longer RFS (HR, 0.52, 95% CI: 0.40–0.68). Subgroup analysis showed a positive prognostic impact of PNI on RFS regarding studies with a sample size >300 and those where patients had been treated only surgically. Sensitivity analysis enabled the identification of one study that was a source of heterogeneity (albeit

Table 1
Baseline characteristics of included studies.

Study	Region	Study type	Age	Gender (male/female)	Sample size	Progression status	Recurrence risk	Treatment	Observation period	Follow-up (mo)	Endpoint	PNI cutoff value	HR analysis	NOS score
Shi 2019	China	Retrospective	57 (23–94)	196/144	340	Primary, localized	Mixed	Surgery and Imatinib	2005.01–2017.12	44.3	RFS	43.9	MV	7
Sun 2019	China	Retrospective	56 (20–80)	209/222	431	Primary, localized	Mixed	Surgery only	2000.01–2017.12	NR	RFS	47.45	MV	7
Li 2020	China	Retrospective	62 (18–83)	124/103	227	NR	Mixed	Surgery and Imatinib	2004.10–2019.09	NR	RFS	47.53	MV	7
Cao 2020	China	Retrospective	61 (49–73)	185/172	357	Primary	Mixed	Surgery only	2008.01–2020.01	56 (2–131)	RFS	47.48	UV	6
Li 2021	China	Retrospective	61 (19–89)	175/217	392	Primary	Mixed	Surgery only	2000.01–2019.10	32 (1–124)	RFS	47.65	MV	7
Wang1 2021	China	Retrospective	≤60,102; >60,98	95/105	200	Primary, localized	Intermediate and high risk	Surgery and Imatinib	2010.01–2018.12	NR	RFS	42.6	MV	7
Wang2 2021	China	Retrospective	62 (32–86)	118/117	235	Primary, localized	Mixed	Surgery only	2009–2016	35 (7–90)	RFS	51.3	MV	6
Jia 2022	China	Retrospective	56 (46–68)	252/193	445	Primary	Mixed	Surgery and Imatinib	2013.01–2021.01	45 (2–95)	RFS	40.7	MV	7

HR = hazard ratio, MV = multivariate, NOS = Newcastle-Ottawa quality assessment, NR = not reported, PNI = prognostic nutritional index, RFS = recurrence-free survival, UV = univariate.

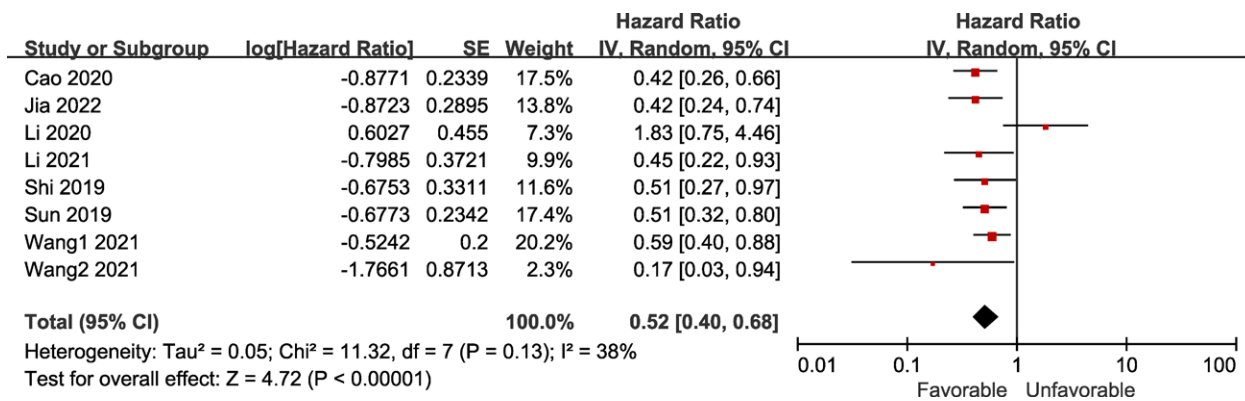


Figure 2. Forest plot of prognostic nutritional index (PNI) in predicting recurrence-free survival (RFS) of gastrointestinal stromal tumors (GISTs) patients.

Table 2
Subgroup analyses of PNI for RFS in GISTs patients.

Analysis	No. of studies	No. of patients	Pooled HR [95%CI]	P value	Heterogeneity	
					I (%)	P value
Overall	8	2627	0.52 [0.42, 0.63]	.001	38	.13
Sample size						
>300	5	1965	0.46 [0.36, 0.58]	.001	0	.97
<300	3	662	0.67 [0.47, 0.95]	.02	74	.02
Treatment						
Surgery only	4	1415	0.45 [0.33, 0.60]	.001	0	.66
Surgery and Imatinib	4	1212	0.63 [0.39, 1.02]	.06	61	.05

CI = confidence interval, GISTs = gastrointestinal stromal tumors, HR = hazard ratio, PNI = prognostic nutritional index, RFS = recurrence-free survival.

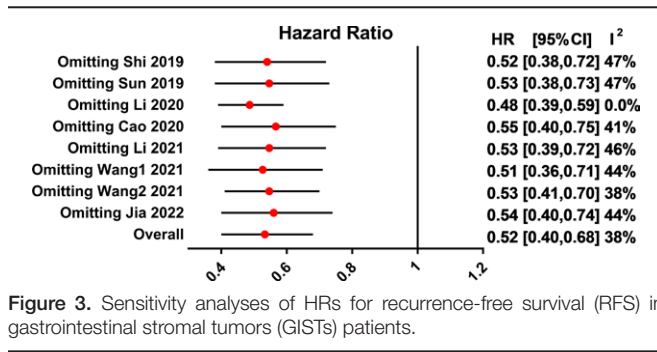


Figure 3. Sensitivity analyses of HRs for recurrence-free survival (RFS) in gastrointestinal stromal tumors (GISTs) patients.

albumin alone is not an independent predictor of prognosis of GISTs according to the limited studies included in the current meta-analysis.^[15,18] Further verification is required for the prognostic value of serum albumin alone in GISTs. On the other hand, the interactions of various different immune organs, tissues, and cells mediates defense against tumors. Different tumor-infiltrating lymphocyte (TIL) phenotypes rather than the lymphocyte count alone can also be used to predict tumor prognosis.^[31,32] Specifically, CD3⁺, CD8⁺, and CD56⁺ TILs were reported to be reliable independent predictors of disease-free survival of GIST patients.^[33] Even after treatment with imatinib, enriched intratumoral CD3⁺ TILs could still be found and still correlated with a better progression-free survival in GISTs.^[34] Based on the above

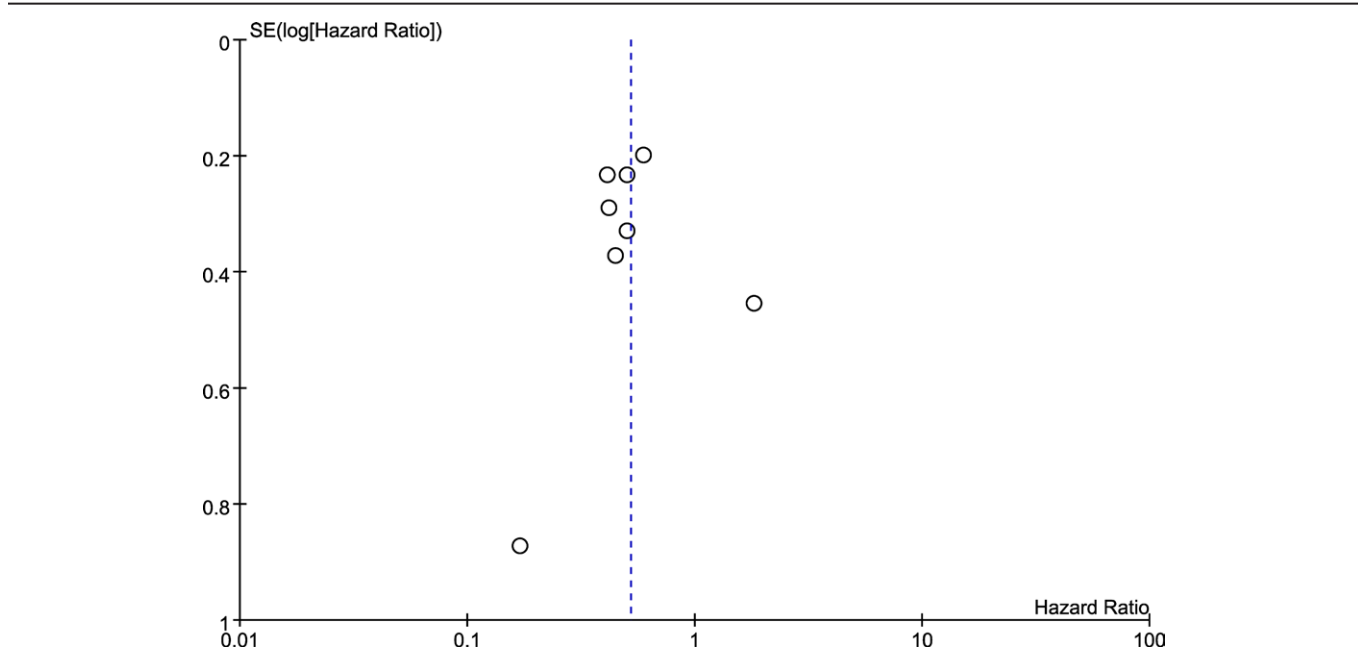


Figure 4. Funnel plot.

Table 3
Assessment for publication bias.

	Number of estimate	t	P for Egger's test	Z value	P for Begg's test
PNI	8	0.01	.995	0.37	.711

PNI = prognostic nutritional index.

this had not statistically significant ($P > .1$). For that publication from 2020,^[12] compared with the other studies analyzed here, we found no indication of the status of the GISTs included (primary or not, and localized or not). Possibly, GISTs at different stages included in that study may explain the heterogeneity due to the lack of its identification of the PNI as independent prognostic factor in by multiple regression analysis.

A limitation of the current analysis is that, due to the lack of data, we were unable to explore relationships between PNI and other clinicopathologic features. Nutritional factors act on the development of cancers by regulating the balance between cell proliferation and death, appropriate cell differentiation, the expression of oncogenes and tumor-suppressor genes.^[7] Serum albumin, as a common reference entity in assessments of nutritional status, is found to be closely connected with the prognosis of various malignancies.^[30] Previous reviews had indicated that hypoalbuminemia is associated with poor cancer survival, including GI cancers.^[30] However, it seems that serum

data and the results of our meta-analysis, PNI, a parameter of immunonutritional status, can be expected to play an important role in prediction of GIST prognosis.

There are several limitations to the current meta-analysis. First, the study design of all the included studies was retrospective, but a randomized controlled trial is logically the pinnacle of the evidence pyramid.^[35] Second, all of the studies included in this comprehensive analysis were from China, so a geographical bias is clearly present, and it remains unknown whether the current pooled results can be generalized to other Asian regions or western countries. Third, the risk stratification standards varied among the included studies, which we considered mixed unless the included publication clearly stated that the study population was of medium to high risk.^[17] Fourth, most of the cutoff values for the PNI were determined by receiver operator characteristic curve analysis and were not consistent,^[8,12,15,16,18] but half of them were concentrated around 47.5.^[8,12,13,16] Therefore, optimal cutoff values still need to be determined by more well-designed studies. Fifth, the sample size of the included studies was <500, ranging from 200 to 445, which may make it difficult to draw firm conclusions. Finally, inclusion of only English literature may lead to a language bias.

6. Conclusion

In conclusion, despite the above limitations, this meta-analysis is the first systematic review concerning the prognostic value

of the PNI for GISTs. The pooled results demonstrate that an elevated PNI is associated with a favorable RFS in patients from China with GISTs. As a parameter of immunonutritional status, PNI may not only be helpful for pretreatment evaluation but also for guiding early nutritional and immunological intervention, although well-designed multi-regional studies not limited to China are required for confirmation of this hypothesis.

Author contributions

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Methodology: Zhenjie Li, Tingyong Tang.

Resources: Tingyong Tang.

Software: Zhenjie Li, Dengming Zhang, Peijin Zhu.

Supervision: Tingyong Tang.

Validation: Zhenjie Li, Dengming Zhang, Tingyong Tang.

Visualization: Zhenjie Li.

Writing – original draft: Zhenjie Li.

Writing – review & editing: Tingyong Tang.

References

- [1] Yamamoto H, Oda Y, Kawaguchi K, et al. c-kit and PDGFRA mutations in extragastrointestinal stromal tumor (gastrointestinal stromal tumor of the soft tissue). *Am J Surg Pathol*. 2004;28:479–88.
- [2] von Mehren M, Joensuu H. Gastrointestinal stromal tumors. *J Clin Oncol*. 2018;36:136–43.
- [3] von Mehren M, Kane JM, Bui MM, et al. NCCN guidelines insights: soft tissue sarcoma, version 1.2021. *J Natl Compr Canc Netw*. 2020;18:1604–12.
- [4] Fletcher CD, Berman JJ, Corless C, et al. Diagnosis of gastrointestinal stromal tumors: a consensus approach. *Hum Pathol*. 2002;33:459–65.
- [5] Miettinen M, El-Rifai W, Sobin LHL, et al. Evaluation of malignancy and prognosis of gastrointestinal stromal tumors: a review. *Hum Pathol*. 2002;33:478–83.
- [6] Miettinen M, Lasota J. Gastrointestinal stromal tumors: review on morphology, molecular pathology, prognosis, and differential diagnosis. *Arch Pathol Lab Med*. 2006;130:1466–78.
- [7] Mayne ST, Playdon MC, Rock CL. Diet, nutrition, and cancer: past, present and future. *Nat Rev Clin Oncol*. 2016;13:504–15.
- [8] Cao X, Cui J, Yu T, et al. Fibrinogen/Albumin ratio index is an independent prognosis predictor of recurrence-free survival in patients after surgical resection of gastrointestinal stromal tumors. *Front Oncol*. 2020;10:1459.
- [9] Ding P, Guo H, Sun C, et al. Relationship between nutritional status and clinical outcome in patients with gastrointestinal stromal tumor after surgical resection. *Front Nutr*. 2022;9:818246.
- [10] Ding P, Guo H, Yang P, et al. Association between the nutritional risk and the survival rate in newly diagnosed GIST patients. *Front Nutr*. 2021;8:743475.
- [11] Jia J, Zhang L, Wang T, et al. Association between preoperative skeletal muscle mass depletion and poor relapse-free survival in patients with gastrointestinal stromal tumors after complete resection. *Nutrition*. 2022;98:111636.
- [12] Li R, Song S, He X, et al. Relationship between fibrinogen to albumin ratio and prognosis of gastrointestinal stromal tumors: a retrospective cohort study. *Cancer Manag Res*. 2020;12:8643–51.
- [13] Li S, Chen D, Li S, et al. Novel prognostic nomogram for recurrence-free survival of patients with primary gastrointestinal stromal tumors after surgical resection: combination of prognostic nutritional index and basic variables. *Front Oncol*. 2020;10:581855.
- [14] Lin Y, Wang M, Jia J, et al. Development and validation of a prognostic nomogram to predict recurrence in high-risk gastrointestinal stromal tumour: a retrospective analysis of two independent cohorts. *EBioMedicine*. 2020;60:103016.
- [15] Shi WK, Zhang XH, Zhang J, et al. Predictive ability of prognostic nutritional index in surgically resected gastrointestinal stromal tumors: a propensity score matching analysis. *Jpn J Clin Oncol*. 2019;49:823–31.
- [16] Sun J, Mei Y, Zhu Q, et al. Relationship of prognostic nutritional index with prognosis of gastrointestinal stromal tumors. *J Cancer*. 2019;10:2679–86.
- [17] Wang F, Tao T, Yu H, et al. Prognostic value of Onodera's nutritional index for intermediate- and high-risk gastrointestinal stromal tumors treated with or without tyrosine kinase inhibitors. *World J Surg Oncol*. 2021;19:227.
- [18] Wang H, Xu YY, You J, et al. Onodera's prognostic nutritional index is a novel and useful prognostic marker for gastrointestinal stromal tumors. *World J Gastrointest Surg*. 2021;13:1202–15.
- [19] Buzby GP, Mullen JL, Matthews DC, et al. Prognostic nutritional index in gastrointestinal surgery. *Am J Surg*. 1980;139:160–7.
- [20] Onodera T, Goseki N, Kosaki G. [Prognostic nutritional index in gastrointestinal surgery of malnourished cancer patients]. *Nihon Geka Gakkai Zasshi*. 1984;85:1001–5.
- [21] Wang Z, Wang Y, Zhang X, et al. Pretreatment prognostic nutritional index as a prognostic factor in lung cancer: review and meta-analysis. *Clin Chim Acta*. 2018;486:303–10.
- [22] Sun K, Chen S, Xu J, et al. The prognostic significance of the prognostic nutritional index in cancer: a systematic review and meta-analysis. *J Cancer Res Clin Oncol*. 2014;140:1537–49.
- [23] Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71.
- [24] Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol*. 2010;25:603–5.
- [25] Hoaglin DC. Misunderstandings about Q and “Cochran's Q test” in meta-analysis. *Stat Med*. 2016;35:485–95.
- [26] Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21:1539–58.
- [27] Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics*. 1994;50:1088–101.
- [28] Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315:629–34.
- [29] Luo XF, Zhou LH. Prognostic significance of neutrophil to lymphocyte ratio in patients with gastrointestinal stromal tumors: a meta-analysis. *Clin Chim Acta*. 2018;477:7–12.
- [30] Gupta D, Lis CG. Pretreatment serum albumin as a predictor of cancer survival: a systematic review of the epidemiological literature. *Nutr J*. 2010;9:69.
- [31] Chen KJ, Zhou L, Xie HY, et al. Intratumoral regulatory T cells alone or in combination with cytotoxic T cells predict prognosis of hepatocellular carcinoma after resection. *Med Oncol*. 2012;29:1817–26.
- [32] Zhou J, Ding T, Pan W, et al. Increased intratumoral regulatory T cells are related to intratumoral macrophages and poor prognosis in hepatocellular carcinoma patients. *Int J Cancer*. 2009;125:1640–8.
- [33] Zhuang C, Ni B, Zhang ZZ, et al. Low distribution of TIM-3(+) cytotoxic tumor-infiltrating lymphocytes predicts poor outcomes in gastrointestinal stromal tumors. *J Immunol Res*. 2021;2021:6647292.
- [34] Rusakiewicz S, Semeraro M, Sarabi M, et al. Immune infiltrates are prognostic factors in localized gastrointestinal stromal tumors. *Cancer Res*. 2013;73:3499–510.
- [35] Andrade C. Understanding the basics of meta-analysis and how to read a forest plot: as simple as it gets. *J Clin Psychiatry*. 2020;81:20f13698.