Dear Editor Scott Fraser and Reviewers,

On behalf of my co-authors, we greatly appreciate the careful review and comments from both you and the reviewers. We believe that by implementing the suggested changes, we now have a stronger manuscript entitled "Clinical characteristics and overall survival nomogram of gastric cancer patients with preoperative anemia: A retrospective study" (ID: 83053) for submission to "World Journal of Gastrointestinal Surgery". We look forward to your positive response to the revised work submitted here.

We present here point-to-point responses for each of the comments in the attached document and have revised our manuscript accordingly. Since the comments from the reviewers are valuable and important, we partially change our statistics (mostly re-analysis and increased some data), but the results remain the same as the previous manuscript. And we hope the revised manuscript could be acceptable for you. Revised sections are identified with red text in the paper.

There are no conflicts of interest regarding this work. All authors have read the revised manuscript and approved its submission to the World Journal of Gastrointestinal Surgery. Please do not hesitate to contact us if we can be of any further assistance.

Thank you and best regards.

Yours Sincerely,

Yan Long

REVIEWER 1 EVALUATION

Title

As the study includes clinicopathological parameters with preoperative anemia, it is suggested to include it in the title. Eg Overall survival in patients with preoperative anemic gastric cancer in relation with clinicopathological parameters.

RESPONSE:

As requested, we changed the title of the article to Clinical characteristics and overall survival nomogram of gastric cancer patients with preoperative anemia: A retrospective study.

Introduction

• How monocyte and lymphocyte count affect the overall survival of GC should be mentioned in the introduction with literature.

RESPONSE: We have made careful revision and the results are in the lines 8 to 13 of introduction, marked in red. Absolute count of lymphocyte and monocytes can predict survival in patients with metastatic cancer and the overall survival rate of reduced lymphocyte count is low and there is an apparent correlation between the monocyte count and survival. Patients with absolute monocyte count of 300 to 899 monocytes per cubic millimeter had a significantly better prognosis than did those with higher or lower counts.

Methodology

1.Study population selection. Author stated, “Histological differentiation type”. - Histological differentiation means “well-, moderately-, poorly differentiated”. - Histology type of gastric cancer means “Intestinal type and diffuse infiltrative type”, based on Lauren classification. In 3rd sentence, author mentioned as “Histological differentiation type”, however in 4th sentence author mentioned as “Histological type”. As they are different, which one author wants to include? Please indicate clearly. Although author stated that “Histological differentiation type” and “Histological type” will be collected in data, they are not included in the “Results” session. In “Result”, author included ulcer, polyp, and diffuse types. They are “Gross pathology type” and not histological type. Parameters mentioned in methodology and indicated in results session need to be same. Please state them clearly.

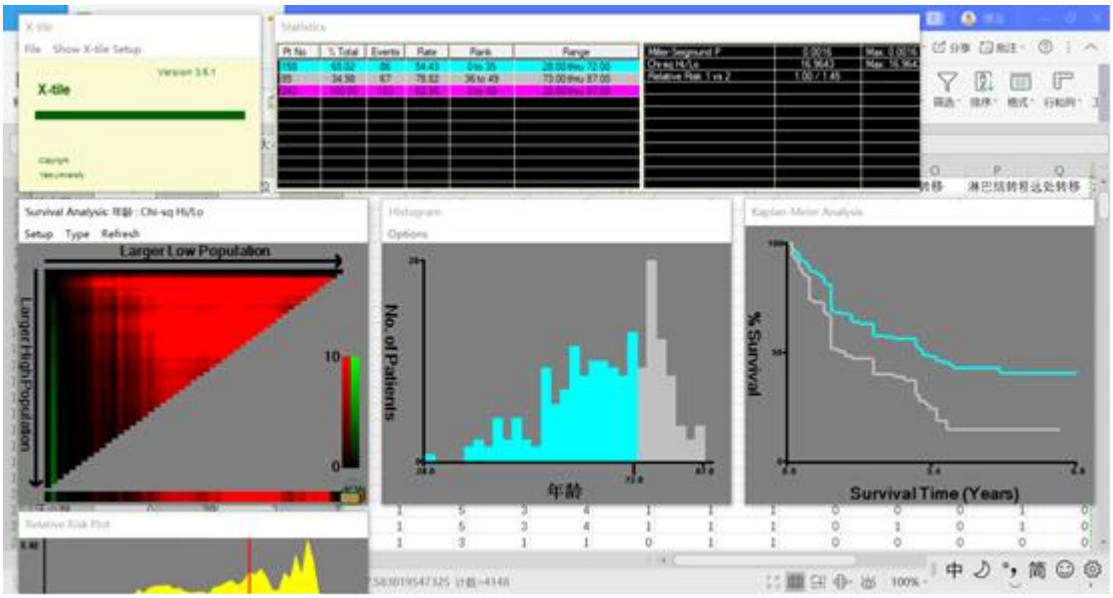
RESPONSE: Thank you for the detailed review, and the comment of the reviewer is important. The article should be a histological differentiation type.

2. Histological types of gastric cancer are important in determining prognosis and survival, it should be included in patient characteristic table.

RESPONSE: Our staging of early gastric cancer pathology is based on the WHO staging and the Japanese gastric cancer staging, which is dominated by the Japanese gastric cancer staging, so the data on histological types are not g complete enough. Also, we included histological differentiation types in the clinical characteristics table.

3. Is there any reason for the cutoff age for overall survival 73 years? If so, please indicate in the methodology.

RESPONSE: In our study, X-tile software (Yale University, New Haven, CT, USA) was utilized to validate the optimal cutoff values for age.



Discussion

Author discussed only on preoperative anemia with OS in GC, not discussed in relation with other clinicopathological characteristics. Discussion needs to be elaborate more especially on significance of monocyte and lymphocyte count, preoperative AFP level, staging, tumor size, histological types, and metastasis etc.

RESPONSE: Thank you for the detailed review, and the comment of the reviewer is important. We have made careful revision and the results are in the second paragraph of discussion, lines 8 to 27, marked in red. Absolute counts of lymphocytes and monocytes predicted survival in patients with metastatic cancer, overall survival was lower with reduced lymphocyte counts and patients with absolute monocyte counts of 300 to 899 monocytes per cubic millimeter had a significantly better prognosis than those with higher or lower counts. Patients with liver metastases more habitually showed high expression of AFP and histopathological type and tumor location did not affect tumor Positive markers, AFP positivity is associated with liver metastases from gastric cancer, and liver metastases from gastric cancer have a poorer prognosis· AFP-producing gastric cancer was associated with venous invasion and deeper invasion of the gastric wall and deeper invasion of the liver metastasis rate, with poorer overall survival in the AFP-positive group than in the AFP-negative group, and a significantly higher incidence of liver metastases, a higher incidence of lymph node metastases, deeper invasion of the gastric wall and a higher frequency of advanced stages in the AFP-producing gastric cancer compared to the AFP-negative group. AFP-producing gastric cancers with liver metastases had deeper gastric wall infiltration and more pronounced lymphatic and venous invasion· Saito et al. had observed that large-size tumor was an independent prognostic factor with worse prognosis. Large size stimulates angiogenesis, which increases tumor cell proliferation.

Conclusion

As effect of preoperative anemia to predict OS is also one of the purposes of this study, it also needs to be included in conclusion how it affects the prognosis and OS in GC.

RESPONSE: Thank you again for your valuable suggestions. We have made careful revision and the results are in the lines 1 to 2 of conclusion, marked in red. Patients with pre-operative anemic gastric cancer have a shorter survival than those without pre-operative anemia.

References

Reference style needs to be standardized for all references according to journal requirement.

RESPONSE: All references have been revised in accordance with journal requirements.

REVIEWER 2 EVALUATION

It would have been better if all the hematological indicators (such as hematocrit, MCV, MCH and etc) of the patients' anemia were mentioned in the manuscript.

RESPONSE: Thank you for the detailed review, and the comment of the reviewer is important. We include the four indicators RDW, HCT, MCV and MCH in our study, adding statistics in table 1and table 1 (in red text).

Table 1

Characteristics (n=347)	Total cohort	Training cohort (n=243)	*Validation cohort* (n=104)
Age, years			
<73	233(67.1%)	75(72.1%)	158(65.0%)
⩾73	114(32.9%)	85(35.0%)	29(27.9%)
Sex			
Female	89(25.6%)	60(24.7%)	29(27.9%)
Male	258(74.4%)	183(75.3%)	75(72.1%)
Tumor size, cm			
<3.5	93(26.8%)	64(26.3%)	29(27.9%)
⩾3.5	254(73.2%)	179(73.7%)	75(72.1%)
Stage			
I	61(17.6%)	42(17.3%)	19(18.3%)
II	83(23.9%)	61(25.1%)	22(21.1%)
III	181(52.1%)	125(51.4%)	56(53.8%)
IV	24(6.3%)	15(6.2%)	7(6.7%)
Liver metastasis			
No	326(94.0%)	227(93.4%)	99(95.2%)
YES	21(6.0%)	16(6.6%)	5(4.8%)
Lymphocyte×10^9/L			
<1.2	134(38.6%)	101(41.6%)	33(31.7%)
⩾1.2	213(61.4%)	142(58.4%)	71(68.3%)
AFP ng/ml			
< 2.6	205(59.1%)	143(58.8%)	62(59.6%)
⩾2.6	142(40.9%)	100(41.2%)	42(43.1%)
Type of surgery			
Partial excision	191(55.0%)	130(53.4%)	61(58.7%)
Total Gastrectomy	156(45.0%)	113(46.6%)	43(41.3%)
General type			
Ulcer type	289(83.3%)	207(85.1%)	82(78.8%)

Polyp type	26(7.5%)	16(6.6%)	10(9.6%)
Diffuse type	11(3.2%)	8(3.3%)	3(2.9%)
Others	21(6.0%)	12(5.0%)	9(8.7%)
Peritoneal metastasis			
NO	322(92.8%)	226(93.1%)	96(92.3%)
YES	25(7.2%)	17(6.9%)	8(7.7%)
Lymphatic metastasis			
NO	95(27.4%)	64(26.6%)	31(29.8%)
YES	252(72.6%)	179(73.4%)	73(70.2%)
Remote metastasis			
NO	323(93.1%)	228(93.8%)	95(91.3%)
YES	24(6.9%)	15(6.2%)	9(8.9%)
Vascular invasion			
NO	195(56.2%)	136(66.0%)	59(56.7%)
YES	152(43.8%)	107(44.0%)	45(43.3%)
Histological differentiation type			
Highly or moderately differentiated	98(28.2%)	70(28.85)	28(26.9%)
Low or undifferentiated	222(64.0%)	155(63.8%)	67 （64.4%）
Indolent cell or mucinous adenocarcinoma	27(7.8%)	18(7.4%)	9 （8.7%）
Monocyte×10^9/L			
<0.47	172(49.6%)	101(41.6%)	71(68.3%)
⩾0.47	175(50.4%)	142(58.4%)	33(31.7%)
Red cell distribution width%			
<18.9	307(88.5%)	216(88.9%)	91(87.5%)
⩾18.9	40(11.5%)	27(11.1%)	13(12.5%)
Red blood cell specific volume L/L			
<0.34	266(76.7%)	192(79.0%)	74(71.2%)
⩾0.34	81(23.3%)	51(21.0%)	30(28.8%)
Mean corpuscular hemoglobin pg			
<30.70	297(85.6%)	211(86.8%)	86(82.7%)
⩾30.70	50(14.4%)	32(13.2%)	18(17.3%)
Mean corpuscular volume fl			
<87.30	187(53.9%)	134(55.1%)	53(51.0%)
⩾87.30	160(46.1%)	109(44.9%)	51(49.0%)

Table 2

Univariate and multivariate Cox analysis of overall survival in patients with Preoperative Anemic Gastric Cancer.

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age, years				
< 73				
⩾73	1.886(1.367-2.602)	<0.001	2.137(1.532-2.981)	<0.001

Sex				
Female				
Male	1.365(0.924-2.016)	0.118		
Tumor size, cm				
<3.5				
⩾3.5	2.399(1.561-3.685)	<0.001		
Stage				
I				
II	2.274(1.142-4.526)	0.019	1.726(0.846-3.521)	0.133
III	5.296(2.827-9.919)	<0.001	4.231(2.192-8.167)	<0.001
IV	14.598(6.501-32.780)	<0.001	4.908(1.426-16.897)	<0.001
Liver metastasis				
No				
Yes	5.046(2.943-8.653)	0.001	3.573(1.302-9.804)	0.013
Monocyte×10^9/L				
<0.47				
⩾0.47	2.006(1.363-2.953)	0.019	1.819(1.225-2.700)	0.003
Lymphocyte×10^9/L				
<1.2				
⩾1.2	0.683(0.498-0.939)	<0.001	0.645(0.463-0.898)	0.009
AFP ng/ml				
< 2.6				
⩾2.6	1.983(1.443-2.725)	<0.001	1.720(1.238-2.390)	0.001
Type of surgery				
Partial excision				
Total Gastrectomy	1.292(0.940-1.775)	0.114		
General type				
Ulcer type				
Polyp type	0.97(0.475-1.979)	0.933	1.527(0.736-3.167)	0.225
Diffuse type	2.715(1.256-5.869)	0.011	5.131(2.266-11.621)	<0.01
Others	0.17(0.042-0.687)	0.013	0.353(0.082-1.517)	0.162
Peritoneal metastasis				
No				
Yes	3.531(2.086-5.595)	<0.001		
Lymphatic metastasis				
No				
Yes	2.879(1.857-4.465)	<0.001		
Vascular invasion				
No				
Yes	1.831(1.332-2.519)	<0.001		
Histological differentiation type				
Highly or moderately differentiated				
Low or				
Undifferentiated	1.848(1.255-2.271)	0.002		

Indolent cell or mucinous adenocarcinoma	1.363(0.690-2.691)	0.372
Red cell distribution width%		
<18.9		
⩾18.9	1.88(1.203-2.938)	0.006
Red blood cell specific volume L/L		
<0.34		
⩾0.34	1.505(0.98-2.31)	0.062
Mean corpuscular hemoglobin pg		
<30.7		
⩾30.7	0.838(0.674-1.042)	0.112
Mean corpuscular volume fl		
<87.30		
⩾87.30	1.114(0.948-1.309)	0.189

Please do not hesitate to contact us if we can be of any further assistance!