REVIEW

3282  Hepatitis B and circadian rhythm of the liver
Skrlec I, Talapko J

3297  Tumor microenvironment in pancreatic ductal adenocarcinoma: Implications in immunotherapy

3314  Crosstalk between dietary patterns, obesity and nonalcoholic fatty liver disease
Ristic-Medic D, Bajerska J, Vucic V

MINIREVIEWS

3334  Application of intravoxel incoherent motion diffusion-weighted imaging in hepatocellular carcinoma

3346  Regulatory T cells and their associated factors in hepatocellular carcinoma development and therapy
Zhang CY, Liu S, Yang M

3359  Single-incision laparoscopic surgery to treat hepatopancreatobiliary cancer: A technical review
Chuang SH, Chuang SC

3370  Probiotics and postbiotics in colorectal cancer: Prevention and complementary therapy
Kvakova M, Kamlarova A, Stofilova J, Benetinova V, Bertkova I

3383  Interventional strategies in infected necrotizing pancreatitis: Indications, timing, and outcomes
Purschke B, Bolm L, Meyer MN, Sato H

3398  Artificial intelligence in liver ultrasound
Cao LL, Peng M, Xie X, Chen GQ, Huang SY, Wang JY, Jiang F, Cui XW, Dietrich CF

3410  Risk factors and diagnostic biomarkers for nonalcoholic fatty liver disease-associated hepatocellular carcinoma: Current evidence and future perspectives
Ueno M, Takeda H, Takai A, Seno H

ORIGINAL ARTICLE

Basic Study

3422  Accumulation of poly (adenosine diphosphate-ribose) by sustained supply of calcium inducing mitochondrial stress in pancreatic cancer cells
Jeong KY, Sim JJ, Park M, Kim HM
RING finger and WD repeat domain 3 regulates proliferation and metastasis through the Wnt/β-catenin signalling pathways in hepatocellular carcinoma

Associations of gut microbiota with dyslipidemia based on sex differences in subjects from Northwestern China

Prognostic significance of hemoglobin, albumin, lymphocyte, platelet in gastrointestinal stromal tumors: A propensity matched retrospective cohort study
Zhao Z, Yin XN, Wang J, Chen X, Cai ZL, Zhang B

Contrast-enhanced ultrasound Liver Imaging Reporting and Data System: Lights and shadows in hepatocellular carcinoma and cholangiocellular carcinoma diagnosis

Novel index for the prediction of significant liver fibrosis and cirrhosis in chronic hepatitis B patients in China
Liao MJ, Li J, Dang W, Chen DB, Qin WY, Chen P, Zhao BG, Ren LY, Xu TF, Chen HS, Liao WJ

Percutaneous transhepatic cholangiography vs endoscopic ultrasound-guided biliary drainage: A systematic review
Hassan Z, Gadour E

Isolated gastric variceal bleeding related to non-cirrhotic portal hypertension following oxaliplatin-based chemotherapy: A case report
Zhang X, Gao YY, Song DZ, Qian BX

Hepatitis B core-related antigen: Are we near a treatment endpoint?
Gupta T
ABOUT COVER
Editorial Board Member of World Journal of Gastroenterology, Govind K Makharia, MD, DM,DNB, Professor, Department of Gastroenterology and Human Nutrition, All India Institute of Medical Sciences, Ansari Nagar, New Delhi 110029, India. govindmakharia@aiims.edu

AIMS AND SCOPE
The primary aim of World Journal of Gastroenterology (WJG, World J Gastroenterol) is to provide scholars and readers from various fields of gastroenterology and hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online. WJG mainly publishes articles reporting research results and findings obtained in the field of gastroenterology and hepatology and covering a wide range of topics including gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, gastrointestinal oncology, and pediatric gastroenterology.

INDEXING/ABSTRACTING
The WJG is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports, Index Medicus, MEDLINE, PubMed, PubMed Central, Scopus, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 edition of Journal Citation Reports® cites the 2021 impact factor (IF) for WJG as 5.374; IF without journal self cites: 5.187; 5-year IF: 5.715; Journal Citation Indicator: 0.84; Ranking: 31 among 93 journals in gastroenterology and hepatology; and Quartile category: Q2. The WJG’s CiteScore for 2021 is 8.1 and Scopus CiteScore rank 2021: Gastroenterology is 18/149.

RESPONSIBLE EDITORS FOR THIS ISSUE
Production Editor: Wen-Wen Qi; Production Department Director: Xiang Li; Editorial Office Director: Jia-Ru Fan.

NAME OF JOURNAL
World Journal of Gastroenterology

ISSN
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE
October 1, 1995

FREQUENCY
Weekly

EDITORS-IN-CHIEF
Andrzej S Tarnawski

EDITORIAL BOARD MEMBERS
http://www.wjgnet.com/1007-9327/editorialboard.htm

PUBLICATION DATE
July 21, 2022

COPYRIGHT
© 2022 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/GerInfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/GerInfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com
Zhou Zhao, Xiao-Nan Yin, Jian Wang, Xin Chen, Zhao-Lun Cai, Bo Zhang

Zhou Zhao, Xiao-Nan Yin, Jian Wang, Xin Chen, Zhao-Lun Cai, Bo Zhang, Department of Gastrointestinal Surgery, Sichuan University West China Hospital, Chengdu 610041, Sichuan Province, China

Corresponding author: Bo Zhang, MD, PhD, Professor, Department of Gastrointestinal Surgery, Sichuan University West China Hospital, No. 37 Guoxue Alley, Wuhou District, Chengdu 610041, Sichuan Province, China. hxwcwk@126.com

Abstract

BACKGROUND
The combined index of hemoglobin, albumin, lymphocyte, and platelet (HALP) can reflect systemic inflammation and nutritional status simultaneously, with some evidence revealing its prognostic value for some tumors. However, the effect of HALP on recurrence-free survival (RFS) in patients with gastrointestinal stromal tumors (GISTs) has not been reported.

AIM
To investigate the prognostic value of HALP in GIST patients.

METHODS
Data from 591 untreated patients who underwent R0 resection for primary and localized GISTs at West China Hospital between December 2008 and December 2016 were included. Clinicopathological data, preoperative albumin, blood routine information, postoperative treatment, and recurrence status were recorded. To eliminate baseline inequivalence, the propensity scores matching (PSM) method was introduced. Ultimately, the relationship between RFS and preoperative HALP was investigated.

RESULTS
The optimal cutoff value for HALP was determined to be 31.5 by X-tile analysis. HALP was significantly associated with tumor site, tumor size, mitosis, Ki67, National Institutes of Health (NIH) risk category, and adjuvant therapy (all \( P < 0.001 \)). Before PSM, GIST patients with an increased HALP had a significantly poor RFS (\( P < 0.001 \)), and low HALP was an independent risk factor for poor RFS [hazard ratio (HR): 0.506, 95% confidence interval (95%CI): 0.291-0.879, \( P = 0.016 \)]. In NIH high-risk GIST patients, GIST patients with low HALP had a worse RFS
than patients with high HALP \((P < 0.05)\). After PSM, 458 GIST patients were identified; those with an increased HALP still had significantly poor RFS after PSM \((P < 0.001)\) and low HALP was still an independent risk factor for poor RFS \((HR: 0.558, 95\%CI: 0.319-0.976, P = 0.041)\).

**CONCLUSION**
HALP was significantly correlated with postoperative pathology and postoperative treatment. Furthermore, HALP showed a strong ability to predict RFS in GIST patients who underwent radical resection.

**Key Words:** Gastrointestinal stromal tumors; Nutrition assessment; Immuno-inflammatory-based prognostic scores; Prognosis; Propensity score

©The Author(s) 2022. Published by Baishideng Publishing Group Inc. All rights reserved.

**INTRODUCTION**
Gastrointestinal stromal tumors (GISTs), a rare type of tumor, are the most frequent mesenchymal tumors arising from the gastrointestinal tract[1]. GISTs may occur anywhere in the digestive tract and even occasionally outside the gastrointestinal tract, with the stomach accounting for 60% and the small intestine 30% of all GISTs[2]. The morphology, immunohistochemistry, and molecular markers are helpful to the diagnosis of GISTs. Surgical resection is the standard treatment for resectable GISTs[3]. Nowadays, novel small molecular tyrosine kinase inhibitors, such as imatinib and sunitinib, have revolutionized the integrated treatment of GISTs and greatly improved the long-term prognosis of patients[4].

Some GIST-specific parameters based on postoperative pathologies, such as tumor size, primary tumor location, mitotic index, and tumor rupture, have been used to stratify the risk of recurrence for GISTs[2,5-7]. Meanwhile, a recent effort has shed light on the role of preoperative cancer-related inflammation and nutrition status in progression of various cancers, such as those of gastric[8], colorectal[9], non-small lung[10], and GIST[11-15]. Several preoperative immuno-inflammatory-based prognostic scores, such as the preoperative neutrophil-to-lymphocyte ratio (NLR), the lymphocyte-to-monocyte ratio (LMR), and the platelet-to-lymphocyte ratio (PLR), reflect the systematic inflammatory response, with some evidence supporting their prognostic ability for GISTs[13-17]. Furthermore, nutritional status, such as measured by the prognostic nutritional index (PNI), has also been shown to play an important role in GIST progression[10,11].

Recent studies have proposed a new combined index of hemoglobin, albumin, lymphocyte, and platelet (HALP) which can reflect systemic inflammation and nutritional status simultaneously[18]. It has already been reported as related to the prognosis of patients with pancreatic cancer[19], renal cancer[20], gastric cancer[18], prostate cancer[21], bladder cancer[22], esophageal cancer[23], and small cell lung cancer[24]. However, there are no studies on the relationship between HALP and recurrence in GIST patients who undergo radical resection. Therefore, this study aimed to investigate the prognostic value of preoperative HALP in resected GIST patients.
**MATERIALS AND METHODS**

**Patient population**
A flow diagram of the patient selection process is shown in Figure 1. Data from consecutive, previously untreated patients who underwent R0 resection for primary, localized GISTs at West China Hospital between December 2008 and December 2016 were included in this study. Patients who were younger than 18 years in age, without complete preoperative blood routine information or medical history, or with infectious diseases, blood counts with white blood cells (WBCs) > 10 × 10^9/L, neutrophils > 8 × 10^9 /L, or lymphocytes > 5 × 10^9/L, other tumors, severe liver, kidney or heart diseases, emergency surgery, or follow-up less than 6 mo were excluded. In total, 591 GIST patients were enrolled for the current analysis.

This study was reviewed and approved by the Ethics Committee of the West China Hospital of Sichuan University, No. 1135(2019) and adhered to the tenets of the Declaration of Helsinki. All patients provided written informed consent.

**Definition**
Recurrence-free survival (RFS) was defined as the time interval between the time of surgery and the time of the first documented appearance of tumor after complete resection. The HALP, PNI, NLR, PLR, and LMR were calculated using the following formulas: HALP = hemoglobin level (g/L) × albumin level (g/L) × lymphocyte count (/L)/platelet count (/L); PNI = albumin level (g/L) + 5 × lymphocyte count (×10^3/mm^3); NLR = neutrophil count (×10^3/mm^3)/lymphocyte count (×10^3/mm^3); PLR = platelet count (×10^3/mm^3)/lymphocyte count (×10^3/mm^3); LMR = lymphocyte count (×10^3/mm^3)/monocyte count (×10^3/mm^3).

**Data collection**
Clinicopathological data, postoperative treatment, and recurrence status were recorded. The following data of each patient were retrieved from the self-built GISTs database: Demographic characteristics, tumor sites, tumor size, mitotic index [mitosis/50 high-power field (HPF) or mitosis/50 mm^2], morphology, immunohistochemistry, molecular markers, preoperative hemoglobin, albumin, WBC count, absolute neutrophil count, monocyte count, platelet count, and lymphocyte count. Tumor risk stratification was determined based on the modified National Institutes of Health (NIH) classification.

**Perioperative evaluation and postoperative histopathological diagnosis**
For all patients, the laboratory tests were evaluated within 1 wk before operation. Preoperative blood routine and blood biochemical examination were performed by the Laboratory Department of Sichuan University West China Hospital. The parameters included complete blood cell count and serum albumin. Histopathological diagnosis was performed by the Department of Pathology of Sichuan University West China Hospital; the postoperative pathological findings included data on gross appearance, tumor size, tumor site, resection margin status, tumor cell morphology, lymph node metastasis status, and immunohistochemical staining, etc.

**Follow-up**
Abdominal/pelvic computed tomography was performed every 3-6 mo in the first 3 years after operation, and then every 6-12 mo, until 5 years after the operation, and then once a year until recurrence. Recurrence status was ascertained up to December 2020.

**Statistical analysis**
The optimal cutoff values for the HALP, PNI, NLR, PLR, and LMR were determined to be 31.5, 48.6, 2.60, 134.8, and 4.0, respectively, by X-tile analysis. Propensity scores matching (PSM) was performed as 1:1 matching and a 0.02 caliper based on the patient’s age, tumor size, tumor site, mitosis, and adjuvant targeted therapy using nearest neighbor matching with the MatchIt R package (https://cran.r-project.org/web/packages/MatchIt/MatchIt.pdf). The categorical variables are reported as n (%) and quantitative variables are reported as mean ± SD or median (range). Statistical significance of group comparisons was analyzed via parametric and nonparametric tests for continuous variables and via chi-square analysis or Fisher’s test for categorical variables. Survival curves of the RFS were calculated by the Kaplan-Meier methods and compared by log-rank tests. Hazard ratio (HR) for recurrence was calculated by Cox regression analysis. Sensitivity and specificity of HALP, PNI, NLR, LMR, and PLR were defined using time-dependent receiver operating characteristic (ROC) curves, and areas under the curve (AUCs) were detected utilizing survival ROC R package. All statistical analyses were performed using SPSS Statistics version 21 (SPSS 21.0; IBM Corp., Armonk, NY, United States) and GraphPad Prism version 7.0 (GraphPad Software, La Jolla, CA, United States). Statistical significance was set at P < 0.05 as two-sided.
RESULTS

Baseline characteristics
The demographic and clinicopathological characteristics of the 591 GIST patients are listed in Table 1 and Supplementary Table 1. The study population consisted of 280 (46.8%) male and 311 (53.2%) female patients. The median age was 57 (range: 21-86) years. The median follow-up time was 56 (range: 4-138) mo. The mean ± SD findings for the HALP, PNI, NLR, PLR, and LMR values were 45.81 ± 33.73, 49.04 ± 5.43, 2.64 ± 1.74, 152.8 ± 84.6 and 5.13 ± 3.00, respectively. The mean ± SD of tumor size was 6.16 ± 4.87 cm. One hundred ninety-one tumors (32.3%) had a mitotic index of > 5/50 HPF. A total of 34.0% (201/691) of the GIST patients received adjuvant therapy with imatinib or sunitinib. According to NIH risk classification, 72 (12.2%) patients were classified as very low risk, 178 (30.1%) patients as low risk, 114 (19.3%) patients as intermediate risk, and 227 (38.4%) patients as high risk. Recurrence occurred in 62 GIST patients.

Association of HALP and clinicopathological factors
The clinicopathological characteristics between the high and low groups of HALP were categorized and analyzed as shown in Table 1 and Supplementary Table 1. Together, 229 patients were assigned to the low HALP group and 362 patients to the high HALP group. The results demonstrated that tumor site, tumor size, mitotic index, Ki67, NIH risk category, and adjuvant therapy were significantly associated with HALP (all \( P < 0.05 \)).

PSM analysis was further carried out to avoid confounding variables that might interfere with the association between RFS and HALP level. After 1:1 matching, PSM analysis identified 229 pairs of GIST patients. After PSM, HALP was still associated with sex, Ki67, and recurrence but not with any other clinicopathological characteristics (Table 1 and Supplementary Table 1).

Association of clinicopathological factors and RFS
Before PSM, tumor site, tumor size, mitotic index, Ki67, NIH risk category, NLR, PLR, PNI, and HALP were associated with RFS (all \( P < 0.05 \)) (Table 2). RFS in GIST patients with low HALP was significantly worse than in those with high HALP (Figure 2). Cox multiple regression analysis showed that HALP was an independent prognostic factor for RFS in GIST patients before PSM (HR: 0.506, 95% confidence interval (CI): 0.291-0.879, \( P = 0.016 \)).

After PSM, tumor site, tumor size, mitotic index, Ki67, NIH risk category, PNI, NLR, PLR, and HALP were still related to RFS (all \( P < 0.05 \)) (Table 2). RFS was also significantly worse in GIST patients with low HALP than in those with high HALP (Figure 2). Furthermore, Cox multiple regression analysis showed that HALP was an independent prognostic factor for RFS in GIST patients (HR: 0.558, 95%CI: 0.319-0.976, \( P = 0.041 \)).

Subgroup analysis
The clinicopathological characteristics of high-risk GIST patients between the high and low groups of HALP were categorized in Supplementary Table 1. Together, 125 patients were assigned to the low HALP group and 102 patients to the high HALP group. The results demonstrated that sex and Ki67 were associated with HALP (both \( P < 0.05 \)). Not surprisingly, patients in the low HALP group had significantly worse survival than patients in the high HALP group (Figure 2). Furthermore, Cox multiple regression analysis indicated that HALP was an independent prognostic factor for RFS in GIST patients (HR: 0.469, 95%CI: 0.245-0.896, \( P = 0.022 \)) (Supplementary Table 2).
Table 1 Baseline characteristics in patients with high or low combination index of hemoglobin, albumin, lymphocyte, and platelet before and after propensity scores matching (mean ± SD)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Before PSM*</th>
<th>After PSM</th>
<th>P value</th>
<th>Before PSM*</th>
<th>After PSM</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Low HALP, &lt; 31.5</td>
<td>High HALP, ≥ 31.5</td>
<td>P value</td>
<td>All</td>
<td>Low HALP, &lt; 31.5</td>
</tr>
<tr>
<td>n (%)</td>
<td>591</td>
<td>229 (38.7)</td>
<td>362 (61.3)</td>
<td>-</td>
<td>458</td>
<td>229 (50)</td>
</tr>
<tr>
<td>Age in yr</td>
<td>56.3 ± 12.0</td>
<td>56.7 ± 12.2</td>
<td>56.1 ± 11.8</td>
<td>56.8 ± 12.1</td>
<td>56.7 ± 12.2</td>
<td>57.0 ± 12.1</td>
</tr>
<tr>
<td>&lt; 60</td>
<td>337 (57.0)</td>
<td>129</td>
<td>208</td>
<td>129</td>
<td>206 (55.9)</td>
<td>129</td>
</tr>
<tr>
<td>≥ 60</td>
<td>254 (43.0)</td>
<td>100</td>
<td>154</td>
<td>0.788</td>
<td>202 (44.1)</td>
<td>100</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>280 (47.4)</td>
<td>98</td>
<td>182</td>
<td>233 (50.9)</td>
<td>131</td>
</tr>
<tr>
<td>Female</td>
<td>311 (52.6)</td>
<td>131</td>
<td>180</td>
<td>0.076</td>
<td>225 (49.1)</td>
<td>98</td>
</tr>
<tr>
<td>Tumor site</td>
<td>Stomach</td>
<td>424 (71.7)</td>
<td>143</td>
<td>281</td>
<td>299 (65.3)</td>
<td>143</td>
</tr>
<tr>
<td>Non-stomach</td>
<td>167 (28.3)</td>
<td>86</td>
<td>81</td>
<td>&lt; 0.001*</td>
<td>159 (34.7)</td>
<td>86</td>
</tr>
<tr>
<td>Tumor size in cm</td>
<td>6.16 ± 4.87</td>
<td>7.69 ± 5.65</td>
<td>5.18 ± 4.02</td>
<td>7.13 ± 5.08</td>
<td>7.69 ± 5.65</td>
<td>6.57 ± 4.38</td>
</tr>
<tr>
<td>≤ 2</td>
<td>86 (14.6)</td>
<td>10</td>
<td>76</td>
<td>27 (5.9)</td>
<td>10</td>
<td>17</td>
</tr>
<tr>
<td>2.1-5.0</td>
<td>251 (42.5)</td>
<td>87</td>
<td>164</td>
<td>177 (38.6)</td>
<td>87</td>
<td>90</td>
</tr>
<tr>
<td>5.1-10.0</td>
<td>184 (31.1)</td>
<td>95</td>
<td>89</td>
<td>184 (40.2)</td>
<td>95</td>
<td>89</td>
</tr>
<tr>
<td>&gt; 10.0</td>
<td>70 (11.8)</td>
<td>37</td>
<td>33</td>
<td>&lt; 0.001*</td>
<td>70 (15.3)</td>
<td>37</td>
</tr>
<tr>
<td>Mitotic index/50 HPF</td>
<td>≤ 5</td>
<td>332 (56.2)</td>
<td>107</td>
<td>225</td>
<td>220 (48.0)</td>
<td>107</td>
</tr>
<tr>
<td>&gt; 10</td>
<td>100 (16.9)</td>
<td>45</td>
<td>55</td>
<td>91 (19.9)</td>
<td>45</td>
<td>46</td>
</tr>
<tr>
<td>Unknown</td>
<td>91 (15.4)</td>
<td>49</td>
<td>42</td>
<td>89 (19.4)</td>
<td>49</td>
<td>40</td>
</tr>
<tr>
<td>Kit67</td>
<td>≤ 10</td>
<td>417 (70.6)</td>
<td>140</td>
<td>277</td>
<td>308 (67.3)</td>
<td>140</td>
</tr>
<tr>
<td>&gt; 10</td>
<td>98 (16.6)</td>
<td>61</td>
<td>37</td>
<td>94 (20.5)</td>
<td>61</td>
<td>33</td>
</tr>
<tr>
<td>Unknown</td>
<td>76 (12.9)</td>
<td>28</td>
<td>48</td>
<td>&lt; 0.001*</td>
<td>58 (12.7)</td>
<td>28</td>
</tr>
<tr>
<td>NIH risk category</td>
<td>Very low risk</td>
<td>72 (12.2)</td>
<td>9</td>
<td>63</td>
<td>21 (4.6)</td>
<td>9</td>
</tr>
<tr>
<td>Low risk</td>
<td>178 (30.1)</td>
<td>52</td>
<td>126</td>
<td>113 (24.7)</td>
<td>52</td>
<td>61</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>114 (19.3)</td>
<td>43</td>
<td>71</td>
<td>100 (21.8)</td>
<td>43</td>
<td>57</td>
</tr>
<tr>
<td>High risk</td>
<td>227 (38.4)</td>
<td>125</td>
<td>102</td>
<td>&lt; 0.001*</td>
<td>224 (48.9)</td>
<td>125</td>
</tr>
<tr>
<td>Adjuvant therapy</td>
<td>Yes</td>
<td>201 (34.0)</td>
<td>99</td>
<td>102</td>
<td>193 (42.1)</td>
<td>99</td>
</tr>
<tr>
<td>No</td>
<td>390 (66.0)</td>
<td>130</td>
<td>260</td>
<td>&lt; 0.001*</td>
<td>265 (57.9)</td>
<td>130</td>
</tr>
<tr>
<td>Recurrence</td>
<td>Yes</td>
<td>62 (10.5)</td>
<td>42</td>
<td>20</td>
<td>61 (13.3)</td>
<td>42</td>
</tr>
<tr>
<td>No</td>
<td>529 (89.5)</td>
<td>187</td>
<td>342</td>
<td>&lt; 0.001*</td>
<td>397 (86.7)</td>
<td>187</td>
</tr>
</tbody>
</table>

*Method = nearest; Clipper value = 0.02.

*P < 0.05 was considered statistically significant.
HALP: Combination index of hemoglobin, albumin, lymphocyte, and platelet; HPF: High-power field; NIH: National Institutes of Health; PSM: Propensity scores matching; SD: Standard deviation.
Associated with the risk and prognosis of GIST.

Low levels of serum albumin have been shown to be an independent prognostic factor of survival in a variety of cancers, including those of colorectal[34], gastric[35], pancreatic[36], and breast[37]. As a result, it is unsurprising that HALP, which reflects systemic inflammation and nutritional status simultaneously, is associated with the risk and prognosis of GIST.

**DISCUSSION**

There is growing evidence that preoperative nutritional status and inflammatory response may be a potentially powerful predictor of the prognosis of cancer patients. Consistent with previous research, the present study found that preoperative inflammation scores, such as NLR and PLR, were associated with the prognosis of GIST patients, both before and after PSM[14,16,30,31] (Supplementary Figure 1). However, LMR seemed to have no effect on the RFS of GIST patients (Supplementary Figure 1), which differs from findings of previous studies[18]. In addition, the PNI, a nutritional score based on albumin levels and lymphocytes, was also related to RFS of GIST patients, both before and after PSM in the present study[11,12] (Supplementary Figure 1).

In this study, we also found that preoperative HALP was significantly correlated with tumor site, tumor size, mitosis, Ki67, NIH risk category, and adjuvant therapy (Table 1). To balance the patient characteristics and standard prognostic factors between groups, we utilized the PSM method to balance patient's age, tumor size, tumor site, mitosis, and adjuvant targeted therapy. After PSM, sex, Ki67, PNI, NLR, LMR, and PLR were still associated with HALP (Supplementary Table 1). Notably, there was no difference in standard prognostic factors (i.e., tumor site, tumor size, mitosis, NIH risk category, and adjuvant therapy) between the low and high HALP groups (Table 1). Given that HALP shared several parameters with PNI, NLR, LMR, and PLR, their statistically significant correlation is unsurprising. The correlation between HALP and sex may be due to the fact that the male and female patients had significantly different hemoglobin levels (123.22 ± 2.08 g/L for males and 105.46 ± 1.84 g/L for females, P < 0.001). Remarkably, recurrence was not associated with either sex or histologic subtype (Supplementary Table 1). Subgroup analysis by sex revealed that a low level of HALP was associated with recurrence in both male and female patients (P = 0.048 and P = 0.018, respectively) (Supplementary Figure 2).

Finally, consistent with previous research on HALP in other tumors[18,19], our findings revealed prognostic value of HALP in GIST[20-24]. HALP was an independent risk factor for GIST patients before PSM, after PSM, and in high-risk subgroups (Table 2 and Supplementary Table 3). Thus, HALP can be used to not only evaluate GIST patients' postoperative risk prior to surgery but also to assess their prognosis. Notably, the HALP index can be utilized to predict the prognosis of patients in a convenient and cost-effective manner.

Although the underlying mechanism of systemic inflammation in tumorigenesis, progression and metastasis remains obscure, some theories suggest that it stimulates angiogenesis, immunosuppression, and formation of the supporting microenvironment. Lymphocytes are well known to play a critical role in tumor growth inhibition[32-34]. A higher lymphocyte signature is associated with improved prognosis in a variety of tumors[34], whereas platelets can infiltrate the tumor microenvironment and interact directly with cancer cells[35,36], assisting circulating tumor cells in adhering to endothelial cells and establishing a niche environment prior to metastasis[37-41].

Anemia is one of the most common symptoms of GIST, which can be caused by both gastrointestinal bleeding and intratumoral bleeding[12]. Yang et al[43] identified GIST with gastrointestinal bleeding as an independent prognostic predictor of poor RFS. Several studies have demonstrated that low hemoglobin levels can result in tumor hypoxia, which is associated with an increased risk of local failure and distant metastasis[31,44]. Furthermore, a hypoxic tumor environment may result in limited drug accumulation and hinder drug efficacy[45]. Most importantly, anemia is a common adverse effect of imatinib[46], which may require the prescribing physician to stop the drug or reduce the dose. High levels of preoperative hemoglobin may help to prevent this adverse effect.

Low levels of serum albumin are also associated with poor long-term survival in GIST patients[44,45], which is consistent with our findings. Serum albumin is generally considered as associated with nutritional status and liver or renal function, both of which may affect the prescribing physician's decision-making, similar to hemoglobin. Additionally, tumor tissues have abnormal vascular endothelial gaps and lack effective lymphatic drainage, allowing macromolecules, such as albumin, to accumulate more readily in tumor tissue than in normal tissue[47,48]. Consequently, serum albumin is suspected of being a possible nutritional source for tumor growth, due to its elevated accumulation in tumors[49-51]. This effect is referred to as the ‘enhanced permeability and retention effect’. Moreover, about 95% of imatinib is bound to serum proteins, mainly albumin and 1-acid glycoprotein, which may facilitate drug accumulation in tumors and improve therapeutic effect[52,53]. Subsequently, serum albumin levels have been shown to be an independent prognostic factor of survival in a variety of cancers, including those of colorectal[54], gastric[55], pancreatic[56], and breast[57]. As a result, it is unsurprising that HALP, which reflects systemic inflammation and nutritional status simultaneously, is associated with the risk and prognosis of GIST.

**Sensitivity analysis**

Time-dependent ROCs were generated for HALP, PNI, NLR, LMR, and PLR to predict 5-year RFS. According to the results, the 5-year AUC reached 0.661 in the HALP group, while PNI, NLR, LMR, and PLR reached 0.622, 0.591, 0.505, and 0.627, respectively (Figure 3).
## Table 2 Univariate and multivariate regression analysis of prognostic factors in patients before and after propensity scores matching

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Before PSM</th>
<th>After PSM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate analysis, HR (95%CI)</td>
<td>Multivariate analysis, HR (95%CI)</td>
</tr>
<tr>
<td></td>
<td>Univariate analysis, P value</td>
<td>Multivariate analysis, P value</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.009 (0.987-1.030)</td>
<td>1.006 (0.984-1.027)</td>
</tr>
<tr>
<td>Sex: Male vs female</td>
<td>0.639 (0.386-1.056)</td>
<td>0.711 (0.429-1.179)</td>
</tr>
<tr>
<td>Tumor site: Stomach vs non-stomach</td>
<td>2.273 (1.377-3.752)</td>
<td>2.979 (1.716-5.171)</td>
</tr>
<tr>
<td>Tumor size in cm: ≤ 2/2.1-5.0/5.1-10.0/&gt; 10.0</td>
<td>2.629 (1.948-3.548)</td>
<td>1.070 (1.032-1.109)</td>
</tr>
<tr>
<td>Mitotic index as/50 HFP: ≤ 5/6-10/&gt; 10/unknown</td>
<td>2.071 (1.686-2.545)</td>
<td>&lt; 0.001 NS</td>
</tr>
<tr>
<td>≤ 5 vs 6-10</td>
<td>5.659 (2.151-14.887)</td>
<td>5.442 (2.067-14.323)</td>
</tr>
<tr>
<td>≤ 5 vs &gt; 10</td>
<td>8.295 (3.140-21.720)</td>
<td>14.722 (6.037-35.904)</td>
</tr>
<tr>
<td>≤ 5 vs unknown</td>
<td>5.299 (2.041-13.757)</td>
<td>9.851 (3.843-25.251)</td>
</tr>
<tr>
<td>CD117: */-</td>
<td>1.231 (0.300-5.059)</td>
<td>NA</td>
</tr>
<tr>
<td>DOG1: */-unknown</td>
<td>1.464 (0.773-2.774)</td>
<td>NA</td>
</tr>
<tr>
<td>Ki67: ≤ 10/&gt; 10/unknown</td>
<td>1.919 (1.453-2.533)</td>
<td>&lt; 0.001 NS</td>
</tr>
<tr>
<td>&lt; 10 vs ≤ 10</td>
<td>3.579 (1.771-7.233)</td>
<td>&lt; 0.001 NS</td>
</tr>
<tr>
<td>Unknown vs ≤ 10</td>
<td>2.844 (1.290-6.270)</td>
<td>0.024 NS</td>
</tr>
<tr>
<td>Histologic subtypes: Spindle/epithelioid/mixed</td>
<td>1.361 (0.981-1.889)</td>
<td>NS</td>
</tr>
<tr>
<td>NIH risk category: Very low/low/intermediate/high</td>
<td>3.218 (2.180-4.751)</td>
<td>NS</td>
</tr>
<tr>
<td>Adjuvant therapy: Yes/no</td>
<td>1.289 (0.768-2.162)</td>
<td>0.336 NS</td>
</tr>
<tr>
<td>NLR: &lt; 2.60/&gt; 2.60</td>
<td>2.025 (1.229-3.337)</td>
<td>0.006 NS</td>
</tr>
<tr>
<td>PLR: &lt; 134.8/&gt; 134.8</td>
<td>2.925 (1.673-5.112)</td>
<td>&lt; 0.001 NS</td>
</tr>
<tr>
<td>LMR: &lt; 4.0/&gt; 4.0</td>
<td>1.296 (0.777-2.163)</td>
<td>0.321 NS</td>
</tr>
<tr>
<td>PNI: &lt; 48.6/&gt; 48.6</td>
<td>0.291 (0.171-0.496)</td>
<td>&lt; 0.001 NS</td>
</tr>
<tr>
<td>HALP: &lt; 31.5/&gt; 31.5</td>
<td>0.341 (0.197-0.590)</td>
<td>&lt; 0.001 NS</td>
</tr>
</tbody>
</table>

*P < 0.05 was considered statistically significant.
CI: Confidence interval; HALP: Combination index of hemoglobin, albumin, lymphocyte, and platelet; HPF: High-power field; HR: Hazard ratio; NA: Not adopted; LMR: Lymphocyte-to-monocyte ratio; NIH: National Institutes of Health; NLR: Neutrophil-to-lymphocyte ratio; NS: Not significant; PLR: Platelet-to-lymphocyte ratio; PNI: Prognostic nutritional index; PSM: Propensity scores matching.

There are some limitations to this study. First, because this is a retrospective study, biases in the data collection process are possible. Second, our cases were collected between 2008 and 2016, the period during which imatinib was used for adjuvant treatment of GIST in China. Despite the adverse reaction...
Zhao Z et al. HALP predicts recurrence in GIST

Figure 2 Kaplan-Meier curves of recurrence-free survival. A: Stratified by low/high levels of the combination index of hemoglobin, albumin, lymphocyte, and platelet (HALP) in gastrointestinal stromal tumors (GISTs) patients before propensity scores matching (PSM); B: Stratified by low/high levels of HALP in GIST patients after PSM; C: Stratified by low/high levels of HALP in high-risk GIST patients. GIST: Gastrointestinal stromal tumors; PSM: Propensity scores matching; HALP: Hemoglobin, albumin, lymphocyte, and platelet.

Figure 3 Comparison of hemoglobin, albumin, lymphocyte, and platelet and other parameters in prediction ability of 5-year recurrence-free survival by receiver operating characteristic curve analysis before propensity scores matching. AUC: Area under the curve; HALP: Hemoglobin, albumin, lymphocyte, and platelet; LMR: Lymphocyte-to-monocyte ratio; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; PNI: Prognostic nutritional index; PSM: Propensity scores matching; ROC: Receiver operating characteristic.

CONCLUSION
HALP was associated with postoperative pathological data (i.e. tumor site, tumor size, mitosis, Ki67, NIH risk category) and adjuvant therapy. Furthermore, HALP was an independent risk factor for RFS in GIST patients who underwent radical resection.
ARTICLE HIGHLIGHTS

Research background
The combination index of hemoglobin, albumin, lymphocyte, and platelet (HALP) has been reported as associated with prognosis in many cancers but not yet in gastrointestinal stromal tumors (GISTs). Therefore, this study aimed to investigate the prognostic value of preoperative HALP in resected GIST patients.

Research motivation
At present, the risk of GIST is mainly based on postoperative pathological indicators. The motivation for this article involved the need to find a convenient, non-invasive, preoperative indicator that will assist in prognostic prediction of GIST.

Research objectives
To investigate the prognostic value of HALP in GIST patients.

Research methods
This retrospective cohort study enrolled patients with GIST using propensity scores matching to explore the relationship between HALP, postoperative clinicopathological data, and the prognostic significance of HALP.

Research results
HALP can be conveniently used preoperatively to assess risk and prognosis of GIST patients. However, the effect of improving nutritional status or immune-inflammatory status on the prognosis of GIST is still unclear and requires further confirmation through clinical studies.

Research conclusions
HALP was associated with postoperative pathological data (i.e. tumor site, tumor size, mitosis, Ki67, National Institutes of Health risk category) and adjuvant therapy. Furthermore, HALP was an independent risk factor for recurrence-free survival in GIST patients who underwent radical resection. This study is the first to report the prognostic significance of HALP in GIST. In this study, HALP was found to be an independent risk factor for GIST patients with R0 resection. Consistent with reports of HALP in other tumors, HALP is also associated with prognosis in GIST. HALP was also found to be an independent risk factor for GIST patients with R0 resection. In clinical practice, convenient and non-invasive preoperative HALP may be used to assist in the prediction of risk and prognosis for GIST patients.

Research perspectives
Through this retrospective cohort study, we found the prognostic significance of HALP in GIST. This study did not evaluate other clinicopathological factors related to prognosis, especially gene mutation status. Subsequent studies should employ a prospective cohort method and incorporate additional factors to further explore the prognostic significance of HALP in GIST patients.

FOOTNOTES

Author contributions: All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; and all authors took part in drafting, revising or critically reviewing the article, gave final approval of the version to be published, agreed on the journal to which the article has been submitted and agreed to be accountable for all aspects of the work.

Supported by: National Natural Science Foundation of China, No. 81572931; and The 1.3.5 Project for Disciplines of Excellence, West China Hospital, Sichuan University, No. ZYJC18034.

Institutional review board statement: The Institutional Review Board of the West China Hospital of Sichuan University provided approval for this study, No. 1135(2019).

Informed consent statement: This study examined only patients' electronic health records. Each patient had been asked to sign an informed consent form authorizing the use of their electronic health record for scientific research. If the patient had not consented, we were unable to access his/her information in the hospital's information system.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.
REFERENCES


Zhao Z et al. HALP predicts recurrence in GIST


Shankaran V, Ikeda H, Bruce AT, White JM, Swanson PE, Old LJ, Schreiber RD. IFNgamma and lymphocytes prevent tumour development and shape tumour immunogenicity. Nature 2001; 410: 1107-1111. [PMID: 11323675 DOI: 10.1038/35074122]


