Respose to the Review Comments

Reviewer #1:

Scientific Quality: Grade A (Excellent)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (High priority)

Specific Comments to Authors: I enjoyed reading this article on the prognostic value of HALP in GIST. The research methodology is sound and the article is very well written.

Response: We appreciate your time in reviewing this article and giving the positive comments above.

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Response: We appreciate your time in reviewing this article and giving constructive suggestions.

Specific Comments to Authors:

(1) The manuscript contains title, abstract, keywords, introduction, materials, methods, experimental procedure, results, discussion, conclusion, acknowledgments, and references.

Response: We appreciate your time in reviewing this issue.

(2) The scientific question proposed in the manuscript is whether the combined index of hemoglobin, albumin, lymphocyte, and platelet (HALP) has a significant correlation with postoperative pathology and postoperative treatment in patients with gastrointestinal stromal tumors (GISTs). This is presented in the Introduction section, along with the pertinent background, rationale, aim, significant findings, and potential significance of the study.

Collectively, this information informs whether the manuscript would be interesting enough to warrant readers' attention.

Response: We appreciate your time in reviewing this issue.

(3) This study was performed on 591 patients who had been operated on with a diagnosis of GIST. The data were analyzed by statistical analysis. It is stated that the data of each patient were retrieved from the self-built GISTs database. I want to ask to the authors to describe in more detail "this self-built database." Besides, I would like to know who performed the histopathological diagnosis of resected specimens because, according to my knowledge, it is not possible to make a definitive diagnosis of GIST without histopathological and immunohistochemical examinations. The immunohistochemical profiles for SMA, Desmin, and CD34 should also be mentioned. Accordingly, immunohistochemical staining should be briefly described.

Response: We appreciate your interest in this issue and thank you for your suggestions.

a. I want to ask to the authors to describe in more detail "this self-built database."

Response: Our self-built database is self-extracted by team members from the HIS (hospital information system) system of West China Hospital of Sichuan University. **The database contains the following information:**

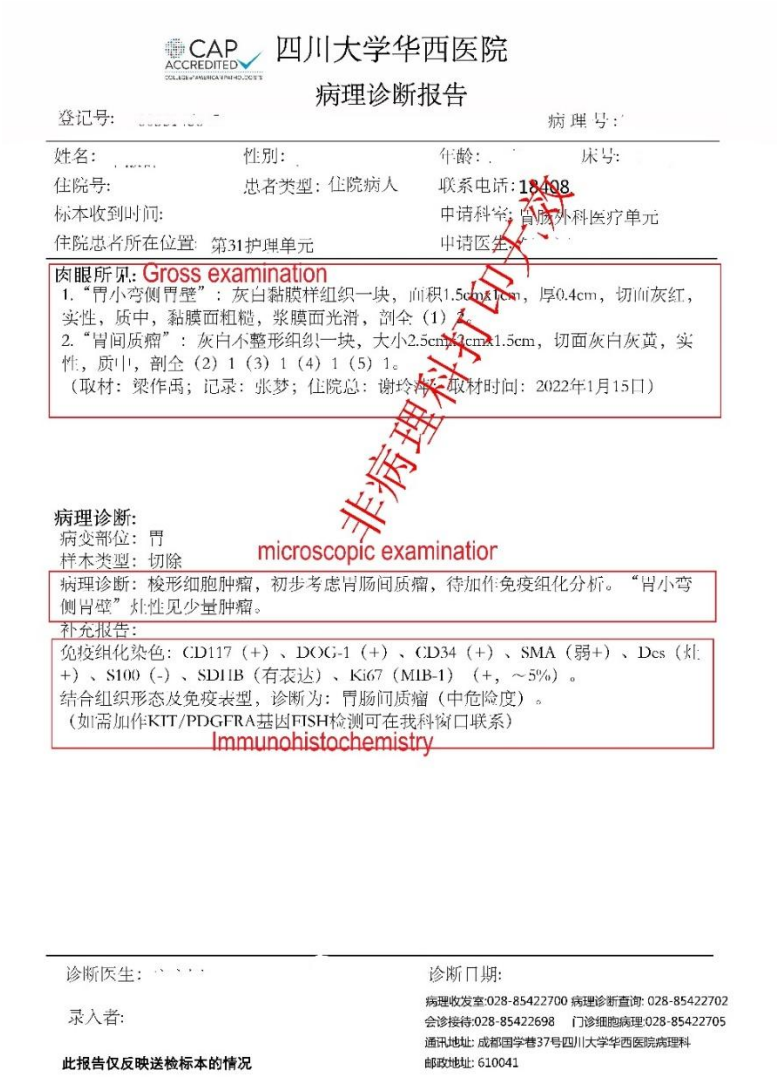
- Patient name & ID
- Basic information (age, sex, height, weight, blood type, admission time, discharge time, contact information)
- Past history, personal history, and family history
- Preoperative endoscopy or endoscopic ultrasonography, preoperative abdominal CT, preoperative blood routine test, and preoperative blood biochemistry test
- Preoperative treatment information

- Surgical information (surgery start time, surgery end time, tumor site assessed during surgery, tumor size measured during surgery, blood transfusion volume)
- Postoperative pathological information (pathology ID, tumor size, tumor site, intratumoral hemorrhage status, intratumoral necrosis status, resection margin status, tumor cell morphology, lymph node metastasis, and immunohistochemical profiles of CD117, CD34, DOG1, SDHA, SDHB, SMA, Desmin, CD34 and Ki67),
- Gene mutation information.
- Follow-up information. Follow-up was conducted through outpatient clinics and telephone calls. Our team members will record the patient's tumor progression, as well as the dose, time and adverse reactions of the drug during follow-up.

Information is stored in Excel and Access software.

b. Besides, I would like to know who performed the histopathological diagnosis of resected specimens because, according to my knowledge, it is not possible to make a definitive diagnosis of GIST without histopathological and immunohistochemical examinations.

Response: Thank you for your kind comments. The histopathological diagnosis was performed by the Department of Pathology of Sichuan University West China Hospital. Preoperative blood routine and blood biochemical examination were performed by the Laboratory Department of Sichuan University West China Hospital. The image (Figure 1) below is a sample of the hospital histopathology diagnosis report.


四川大学华西医院

病理诊断报告

登记号:　　病理号:

姓名:　　性别:　　年龄:　　床号:

住院号:　　患者类型: 住院病人　　联系电话: 18408

标本收到时间:　　申请科室: 胃肠外科医疗单元

住院患者所在位置: 第31护理单元　　申请医生:

肉眼所见: Gross examination

1. "胃小弯侧胃壁": 灰白黏膜样组织一块, 面积1.5cm×1cm, 厚0.4cm, 切面灰红, 实性, 质中, 黏膜面粗糙, 浆膜面光滑, 剖全 (1) 。

2. "胃间质瘤": 灰白不整形组织一块, 大小2.5cm×2cm×1.5cm, 切面灰白灰黄, 实性, 质中, 剖全 (2) 1 (3) 1 (4) 1 (5) 1。

(取材: 梁作禹; 记录: 张梦; 住院总: 谢玲; 取材时间: 2022年1月15日)

非病理科印章

病理诊断:

病变部位: 胃

样本类型: 切除　　microscopic examinatior

病理诊断: 梭形细胞肿瘤, 初步考虑胃肠间质瘤, 待加作免疫组化分析。"胃小弯侧胃壁"灶性见少量肿瘤。

补充报告:

免疫组化染色: CD117 (+) 、DOG-1 (+) 、CD34 (+) 、SMA (弱+) 、Des (灶+) 、S100 (-) 、SDHB (有表达) 、Ki67 (MIB-1) (+, ~5%) 。

结合组织形态及免疫表型, 诊断为: 胃肠间质瘤 (中危险度) 。

(如需加作KIT/PDGFRA基因FISH检测可在我科窗口联系)

Immunohistochemistry

诊断医生:　　诊断日期:

录入者:

病理收发室:028-85422700 病理诊断查询: 028-85422702

会诊接待:028-85422698　门诊细胞病理:028-85422705

通讯地址: 成都国学巷37号四川大学华西医院病理科

邮政地址: 610041

此报告仅反映送检标本的情况

Figure 1 A sample of histopathology diagnosis report of West China Hospital.

c. The immunohistochemical profiles for SMA, Desmin, and CD34 should also be mentioned. Accordingly, immunohistochemical staining should be briefly described.

Response: Thank you for underlining this deficiency. **We have added statistics for CD34, SMA and Desmin in Table S1 and Table S2. We also described immunohistochemical staining in detail in the section "MATERIALS AND METHODS-Perioperative evaluation and postoperative histopathological diagnosis".** The specific sentences are as follows in red font:

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.

In our data, the positive rates for SMA and Desmin were 21.8% and 3.6%, respectively (Table S1 and Table S2). Figure 2 showed the positive rates of SMA and Desmin in UpToDate, which was slightly different from our data.

Immunohistochemical schema for the differential diagnosis of spindle cell tumors of the gastrointestinal tract

Type	CD117	DOG-1	PKC-theta	CD34	SMA*	S100 protein	Desmin
GISTs	+ (>95%)	+ (97%)	+ (72%)	+ (60 to 70%)	+/- (30 to 40%)	- (5% +)	Very rare
Leiomyoma	-	-		+ (10 to 15%)	+	-	+
Leiomyosarcoma	-	-	+ (10%)	-	+	-	+
Schwannoma	-	-	+ (10%)	-	-	+	-

DOG-1: discovered on GIST-1; PKC-theta: protein kinase C theta; GISTs: gastrointestinal stromal tumors.
* Alpha smooth muscle actin.

Figure 2 immunohistochemical schema for the differential diagnosis of spindle cell tumors of the gastrointestinal tract. (The chart comes from the website https://www.uptodate.com/contents/clinical-presentation-diagnosis-and-prognosis-of-gastrointestinal-stromal-tumors).

Table S1. Baseline characteristics in patients with high or low HALP before

and after PSM.

Characteristics	Before PSM#				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)	-
……	……	……	……	……	……	……	……	……
CD117								
(+)	573 (97.0)	225	348		443 (96.7)	225	218	
(-)	18 (3.0)	4	14	0.218	15 (3.3)	4	11	0.066
CD34								
(+)	527 (89.2)	201	326		397 (86.7)	201	196	
(-)	64 (10.8)	28	36	0.416	61 (13.3)	28	33	0.583
DOG1								
(+)	529 (89.5)	211	318		412 (90.0)	211	201	
(-)	10 (1.7)	3	7		38 (8.3)	15	23	
unknown	52 (8.8)	15	37	0.254	8 (1.7)	3	5	0.297
SMA								
(+)	44 (7.4)	22	22		34 (7.4)	22	12	
(+, partial)	85 (14.4)	37	48		66 (14.4)	37	29	
(-)	462 (78.2)	170	292	0.147	358 (78.2)	170	188	0.090
Desmin								
(+)	5 (0.8)	0	5		1 (0.2)	0	1	
(+, partial)	16 (2.8)	5	11		10 (2.2)	5	5	
(-)	570 (96.4)	224	346	0.164	447 (97.6)	224	223	0.409
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*	26 (12.2)	28	28	0.004*
……	……	……	……	……	……	……	……	……

#Method=nereast; Cliper value=0.02

*P < 0.05 was considered statistically significant.

Table S2. Demographic and clinicopathologic features of 227 resected high-risk GIST patients with high or low HALP.

Characteristics	n=227	Low HALP (<31.5)	High HALP (≥31.5)	P-value
……	……	……	……	……
CD117 (+)				
(+)	223 (98.2)	124	99	
(-)	4(1.8)	1	3	0.329
CD34 (+)				
(+)	198 (87.2)	110	88	
(-)	29 (12.8)	15	14	0.696
DOG1 (+ / - / unknown)				
(+)	204 (89.9)	113	91	
(-)	5 (2.2)	2	3	
unknown	18 (7.9)	10	8	0.816
SMA				
(+)	18 (7.9)	15	3	
(+, partial)	35 (15.4)	23	12	
(-)	174 (76.7)	87	87	0.01*
Desmin				
(+)	0	0	0	
(+, partial)	5 (2.2)	2	3	
(-)	222 (97.8)	123	99	0.659
Ki67 (≤10 / >10 / unknown)				
≤10	111 (48.9)	52	59	
>10	89 (39.2)	59	30	
unknown	27 (11.9)	14	13	0.022*
……	……	……	……	……

*P < 0.05 was considered statistically significant.

(4) The information in the results section indicates the academic significance of the main findings (including figures and tables).

Response: We appreciate your time in reviewing this issue.

(5) Briefly, the results obtained from the data show a significant correlation between HALP and postoperative treatment in patients with gastrointestinal stromal tumors (GISTs). Low levels of HALP were found as an independent

risk factor for poor recurrence-free survival in patients with GIST. This information makes up the Discussion section and answers the questions of whether the results answered the proposed scientific question, achieved the aim of the study, or confirmed or rejected the hypothesis proposed in the manuscript.

Response: We appreciate your time in reviewing this issue.

(6) the manuscript concludes that HALP could be useful in predicting tumor behavior in patients with GIST and could be used as an independent prognostic factor in the follow-up of the patients. These are presented in the Conclusion section.

Response: We appreciate your time in reviewing this issue.

(7) The manuscript cites all important, relevant, and timely references.

Response: We appreciate your time in reviewing this issue.

(8) There is no indication of academic misconduct in the manuscript.

Response: We appreciate your time in reviewing this issue.

(9) The manuscript conforms to the academic rules and norms.

Response: We appreciate your time in reviewing this issue.

(10) Although the manuscript does not describe any essential new methods, it poses new directions for research.

Response: Thank you for your kind comments.

(11) The manuscript does not contribute to understanding the pathogenesis of diseases.

Response: We appreciate your time in reviewing this issue.

(12) The title of the manuscript contains keywords, and the title is interesting enough to attract readers' attention.

Response: We appreciate your time in reviewing this issue.

(13) The topic of the manuscript falls within the scope of The World Journal of Gastroenterology

Response: We appreciate your time in reviewing this issue.

(14) The language of the manuscript reaches the standard of publishing.

Response: We appreciate your time in reviewing this issue.

3. Peer-reviewers' conclusions

(1) The new vision that the manuscript offers to readers is HALP could be a valuable tool in the follow-up in patients with GIST

Response: We appreciate your time in reviewing this issue.

(2) The study's weakness arises from the lack of detailed explanation of GIST diagnosis and additional immunohistochemical staining as pointed above in (3).

Response: We describe this section in detail in the section "MATERIALS AND METHODS-Perioperative evaluation and postoperative histopathological diagnosis". The specific sentence is as follows in red font:

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.

(3) The experiences and lessons presented in the manuscript could improve the readers' practice.

Response: We appreciate your time in reviewing this issue.

(4) The content of the manuscript has value for publication.

Response: We appreciate your time in reviewing this issue.

(5) The manuscript is concise, clear, comprehensive, and convincing.

Response: We appreciate your time in reviewing this issue.

RESPONCE TO EDITORIAL OFFICE' S COMMENTS

(1) Science editor:

This retrospective cohort study focused on the prognostic significance of HALP (hemoglobin, albumin, lymphocyte, platelet) in gastrointestinal stromal tumors and found that HALP is a remarkable indicator of systemic inflammation and nutritional status in patients with gastrointestinal stromal tumors, which is an important and significant topic for clinical work. The quality of the manuscript is good, the description is smooth, and it would be nice if the resolution of the pictures were a bit higher. The structure and content of the article are complete, and the references are complete and new.

Language Quality: Grade A (Priority publishing)

Scientific Quality: Grade B (Very good)

a. The quality of the manuscript is good, the description is smooth, and it would be nice if the resolution of the pictures were a bit higher.

Response: Thank you for underlining this deficiency. We apologize for the low-resolution-images in our manuscript. We found that WORD software automatically compresses our images to a resolution of 220 ppi, which made our pictures not clear enough. We have changed the image compression rate of WORD software to a resolution of 330 ppi. Moreover, we provide uncompressed pictures in PowerPoint software.

(2) Company editor-in-chief:

I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Before final acceptance, uniform presentation should be used for figures showing the same or similar

contents; for example, “Figure 1Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...”. Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file. Please authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content. In order to respect and protect the author’s intellectual property rights and prevent others from misappropriating figures without the author's authorization or abusing figures without indicating the source, we will indicate the author's copyright for figures originally generated by the author, and if the author has used a figure published elsewhere or that is copyrighted, the author needs to be authorized by the previous publisher or the copyright holder and/or indicate the reference source and copyrights. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is ‘original’, the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022.

Response: We thank the company editor-in-chief for pointing out this issue.

1. Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, “Figure 1Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...”.

Response: We have unified the legend format of the pictures as required.

2. Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file.

Response: We have provided PowerPoint files as requested.

3. If the picture is ‘original’, the author needs to add the following copyright

information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022.

Response: We have added the copyright information in the PowerPoint file as requested.