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AIMS AND SCOPE

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ORIGINAL ARTICLE

Retrospective Cohort Study

Prognostic significance of hemoglobin, albumin, lymphocyte, platelet in gastrointestinal stromal tumors: A propensity matched retrospective cohort study

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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

Core Tip: The combined index of hemoglobin, albumin, lymphocyte, and platelet (HALP) can reflect systemic inflammation and nutritional status simultaneously. We demonstrated that HALP has a statistically significant correlation with postoperative pathology and postoperative treatment in patients with gastrointestinal stromal tumors (GISTs). Furthermore, we revealed that a low level of HALP was an independent risk factor for poor recurrence-free survival in GIST patients following radical resection before and after propensity scores matching.

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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)[19]; PNI = albumin level (g/L) + 5 × lymphocyte count (n/mm^3)[25]; NLR = neutrophil count (n/mm^3)/lymphocyte count (n/mm^3)[15,16]; PLR = platelet count (n/mm^3)/lymphocyte count (n/mm^3)[14]; LMR = lymphocyte count (n/mm^3)/monocyte count (n/mm^3)[26].

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 [27].

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[28]. 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[29]. 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.

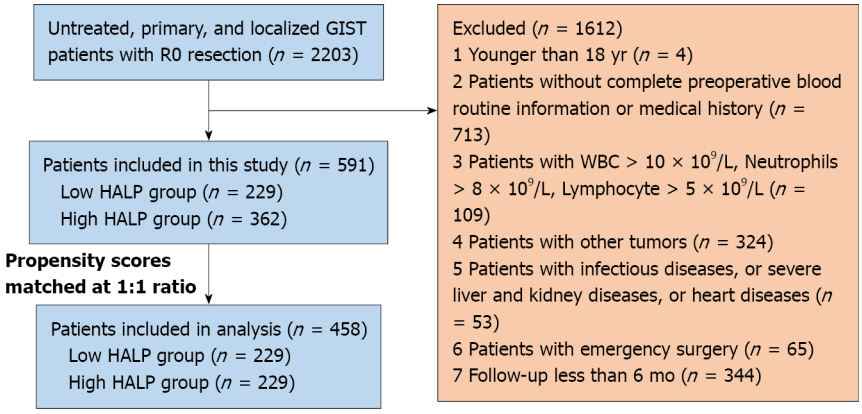

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Figure 1 Flow diagram of the patient selection process. GIST: Gastrointestinal stromal tumor; HALP: Combination index of hemoglobin, albumin, lymphocyte, and platelet; WBC: White blood cell.

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)

Characteristics	Before PSM[1]				After PSM			
	All	Low HALP, < 31.5	High HALP, ≥ 31.5	*P* value	All	Low HALP, < 31.5	High HALP, ≥ 31.5	*P* value
n (%)	591	229 (38.7)	362 (61.3)	-	458	229 (50)	229 (50)	-
Age in yr	56.3 ± 12.0	56.7 ± 12.2	56.1 ± 11.8		56.8 ± 12.1	56.7 ± 12.2	57.0 ± 12.1	
< 60	337 (57.0)	129	208		256 (55.9)	129	127	
≥ 60	254 (43.0)	100	154	0.788	202 (44.1)	100	102	0.851
Sex								
Male	280 (47.4)	98	182		233 (50.9)	131	102	
Female	311 (52.6)	131	180	0.076	225 (49.1)	98	127	0.007[a]
Tumor site								
Stomach	424 (71.7)	143	281		299 (65.3)	143	156	
Non-stomach	167 (28.3)	86	81	< 0.001[a]	159 (34.7)	86	73	0.202
Tumor size in cm	6.16 ± 4.87	7.69 ± 5.65	5.18 ± 4.02		7.13 ± 5.08	7.69 ± 5.65	6.57 ± 4.38	
≤ 2	86 (14.6)	10	76		27 (5.9)	10	17	
2.1-5.0	251 (42.5)	87	164		177 (38.6)	87	90	
5.1-10.0	184 (31.1)	95	89		184 (40.2)	95	89	
> 10.0	70 (11.8)	37	33	< 0.001[a]	70 (15.3)	37	33	0.514
Mitotic index/50 HPF								
≤ 5	332 (56.2)	107	225		220 (48.0)	107	113	
6-10	100 (16.9)	45	55		91 (19.9)	45	46	
> 10	91 (15.4)	49	42		89 (19.4)	49	40	
Unknown	68 (11.5)	28	40	0.001[a]	58 (12.7)	28	30	0.764
Ki67								
≤ 10	417 (70.6)	140	277		308 (67.3)	140	168	
> 10	98 (16.6)	61	37		94 (20.5)	61	33	
Unknown	76 (12.9)	28	48	< 0.001[a]	26 (12.2)	28	28	0.004[a]
NIH risk category								
Very low risk	72 (12.2)	9	63		21 (4.6)	9	12	
Low risk	178 (30.1)	52	126		113 (24.7)	52	61	
Intermediate risk	114 (19.3)	43	71		100 (21.8)	43	57	
High risk	227 (38.4)	125	102	< 0.001[a]	224 (48.9)	125	99	0.106
Adjuvant therapy								
Yes	201 (34.0)	99	102		193 (42.1)	99	94	
No	390 (66.0)	130	260	< 0.001[a]	265 (57.9)	130	135	0.636
Recurrence								
Yes	62 (10.5)	42	20		61 (13.3)	42	19	
No	529 (89.5)	187	342	< 0.001[a]	397 (86.7)	187	210	0.002[a]

[1]Method = nearest; Cliper value = 0.02.

[a]$P < 0.05$ 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.

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).

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[14]. 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[42]. 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.

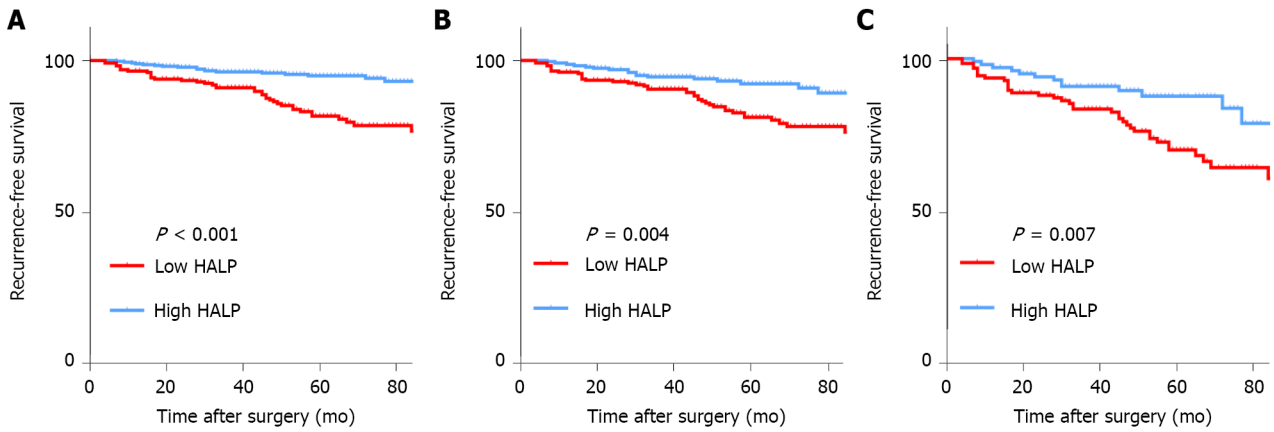
Table 2 Univariate and multivariate regression analysis of prognostic factors in patients before and after propensity scores matching

Risk factors	Before PSM				After PSM			
	Univariate analysis, HR (95%CI)	Univariate analysis, *P* value	Multivariate analysis, HR (95%CI)	Multivariate analysis, *P* value	Univariate analysis, HR (95%CI)	Univariate analysis, *P* value	Multivariate analysis, HR (95%CI)	Multivariate analysis, *P* value
Age	1.009 (0.987-1.030)	0.431		NS	1.006 (0.984-1.027)	0.607		NS
Sex: Male *vs* female	0.639 (0.386-1.056)	0.081		NS	0.711 (0.429-1.179)	0.186		NS
Tumor site: Stomach *vs* non-stomach	2.273 (1.377-3.752)	0.001[a]	2.979 (1.716-5.171)	< 0.001[a]	1.702 (1.028-2.818)	0.039[a]	2.865 (1.631-5.032)	< 0.001[a]
Tumor size in cm: ≤ 2/2.1-5.0/5.1-10.0/> 10.0	2.629 (1.948-3.548)	< 0.001[a]	1.070 (1.032-1.109)	0.001[a]	1.086 (1.056-1.116)	< 0.001[a]	1.068 (1.029-1.107)	< 0.001[a]
Mitotic index as/50 HPF: ≤ 5/6-10/> 10/unknown	2.071 (1.686-2.545)	< 0.001[a]		< 0.001[a]		< 0.001[a]		0.001[a]
≤ 5 *vs* 6-10			5.659 (2.151-14.887)	0.002[a]	5.442 (2.067-14.323)	0.001[a]	5.444 (1.955-15.162)	0.001[a]
≤ 5 *vs* > 10			8.259 (3.140-21.720)	< 0.001[a]	14.722 (6.037-35.904)	< 0.001[a]	7.675 (2.759-21.348)	< 0.001[a]
≤ 5 *vs* unknown			5.299 (2.041-13.757)	< 0.001[a]	9.851 (3.843-25.251)	< 0.001[a]	5.107 (1.873-13.923)	0.001[a]
CD117: +/-	1.231 (0.300-5.059)	0.773		NA	1.291 (0.314-5.313)	0.723	-	NA
DOG1: +/-/unknown	1.464 (0.773-2.774)	0.242		NA	1.626 (0.853-3.102)	0.140	-	NA
Ki67: ≤ 10/> 10/unknown	1.919 (1.453-2.533)	< 0.001[a]		0.001[a]		< 0.001[a]		0.001[a]
< 10 *vs* ≤ 10			3.579 (1.771-7.233)	< 0.001[a]	8.625 (4.750-15.660)	< 0.001[a]	3.710 (1.811-7.599)	< 0.001[a]
Unknown *vs* ≤ 10			2.844 (1.290-6.270)	0.024[a]	3.310 (1.528-7.169)	0.002[a]	3.050 (1.365-6.816)	0.007
Histologic subtypes: Spindle/epithelioid/mixed	1.361 (0.981-1.889)	0.065		NS	1.236 (0.891-1.715)	0.204	-	NA
NIH risk category: Very low/low/intermediate/high	3.218 (2.180-4.751)	< 0.001[a]		NS	2.892 (1.865-4.484)	< 0.001[a]	-	NS
Adjuvant therapy: Yes/no	1.289 (0.768-2.162)	0.336	0.445 (0.257-0.769)	0.004[a]	0.923 (0.549-1.551)	0.761		0.003[a]
NLR: < 2.60/≥ 2.60	2.025 (1.229-3.337)	0.006[a]		NS	1.746 (1.055-2.890)	0.030[a]		NS
PLR: < 134.8/≥ 134.8	2.925 (1.673-5.112)	< 0.001[a]		NS	1.991 (1.137-3.486)	0.016[a]		NS
LMR: < 4.0/≥ 4.0	1.296 (0.777-2.163)	0.321		NA	1.088 (0.650-1.821)	0.749	-	NA
PNI: < 48.6/≥ 48.6	0.291 (0.171-0.496)	< 0.001[a]		NS	1.991 (1.137-3.486)	0.016[a]		NS
HALP: < 31.5/≥ 31.5	0.341 (0.197-0.590)	< 0.001[a]	0.506 (0.291-0.879)	0.016[a]	0.457 (0.265-0.785)	0.005[a]	0.558 (0.319-0.976)	0.041[a]

[a]*P* < 0.05 was considered statistically significant.

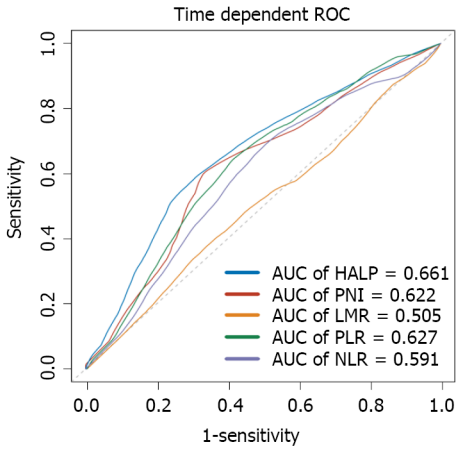
CI: Confidence interval; HALP: Combination index of hemoglobin, albumin, lymphocyte, and platelet; HPF: High-power field; HR: Hazard ratio; NA: Not adopted; LMR: Lymphocyte-to-monocyte ratio; NIH: National Institutes of Health; NLR: Neutrophil-to-lymphocyte ratio; NS: Not significant; PLR: Platelet-to-lymphocyte 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



DOI: 10.3748/wjg.v28.i27.3476

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.



DOI: 10.3748/wjg.v28.i27.3476

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.

and high costs, 201/591 (34.0%) of GIST patients still received adjuvant imatinib therapy. As an important treatment after GIST, adjuvant imatinib therapy can significantly improve the prognosis of GIST patients[58], and its benefits are also shown in the present study (Supplementary Figure 3). However, there was no adequate collection and analysis of the time, dose, and adverse reactions of patients with imatinib or sunitinib therapy, which may also be related to HALP. Moreover, this study did not evaluate other clinicopathological factors related to prognosis, especially gene mutation status. Furthermore, the effect of preoperative or postoperative improvement of nutritional status or inflammation response on the prognosis of GIST remains obscure, and will require further confirmation in clinical studies.

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.

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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.

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Data sharing statement: The data that supporting the findings of this study are available from the corresponding author (e-mail: hxwcwk@126.com) upon reasonable request.

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