Combined Index of Hemoglobin, Albumin, Lymphocyte, and Platelet (HALP) Predict Recurrence After Radical Resection in Gastrointestinal Stromal Tumors: a propensity scores matching analysis

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Abstract

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 of gastrointestinal stromal tumors (GISTs) has not been reported. Therefore, the present study aimed 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 the baseline inequivalence, the propensity scores matching (PSM) method was introduced. The relationship between RFS and preoperative HALP was investigated. Results The optimal cutoff value for the HALP was determined by the x-Tile analysis at 31.5. HALP was significantly associated with tumor site, tumor size, mitosis, Ki67, 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 (HR=0.0551, 95% CI: 0.313 - 0.968, P=0.038). 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, 188 pairs of GIST patients were identified, GIST patients with an increased HALP still had a significantly poor RFS after PSM (P<0.001), and low HALP was still an independent risk factor for poor RFS (HR=0.585, 95% CI: 0.316 - 0.972, P=0.042). Conclusions HALP had a statistically significant correlation with postoperative pathology and postoperative treatment. Furthermore, HALP has a strong ability to predict the RFS in GIST patients with radical resection.

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ABSTRACT

BackgroundThe 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 of gastrointestinal stromal tumors (GISTs) has not been reported. Therefore, the present study aimed 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 the baseline inequivalence, the propensity scores matching (PSM) method was introduced. The relationship between RFS and preoperative HALP was investigated.

Results The optimal cutoff value for the HALP was determined by the x-Tile analysis at 31.5. HALP was significantly associated with tumor site, tumor size, mitosis, Ki67, 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 (HR=0.0551, 95% CI: 0.313 - 0.968, P=0.038). 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, 188 pairs of GIST patients were identified, GIST patients with an increased HALP still had a significantly poor RFS after PSM (P<0.001), and low HALP was still an independent risk factor for poor RFS (HR=0.585, 95% CI: 0.316 - 0.972, P=0.042).

Conclusions HALP had a statistically significant correlation with postoperative pathology and postoperative treatment. Furthermore, HALP has a strong ability to predict the RFS in GIST patients with radical resection.

Key Words: gastrointestinal stromal tumors (GISTs); Combined index of hemoglobin, albumin, lymphocyte, and platelet (HALP); recurrence-free survival (RFS).

What's known?

The comprehensive index of hemoglobin, albumin, lymphocytes, and platelets (HALP) can indicate both systemic inflammation and nutritional status. Some evidence suggested that it has prognostic value for certain tumors, but excluded gastrointestinal stromal tumors.

What's new?

HALP had a statistically significant correlation with postoperative pathology and postoperative treatment in GIST. Furthermore, HALP has a strong ability to predict the RFS in GIST patients with radical resection.

INTRODUCTION

Gastrointestinal stromal tumors (GISTs), a rare type of tumor, are the most frequent mesenchymal tumors arising from gastrointestinal tract[1]. GISTs may occur anywhere in the digestive tract and even outside the gastrointestinal tract occasionally, with the stomach accounting for 60% and the small intestine 30%[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].

Currently, 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, the recent effort has shed light on the role of preoperative cancer-related inflammation and nutrition status in cancer progression, such as gastric cancer[8], colorectal cancer[9], non-small lung

cancer[10], and gastrointestinal stromal tumor[11-16]. 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 revealing that they are prognostic for GISTs[13-17]. Furthermore, nutritional status, such as 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 is composed of hemoglobin, albumin, lymphocytes and platelets, and can reflect systemic inflammation and nutritional status simultaneously[18]. It has been reported to be 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 with radical resection. Therefore, this study aimed to investigate the prognostic value of preoperative HALP in resected GIST patients.

METHOD

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 younger than 18 years, without complete preoperative blood routine information or medical history, with infectious diseases, WBC >10 × 10ˆ9/L, neutrophils > 8 × 10ˆ9/L, or lymphocyte > 5 × 10ˆ9/L, with other tumors, with severe liver, kidney, or heart diseases, with emergency surgery, and follow-up less than 6 months were excluded. Finally, 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. All patients provided written informed consent.

Definition

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: hemoglobin level (g/L) × albumin level (g/L) × lymphocyte count (/L) / platelet count (/L)[19], albumin level (g/L) + 5 × lymphocyte count (number/mm^3)[25], neutrophil count (number/mm^3)/ lymphocyte count (number/mm^3)[15,16], platelet count (number/mm^3) / lymphocyte count (number/mm^3)[14], lymphocyte count (number/mm^3) / monocyte count (number/mm^3)[26], respectively.

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 or mitosis / 50 mm^2), morphology, immunohistochemistry, molecular markers, preoperative hemoglobin, albumin, white blood cells 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 Follow-up

The laboratory tests were evaluated within 1 week before operation. The parameters included complete blood cell count and serum albumin. Abdominal ultrasonography or computed tomography was performed every 3 - 6 months in the first 3 years after operation, and then every 6 - 12 months until 5 years after the operation, and then once a year until recurrence. The recurrence status of patients was ascertained by December 2020.

Statistical analysis

The optimal cutoff values for the HALP, PNI, NLR, PLR, and LMR were determined by the x-Tile analysis at 31.5, 48.6, 2.60, 134.8, and 4.0, respectively[28]. PSM was performed as 1:1 matching with nearest neighbor matching and a 0.1 caliper based on the patient's age, tumor size, tumor site, mitosis, Ki67, intratumoral hemorrhage, intratumoral necrosis and postoperative targeted therapy using nearest neighbor matching with MatchIt R package. The categorical variables are reported as numbers (%) and quantitative variables are reported as the means ± SD or medians (range). Statistical significance of group comparisons was analyzed via parametric and nonparametric tests for continuous variables and via chi-square analysis or Fisher test for categorical variables. Survival curves of the RFS were calculated by the Kaplan-Meier methods and compared by log-rank tests. Hazard ratios for recurrence were calculated by Cox regression analysis. Sensitivity and specificity HALP, PNI, NLR, LMR, and PLR were defined using time dependent receiver operating characteristics (ROC) curves, and areas under the curve (AUC) were detected utilizing survivalROC R package[29]. All statistical analyses were performed using SPSS Statistics version 21 (SPSS 21.0; SPSS Inc) and GraphPad Prism version 7.0 (GraphPad Software). Statistical significance was set at $P < 0.05$ as two-sided.

RESULTS

Baseline characteristics

The demographic and clinicopathological characteristics of the 591 GIST patients were listed in *Table 1* . The study population consisted of 280 (46.8%) male and 311 (53.2%) female patients. The median (range) age was 57 (21 - 86) years. The median follow-up time was 56 months (range, 4-138). The means ± SD for the HALP, the PNI, the NLR, the PLR, and the 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 means ± SD of tumor size was 6.16 ± 4.87 cm. 191 tumors (32.3%) had a mitotic index of > 5/50 high-power field. 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 were classified as low risk, 114 (19.3%) patients were classified as intermediate risk, and 227 (38.4%) patients were classified 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 in*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, intratumoral hemorrhage, intratumoral necrosis, NIH risk category, and adjuvant therapy were 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 188 pairs of GIST patients. After PSM, HALP were still associated with gender, histologic subtypes, NLR, PLR, LMR, and PNI, but not with other clinicopathological characteristics (*Table 1*).

Association of clinicopathological factors and RFS

Before PSM, tumor site, tumor size, mitotic index, Ki67, intratumoral hemorrhage, intratumoral necrosis, NIH risk category, albumin, neutrophils, platelets, NLR, PLR, PNI, and HALP were associated with RFS (all $P < 0.05$) (*Table 2*). RFS in GIST patients with low HALP were significantly poor than patients 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% CI: 0.291-0.879, P=0.016).

After PSM, tumor site, tumor size, mitotic index, Ki67, intratumoral hemorrhage, intratumoral necrosis, NIH risk category, albumin, neutrophils, PNI, and HALP were still related to RFS (all P < 0.05) (*Table 2*). RFS was also significantly poor in GIST patients with low HALP than patients with high HALP. (*Figure 2*). Furthermore, Cox multiple regression analysis showed that HALP was an independent prognostic factor for RFS in GIST patients (HR=0.585, 95% CI: 0.316 - 0.972, P=0.042).

Subgroup analysis

The clinicopathological characteristics of high-risk GIST patients between the high and low groups of HALP were categorized in *Table S1* . Together, 125 patients were assigned to the low HALP group and 102 patients to the high HALP group. The results demonstrated that gender, Ki67, intratumoral hemorrhage, intratumoral necrosis were associated with HALP (all 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) (*Table S2*).

Sensitivity analysis

As sensitivity analysis, time dependent ROC was generated for HALP, PNI, NLR, LMR, and PLR to predict five-year RFS. According to the results, HALP had the highest sensitivity and accuracy (AUC=0.661) in predicting five-year RFS, while the AUC of PNI, NLR, LMR, and PLR were 0.622, 0.591, 0.505, and 0.627, respectively (*Figure 3*).

In addition, to assess consistency of HALP prediction, Cox multiple regression analysis in GIST patients before PSM, after PSM and in high-risk subgroups were performed to better assess the impact of each type of covariates on the association between HALP and RFS. In the three models, tumor site, mitotic index, Ki67, adjuvant therapy, and HALP were all proved as independent prognostic factors for poor RFS, but tumor size was not in high-risk GIST patients (*Table 2* & *Table S2*).

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, preoperative inflammation scores, such as NLR and PLR, were associated with the prognosis of GIST patients before PSM and after PSM in the present study[14,16,30,31]. However, LMR seemed to be irrelevant to the RFS of GIST patients, which is different from previous studies[14]. In addition, the PNI, a nutritional score based on albumin levels and lymphocytes, was also related to RFS of GIST patients before PSM and after PSM in present study[11,12] (*Figure S1*).

In this study, we found that preoperative HALP was significantly correlated with tumor site, tumor size, mitosis, Ki67, intratumoral hemorrhage, intratumoral necrosis, NIH risk category and adjuvant therapy. Anemia is one of the most common symptoms of GIST, which may be caused by gastrointestinal bleeding and intratumoral bleeding[32]. Additionally, since tumor cells synthesize proteins with albumin, this will result in hypoalbuminemia in GIST patients. As a result, it is unsurprising that HALP, which is composed of hemoglobin and albumin, is associated with parameters indicating the degree of malignancy in GIST.

To avoid the impact of these biases on RFS, we utilized the PSM method to balance tumor site, tumor size, mitosis, Ki67, intratumoral hemorrhage, intratumoral necrosis, and adjuvant therapy. After PSM, gender, histologic subtypes, PNI, NLR, LMR, and PLR were still associated with HALP. Importantly, there were no difference in risk factors (tumor site, tumor size, mitosis, Ki67, NIH risk category, and adjuvant therapy) in the low/high HALP group. Given that HALP shared the same parameters with PNI, NLR, LMR, and PLR, their statistically significant correlation is unsurprising. The correlation between HALP and gender mainly attributed to the difference of hemoglobin level between male and female patients (123.22 ± 2.08 g/L for male and 105.46 ± 1.84 g/L for female, P < 0.001). Additionally, the correlation between HALP and histologic

subtypes mainly attributed to insufficient sample size in epithelioid subgroup, where the patients of low HALP group was 0, while patient of the high HALP group was eight. Notably, neither gender nor histologic subtype was associated with recurrence (*Table S1*). Subgroup analysis based on gender demonstrated that a low level of HALP was associated with recurrence in female patients but not in male patients. However, there was still a trend of poor prognosis in male patients with lower HALP (*Figure S2*). The reason for this phenomenon might be the insufficient sample size, but further research was needed.

Finally, consistent with previous research on HALP in other tumor[18-24], our findings revealed prognostic value of HALP in GIST. HALP was an independent risk factor for GIST patients before PSM, after PSM, and in high-risk subgroups. GIST patients with low HALP before PSM, after PSM, and in high-risk subgroups all had a poor prognosis. Thus, HALP can be used not only to evaluate the postoperative risk classification of GIST patients prior to surgery, but also to assess their prognosis. Notably, the HALP index can be conveniently and inexpensively applied to predict the prognosis of patients.

Although the underlying mechanism of systemic inflammation in tumorigenesis, progression and metastasis remains obscure, there are some theories that it stimulates angiogenesis, immunosuppression and the formation of supporting microenvironment. It is well known that lymphocytes play an important role in inhibiting tumor growth[33-35]. A higher lymphocyte signature was associated with improved prognosis in a variety of tumors[35]. Whereas, platelets could infiltrate into the tumor microenvironment and interact with cancer cells directly, helping circulating tumor cell attach to endothelial cells and providing signals to establish a niche environment before metastasis[36-42]

Zheng-Yang Yang et al. found that GIST with gastrointestinal bleeding was independent prognostic predictors for poor RFS[43]. Some studies have shown that low hemoglobin can lead to tumor hypoxia, which has a higher risk of local failure and distant metastasis[31,44]. Furthermore, a hypoxic tumor environment could induce limited accumulation of drugs and hinder the efficacy of drugs[45]. Additionally, one of the primary adverse effects of imatinib is anemia[46], which may be prevented by a normal preoperative hemoglobin levels, thus improving imatinib treatment compliance.

Low levels of serum albumin were also associated with poor long-term survival in GIST patients[44,45], which was consistent with our findings. Serum albumin is generally considered to be associated with nutritional status and liver or renal function, both of which may affect patients' compliance with imatinib therapy, similar to hemoglobin. Moreover, about 95% of imatinib is bound to serum proteins, mainly albumin and 1-acid glycoprotein[47]. Tumors tissues have abnormal vascular endothelial gaps and lack effective lymphatic drainage, allowing macromolecules more likely to accumulate in the tumor tissue than normal tissue[48,49]. This effect is referred to as the enhanced permeability and retention effect. Albumin exerts this effect as a result of its unique molecular size, which may facilitate drug accumulation in tumors and improve therapeutic effect[50].

There are some limitations to this study. Firstly, this study is a retrospective study, so there may be biases in the process of data collection. Secondly, our cases were collected from 2008 to 2016, during which time imatinib has been used in the adjuvant treatment of GIST in China. Despite the adverse reaction and higher 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[51], and its benefits are also shown in present study. However, there was no adequate collection and analysis of the time, dose and adverse reactions of patients with imatinib or sunitinib therapy, which may be also related to HALP. Moreover, this study also did not evaluate other clinicopathological factors, especially gene mutation status, which also relate to prognosis. Most importantly, nutritional status may be associated with the economic status, which is a critical factor influencing medication compliance and prognosis. Furthermore, the effect of preoperative or postoperative improvement of nutritional status or inflammation response on the prognosis of GIST remained obscure, which needed to be further confirmed in clinical studies.

CONCLUSION

A low level of HALP was related to tumor site, tumor size, mitosis, Ki67, NIH risk category and adjuvant therapy. A low level of HALP was considered to be an important risk factor for RFS in GIST patients with R0 resection.

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CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTION

Zhou Zhao: wrote the manuscript and followed up.

Xiaonan Yin: collected the clinicopathological data.

Jian Wang: performed statistical analysis.

Xin Chen: collected the clinicopathological data and followed up.

Zhaolun Cai: supervised the resolved disputes in the data collection.

Bo Zhang: supervised and revised the report

Table 1. Baseline characteristics in patients with high or low HALP before and after PSM.

Characteristics	Before PSM All	Before PSM Low HALP (<31.5)
n (%)	591	229 (38.7)
Age (yrs, mean ± SD)	56.3 ± 12.0	56.7 ± 12.2
<60	337 (57.0)	129
60	254 (43.0)	100
Gender		
Male	280 (47.4)	98
Female	311 (52.6)	131
Tumor site		
Stomach	424 (71.7)	143
Non-stomach	167 (28.3)	86
Tumor size (cm, mean ± SD)	6.16 ± 4.87	7.69 ± 5.65
2	86 (14.6)	10
2.1-5.0	251 (42.5)	87
5.1-10.0	184 (31.1)	95
>10.0	70 (11.8)	37
Mitotic index /50HPF		
5	332 (56.2)	107
6-10	100 (16.9)	45
>10	91 (15.4)	49

unknown	68 (11.5)	28
CD117		
(+)	573 (97.0)	225
(-)	18 (3.0)	4
CD34		
(+)	527 (89.2)	201
(-)	64 (10.8)	28
DOG1		
(+)	529 (89.5)	211
(-)	10 (1.7)	3
unknown	52 (8.8)	15
Ki67		
10	417 (70.6)	140
>10	98 (16.6)	61
unknown	76 (12.9)	28
Histologic subtypes		
spindle	518 (87.6)	197
epithelioid	13 (2.2)	3
mixed	60 (10.2)	29
Intratumoral hemorrhage		
Yes	108 (18.3)	64
No	483 (81.7)	165
Intratumoral necrosis		
Yes	117 (19.8)	71
No	474 (80.2)	158
NIH risk category		
Verylowrisk	72 (12.2)	9
Lowrisk	178 (30.1)	52
Intermediaterisk	114 (19.3)	43
Highrisk	227 (38.4)	125
Adjuvant therapy		
Yes	201 (34.0)	99
No	390 (66.0)	130
Hemoglobin	118.30 ± 26.80	94.60 ± 22.81
Albumin	41.68 ± 4.38	39.52 ± 4.40
White blood cell	5.38 ± 1.47	5.32 ± 1.55
Neutrophils	3.40 ± 1.24	3.60 ± 1.40
Lymphocyte	1.47 ± 0.53	1.21 ± 0.42
Mononuclear cell	0.33 ± 0.15	0.33 ± 0.17
Platelets	201.6 ± 88.2	261.6 ± 95.7
NLR (mean ± SD)	2.63 ± 1.74	3.41 ± 2.36
NLR<2.60	369 (62.4)	99
NLR[?]2.60	222 (37.6)	130
PLR (mean ± SD)	152.8 ± 84.6	228.7 ± 84.1
PLR<134.8	304 (51.4)	12
PLR[?]134.8	287 (48.6)	217
LMR (mean ± SD)	5.13 ± 3.00	4.45 ± 3.05
LMR<4.0	381 (64.4)	110
LMR[?]4.0	210 (35.6)	119
PNI (mean ± SD)	49.04 ± 5.43	45.6 ± 5.03
PNI<48.6	270 (45.7)	171

PNI[?]48.6	321 (54.3)	58
Recurrence		
Yes	62 (10.5)	42
No	529 (89.5)	187
[1]Method=nereast; Cliper value=0.1	[1]Method=nereast; Cliper value=0.1	[1]Method=nereast; C
P < 0.05 was considered statistically significant.	*P < 0.05 was considered statistically significant.	*P < 0.05 was consid

Table 2. Univariate and multivariate regression analysis of prognostic factors in patients before and after PSM.

Risk factors						
Age						
Gender (male vs female)						
Tumor site (stomach vs non-stomach)						
Tumor size (cm) ([?]2 / 2.1-5.0 / 5.1-10.0 / >10.0)						
Mitotic index (/50HPF) ([?]5 / 6-10 / >10 / unknown)						
5 vs 6-10						
5 vs >10						
5 vs unknown						
CD117 (+ / -)						
CD34 (+ / -)						
DOG1 (+ / - / unknown)						
Ki67 ([?]10 / >10 / unknown)						
>10 vs [?]10						
unknown vs [?]10						
Histologic subtypes (spindle / epithelioid / mixed)						
Intratumoral hemorrhage (yes / no)						
Intratumoral necrosis (yes / no)						
NIH risk category (very low/low/intermediate/high)						
Hemoglobin						
Albumin						
White blood cell						
Neutrophils						
Lymphocyte						
Monocyte						
Platelets						
Adjuvant therapy (yes / no)						
NLR (<2.60 / [?]2.60)						
PLR (<134.8 / [?]134.8)						
LMR (<4.0 / [?]4.0)						
PNI (<48.6 / [?]48.6)						
HALP (<31.5 / [?]31.5)						
HR: Hazard ratio; CI: Confidence interval; NA: Not adopted; NS: Not significant. *P < 0.05 was considered statistically sig						

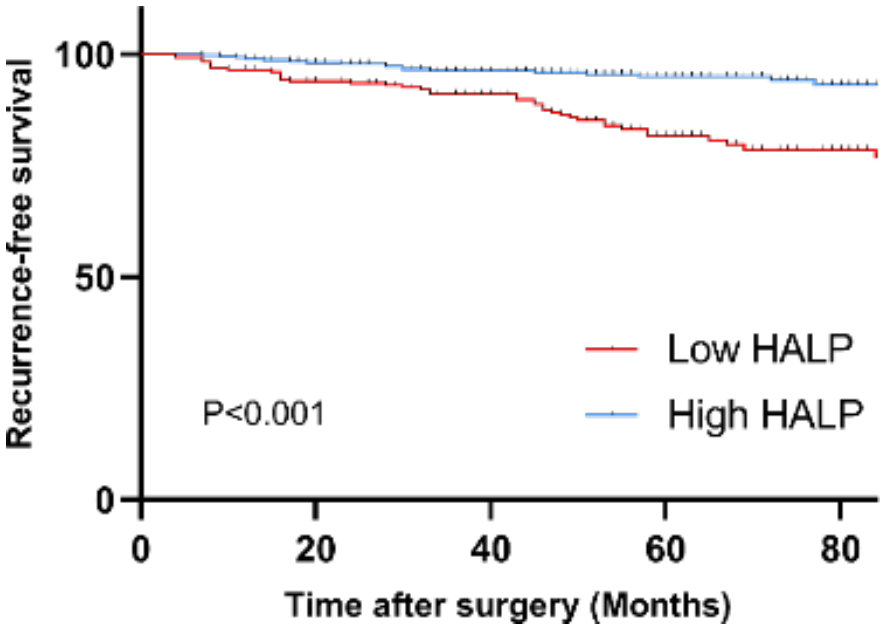
Table S1. Demographic and clinicopathologic features of 227 resected high-risk GIST patients with high or low HALP.

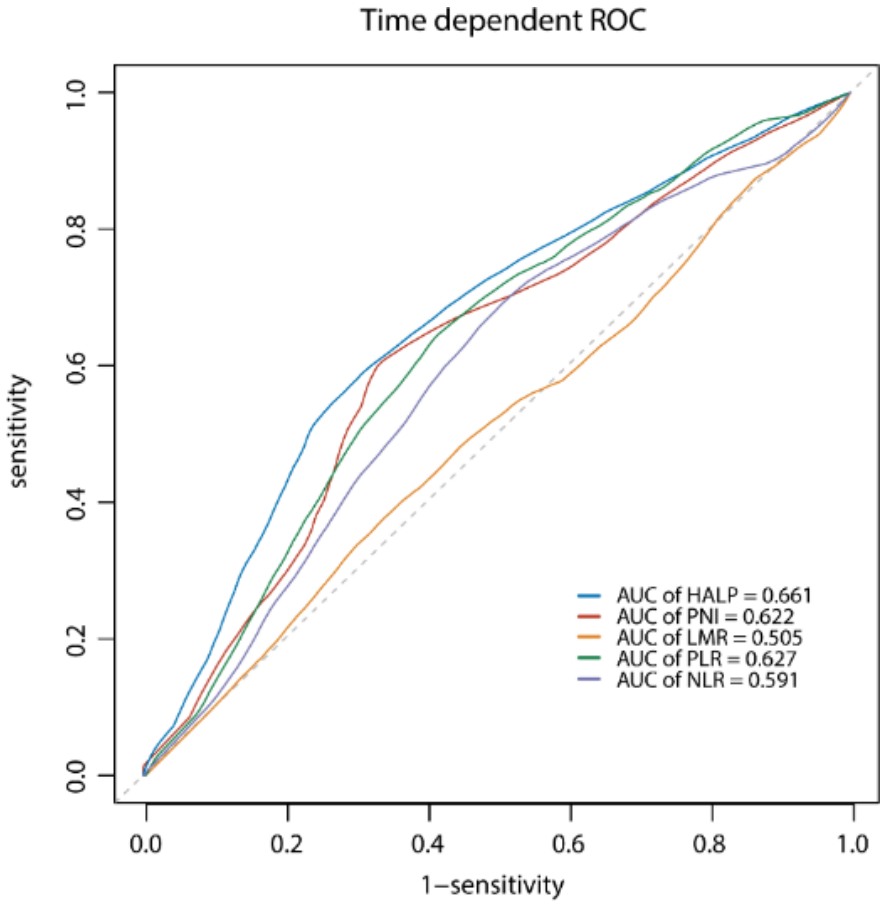
Characteristics	n=227	Low HALP (<31.5)

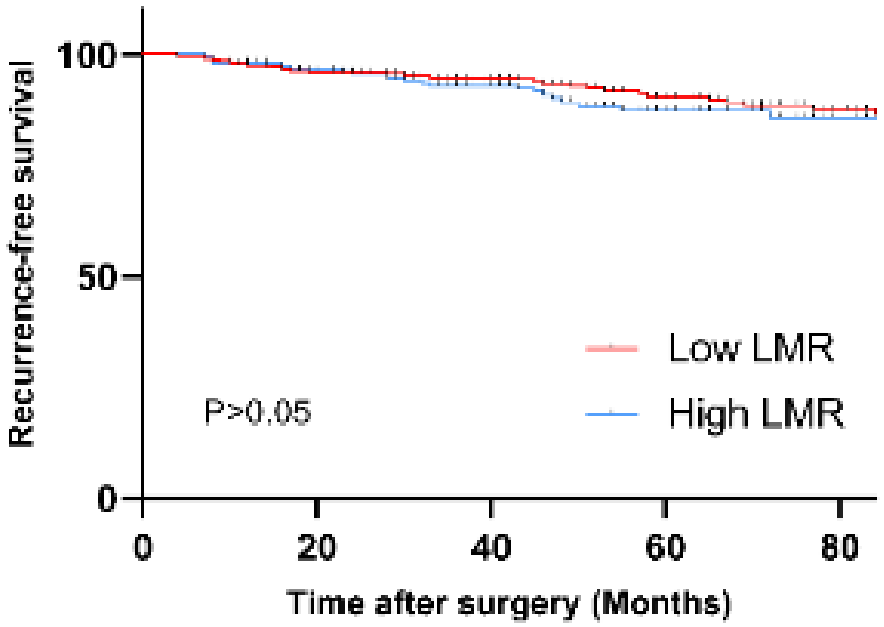
Age (yrs, mean ± SD)	56.1 ± 12.5	
<60	130 (57.3)	70
60	97 (42.7)	55
Gender		
Male	134 (59.0)	63
Female	93 (41.0)	62
Tumor site (stomach vs non-stomach)		
Stomach	129 (56.8)	69
Non-stomach	98 (43.2)	56
Tumor size (cm, mean ± SD)	9.68 ± 5.86	
2	1 (0.4)	0
2.1-5.0	41 (18.1)	20
5.1-10.0	116 (51.1)	68
>10.0	69 (30.4)	37
Mitotic index /50HPF		
5	45 (19.8)	28
6-10	61 (26.9)	28
>10	89 (39.2)	48
unknown	32 (14.1)	21
CD117 (+)		
(+)	223 (98.2)	124
(-)	4(1.8)	1
CD34 (+)		
(+)	198 (87.2)	110
(-)	29 (12.8)	15
DOG1 (+ / - / unknown)		
(+)	204 (89.9)	113
(-)	5 (2.2)	2
unknown	18 (7.9)	10
Ki67 ([?]10 / >10 / unknown)		
10	111 (48.9)	52
>10	89 (39.2)	59
unknown	27 (11.9)	14
Histologic subtypes		
spindle	183 (80.6)	104
epithelioid	6 (2.6)	2
mixed	38 (16.7)	19
Intratumoral hemorrhage (yes / no)		
Yes	81 (35.7)	73
No	146 (64.3)	52
Intratumoral necrosis (yes / no)		
Yes	92 (40.5)	64
No	135 (59.5)	61
Adjuvant therapy (yes / no)		
Yes	89 (39.2)	51
No	138 (60.8)	74
Recurrence (yes / no)		
Yes	51 (22.5)	38
No	176 (77.5)	87
Hemoglobin	112.97 ± 28.82	-
Albumin	40.11 ± 4.92	-

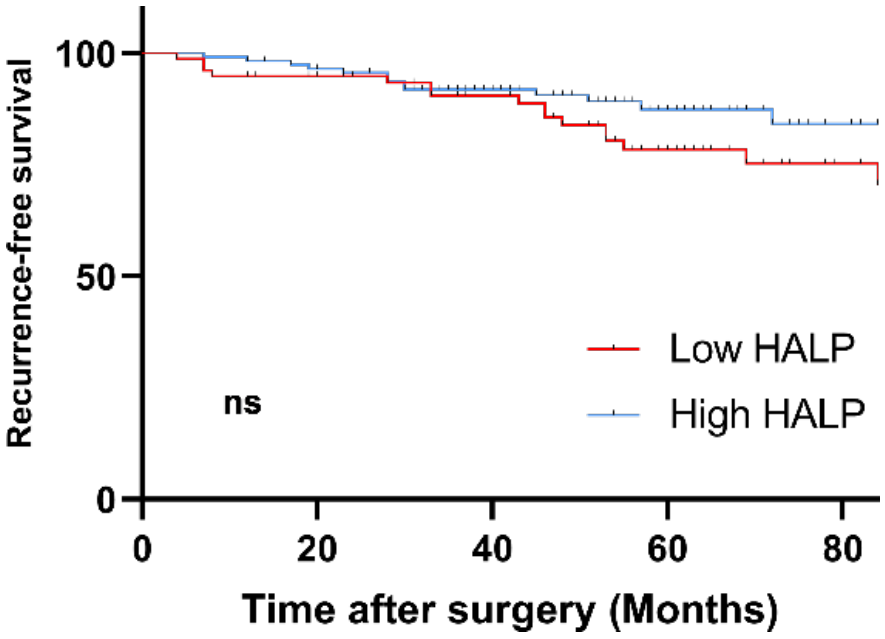
White blood cell	5.63 ± 1.46	-
Neutrophils	3.65 ± 1.21	-
Lymphocyte	1.44 ± 0.55	-
Mononuclear cell	0.35 ± 0.15	-
Platelets	222.8 ± 96.3	-
NLR (mean ± SD)	2.96 ± 2.09	
NLR<2.60	123 (54.2)	52
NLR[?]2.60	104 (45.8)	73
PLR (mean ± SD)	172.04 ± 87.54	
PLR<134.8	88 (38.8)	6
PLR[?]134.8	139 (61.2)	119
LMR (mean ± SD)	4.88 ± 3.69	
LMR<4.0	128 (56.4)	61
LMR[?]4.0	99 (43.6)	64
PNI (mean ± SD)	47.31 ± 5.50	
PNI<48.6	131 (57.7)	96
PNI[?]48.6	96 (42.3)	29
HALP (mean ± SD)	37.41 ± 30.15	
HALP<31.5	125 (55.1)	-
HALP[?]31.5	102 (44.9)	-
P < 0.05 was considered statistically significant.	*P < 0.05 was considered statistically significant.	*P < 0.05 was consi

Table S2. Univariate and multivariate regression analysis of prognostic factors in high-risk patients	**Table**
Characteristics	Univar
	HR (95
Age	1.011 (
Gender	0.954 (
Tumor site (stomach vs non-stomach)	1.035 (
Tumor size (cm) ([?]2 / 2.1-5.0 / 5.1-10.0 / >10.0)	1.353 (
Mitotic index (/50HPF) ([?]5 / 6-10 / >10 / unknown)	1.968 (
6-10 vs [?]5	
>10 vs [?]5	
unknown vs [?]5	
CD117 (+ / -)	1.099 (
CD34 (+ / -)	0.705 (
DOG1 (+ / - / unknown)	1.976 (
Ki67 ([?]10 / >10 / unknown)	1.959 (
10 vs >10	
10 vs unknown	
Histologic subtypes (spindle / epithelioid / mixed)	1.024 (
Intratumoral hemorrhage (yes / no)	1.969 (
Intratumoral necrosis (yes / no)	2.086 (
Adjuvant therapy (yes / no)	0.379 (
NLR (<2.60 / [?]2.60)	1.784 (
PLR (<134.8 / [?]134.8)	2.251 (
LMR (<4.0 / [?]4.0)	0.925 (
WHR (<5.60 / [?]5.60)	1.506 (
PNI (<48.6 / [?]48.6)	0.430 (
HALP (<31.5 / [?]31.5)	0.504 (
P < 0.05 was considered statistically significant.	









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