Original Article

Investigation of unfavorable prognostic factors for survival in Chinese patients with gastric gastrointestinal stromal tumors

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Background: Gastrointestinal stromal tumor (GIST) was very rare in the gastrointestinal (GI) tract. Most GISTs were asymptomatic at early stage. Therefore, it was of great significance to explore the prognostic factors of patients with GIST. This investigation aimed to assess the unfavorable prognostic factors for overall survival (OS) and disease-free survival (DFS) in 106 Chinese patients with GISTs.

Methods: A total of 106 Chinese patients, including 68 women and 38 men, with confirmed gastric GIST treated at the General Hospital of Ningxia Medical University in China from 2012 to 2018 were included. Kaplan-Meier analysis and Cox regression models were applied to evaluate the unfavorable prognostic risk factors for survival.

Results: Kaplan-Meier analysis demonstrated that blood type A was significantly related to poor OS (P=0.01), and tumor invasion, higher Ki-67 index, synchronous gastric cancer (GC), and tumor necrosis were significantly associated with poor DFS (all P<0.05). Multivariate analysis further demonstrated that blood type A was a significant independent prognostic factor with both OS and DFS (both P<0.05). Synchronous GC and age ≥60 years were also significant independent prognostic factor for DFS (both P<0.05).

Conclusions: Blood type A, age ≥60 years, and synchronous GC were unfavorable prognostic factors for survival in Chinese patients with gastric GISTs. The mechanism underlying the prognostic role of these factors warrants further investigation.

Keywords: Blood type A; gastrointestinal stromal tumors (GISTs); synchronous gastric cancer; prognostic risk factors

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Introduction

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor of the gastrointestinal (GI) tract (1), with 60% of GISTs occurring in the stomach; however, GISTs account for less than 1% of all GI tumors (2,3). The term "stromal tumor" was first introduced by Mazur and Clark in 1983 (4), and it is widely accepted that GISTs originate from the interstitial cells of Cajal (5). Some GISTs are vascular tumors, and the main symptoms are GI bleeding, pain, and/or obstruction (6). However, 30% are asymptomatic or discovered at autopsy (7). Additionally, as most GISTs are asymptomatic, they are not easily recognized at early stage. Consequently, worldwide incidence of GIST is estimated to be one to two per 100,000 and prevalence of 13 people per 100,000 (8).

Although several recent retrospective multicenter studies suggested that patients from East Asia with gastric GISTs had more favorable outcomes than those from Western countries (9,10), an in-depth exploration of the prognostic factors with GISTs is lacking.

According to the Version 2.2018 of National Comprehensive Cancer Network (NCCN) guidelines (11) and French Intergroup Clinical Practice guidelines (12), tumor size, tumor rupture, adjuvant Imatinib, and mitotic rate were recognized as markers associated with survival prognosis. For example, Small-sized GISTs often did not have any symptoms (13), whereas GISTs smaller than 2 cm with mitotic activity ≤5/50 high-power fields (HPFs) were considered to be at extremely low risk, and as tumor size and mitotic activity increase, tumors usually became more aggressive and invasive, and finally became fatal (14,15).

Highlight box

Key findings

- Blood type A, age ≥60 years, and synchronous gastric cancer (GC) were unfavorable prognostic factors for survival in Chinese patients with gastric gastrointestinal stromal tumors (GISTs).

What is known and what is new?

- It is known that age and synchronous GC as markers associated with survival prognosis.
- This study provides insights that blood type A was unfavorable prognostic factors for survival in Chinese patients with gastric GISTs.

What is the implication, and what should change now?

- Blood group A may be an unfavorable prognostic factor and used as a potential biomarker for the diagnosis of gastric GISTs.

Besides, ABO blood type antigens on the surface of cancer cells have also been reported to be useful prognostic and diagnostic markers in different types of human cancers (16-18). Several studies supported the association of blood type A with the risk of gastric cancer (GC) and the survival of GC patients (19-22). However, the relationship between the ABO blood types, as well as several relevant clinical factors and prognosis of GIST still needs to be examined in different GIST populations.

In this retrospective study, we focused on demographic factors, clinicopathologic characteristics, and the survival status of 106 Chinese patients with gastric GISTs to identify risk factors for both overall survival (OS) and disease-free survival (DFS). We present this article in accordance with the REMARK reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-1042/rc).

Methods

Patients

One hundred and six patients who had been pathologically diagnosed with gastric GIST and admitted to the General Hospital of Ningxia Medical University in China from 2012 to 2018 were included in this retrospective study. All enrolled gastric GIST patients received surgical treatment, and patients without follow-up information or patients with other GI malignancies were excluded. The diagnosis of gastric GIST was based on histopathological evaluation and immunohistochemistry for KIT (CD117). For specimens that did not have KIT staining, diagnosis of GIST could be confirmed using immunohistochemistry for CD34 and alpha-smooth muscle actin (α-SMA). The morphological features of GIST included spindle, epithelioid, and mixed cell types. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of Ningxia Medical University (2014-032) and the Ethics Committee of Hainan Medical University (HYLL-2021-339) and individual consent for this retrospective analysis was waived.

The retrospective analysis assessed demographic and clinicopathological factors, which included age at diagnosis, sex, symptoms, genetic biomarkers, type of surgical procedure, and pathological type. The tumor size referred to the largest diameter of the tumor in any dimension after formalin fixation. Mitotic index was calculated in the area with the highest proliferation, and the number of mitoses in 50 HPFs was measured. The number of Ki-67-positive

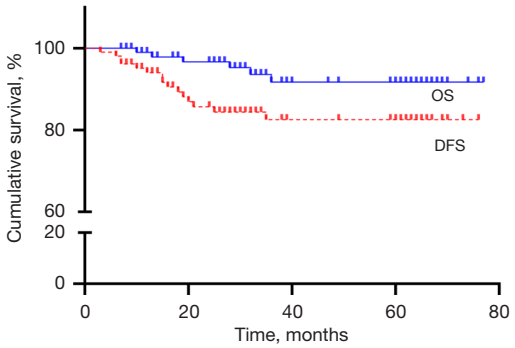

Figure 1 Cumulative survival of both OS and DFS in gastric GIST patients. GIST, gastrointestinal stromal tumor; OS, overall survival; DFS, disease-free survival.

cells in a field of 1,000 cells was used as a marker of the proliferative index (23). The tumors were classified into those with <10% positive cells and those with ≥10% positive cells. According to the NCCN guidelines and the modified National Institutes of Health (NIH) risk system, the cases were classified into very low-, low-, medium-, and high-risk groups (11). Twelve patients had both gastric GIST and GC and were analyzed separately. Please refer to the Appendix 1 for the immunohistochemical experiments involved in this study.

Follow-up

All patients were first followed up with the local death registry or patients' medical records, and then confirmed by our telephone interviews or text messages throughout July 2019. Follow-up questionnaires mainly inquired regarding the patients' survival situation. In case of death, both the exact date and the cause of death were recorded. If patients were alive, their quality of life, including tumor recurrence and metastasis, was also recorded. The cut-off point for the follow-up was death, recurrence, or metastasis. Death was the only observation point for OS. Death, recurrence, and metastasis were all observation points for DFS. Those patients who were either without information in the local death registry or medical records or without response after three phone calls or text messages were deemed lost to follow-up. Imaging exams, including computed tomography or upper GI contrast and color ultrasonography, were conducted annually during routine follow-up. Gastroscopy was also performed to detect tumor recurrence or metastasis.

OS was calculated from the date of diagnosis to the date of death or the last follow-up examination for survivors. Similarly, DFS was calculated from the date of surgery to the date of disease progression or the date of death, whichever occurred first. Patients who were alive without disease recurrence or metastasis at the date of the last follow-up examination were censored. Among the 106 patients in this study, 91 (85.8%) were followed up, and 14 (14.2%) were lost to follow-up.

Statistical analysis

Statistical analyses were performed with IBM SPSS, version 17.0 (IBM Corp., Armonk, NY, USA). Survival curves were created using the GraphPad Prism 8.2 software (GraphPad Software, Inc., La Jolla, CA, USA). All data were shown as the mean ± standard deviation or number and percentage of patients. Kaplan-Meier analysis was used to estimate OS and DFS, and the log-rank test was applied to compare differences in survival. The hazard ratios (HRs) and 95% confidence intervals (CIs) for DFS and OS between groups were analyzed with a Cox proportional hazards regression model after adjustment. Survival was measured in months. All tests were two-sided, and a P value less than 0.05 was considered statistically significant.

Results

Distribution of characteristics in patients with gastric GISTs

There was a total of 106 patients (38 men and 68 women) with confirmed gastric GIST, with a median age of 61 years (range, 30–79 years). The detailed characteristics of the 106 patients are listed in Table S1.

Demographic and clinicopathological characteristics for predicting prognosis

The cumulative OS rate of gastric GIST patients was 92.5%, and the corresponding DFS rate was 84.0% (*Figure 1*). As shown in *Table 1*, the univariate analysis demonstrated that patients with blood type A had a significantly lower OS rate (82.4% *vs.* 97.2%, P=0.01) than patients with other blood types (AB, B, and O). In addition, blood type A was a poor prognostic factor for DFS and OS in patients with GIST alone (P<0.05), as shown in Table S2. A higher Ki-67 index was significantly associated with a worse DFS

Table 1 Univariate analysis of OS and DFS in 106 patients with gastric GISTs

Variables	No. (%)	DFS		OS	
		Rate (%)	P	Rate (%)	P
Gender			0.30		0.37
Female	68 (64.2)	86.8		94.1	
Male	38 (35.8)	78.9		89.5	
Age			0.07		0.31
<60 years	47 (44.3)	91.5		95.7	
≥60 years	59 (55.7)	78.0		89.8	
ABO blood type†			0.09		0.01*
A	34 (32.4)	73.5		82.4	
Non-A (B/AB/O)	71 (67.6)	88.7		97.2	
Cigarette smoking			0.97		0.55
Yes	17 (16.0)	82.4		88.2	
No	89 (84.0)	84.3		93.3	
Alcohol drinking			0.63		0.57
Yes	7 (6.6)	85.7		85.7	
No	99 (93.4)	83.8		92.9	
Histologic subtype†			0.61		0.72
Spindle	90 (97.8)	85.6		92.2	
Epithelioid and mixed	2 (2.2)	100.0		100.0	
Tumor size			0.52		0.33
<5 cm	56 (52.8)	85.7		94.6	
≥5 cm	50 (47.2)	82.0		90.0	
Tumor location†			0.13		0.33
Upper + middle	90 (87.4)	82.2		92.2	
Lower	13 (12.6)	100.0		100.0	
Mitosis count†			0.10		0.84
≤5/50 HPF	68 (71.6)	86.8		91.2	
>5/50 HPF	27 (28.4)	74.1		92.6	
Modified NIH risk†			0.42		0.63
Very low + low	40 (41.2)	87.5		95.0	
Medium	21 (21.6)	85.7		90.5	
High	36 (37.1)	77.8		88.9	
Tumor invasion†			0.04*		0.24
Mucosa + submucosa	35 (33.7)	94.3		97.1	
Muscular + serosa	69 (66.3)	78.3		89.9	

Table 1 *(continued)*

Table 1 *(continued)*

Variables	No. (%)	DFS		OS	
		Rate (%)	P	Rate (%)	P
GI-bleeding†			0.24		0.18
Yes	29 (29.3)	75.9		86.2	
No	70 (70.7)	85.7		94.3	
Ki-67 index†			0.04*		0.29
<10%	73 (76.8)	86.3		93.2	
≥10%	22 (23.2)	68.2		86.4	
CD117†			0.28		0.23
Positive	86 (86.0)	81.4		90.7	
Negative	14 (14.0)	92.9		100.0	
CD34†			0.30		0.52
Positive	93 (96.9)	81.7		91.4	
Negative	3 (3.1)	100.0		100.0	
PDGFRα†			0.93		0.75
Positive	84 (87.5)	83.3		92.9	
Negative	12 (12.5)	83.3		91.7	
α-SMA†			0.46		0.68
Positive	40 (42.1)	85.0		92.5	
Negative	55 (57.9)	80.0		90.9	
Synchronous GC			0.01*		0.98
Yes	12 (11.3)	58.3		91.7	
No	94 (88.7)	87.2		92.6	
Rupture†			0.95		0.49
Yes	6 (5.7)	83.3		100.0	
No	99 (94.3)	83.8		91.9	
Tumor necrosis†			0.01*		0.10
Yes	26 (26.3)	69.2		84.6	
No	73 (73.7)	87.7		94.5	

†, partial data were missing. *, P<0.05. OS, overall survival; DFS, disease-free survival; GIST, gastrointestinal stromal tumor; HPF, high-power field; NIH, National Institutes of Health; GI, gastrointestinal; PDGFRα, platelet-derived growth factor receptor alpha; SMA, smooth muscle actin; GC, gastric cancer.

(68.2% *vs.* 86.3%, P=0.04). Additionally, synchronous GC, more muscular or serosal invasion, and tumor necrosis were significantly associated with a poor DFS (58.3% *vs.* 87.2%, P=0.01; 78.3% *vs.* 94.3%, P=0.04, and 69.2% *vs.* 87.7%, P=0.01, respectively). The Kaplan-Meier curves for OS and DFS according to blood type, Ki-67 index, synchronous GC, and tumor necrosis are shown in *Figures 2*,*3*. The immunohistochemistry staining of the Ki-67 index expression in gastric GIST tissues is also shown in *Figure 3*.

Multivariate analysis demonstrated that blood type A was a significant independent prognostic factor with both OS (HR: 7.09, 95% CI: 1.15–43.73, P=0.04) and DFS

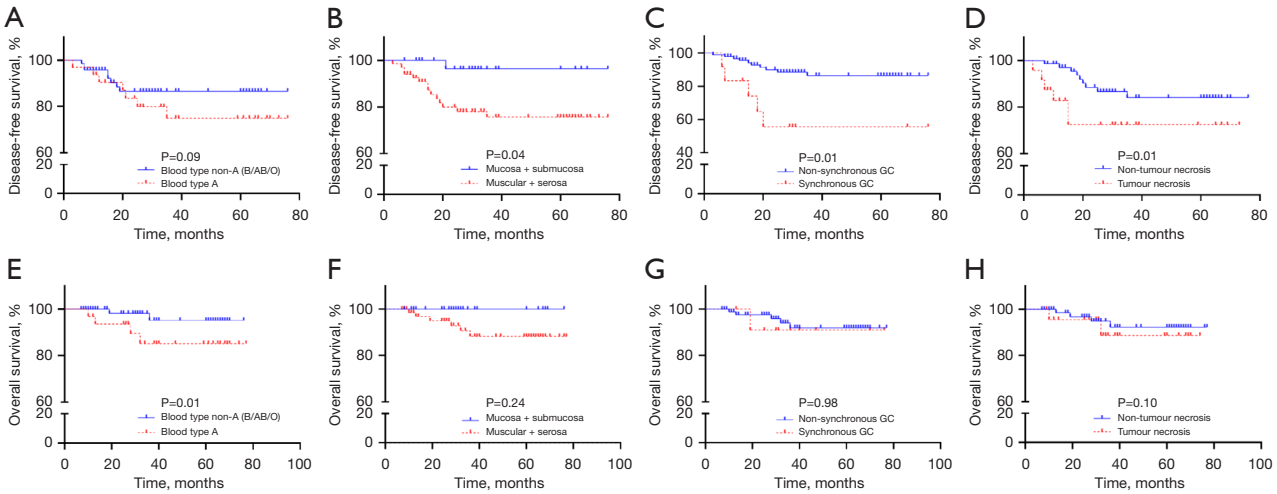

Figure 2 Disease-free survival and overall survival showed by Kaplan-Meier curves in 106 patients with gastric GIST according to subgroups. (A-D) Disease-free survival of blood types (A), tumor invasion (B), synchronous GC (C) and tumor necrosis (D). (E-H) Overall survival of blood types (E), tumor invasion (F), synchronous GC (G) and tumor necrosis (H). GIST, gastrointestinal stromal tumor; GC, gastric cancer.

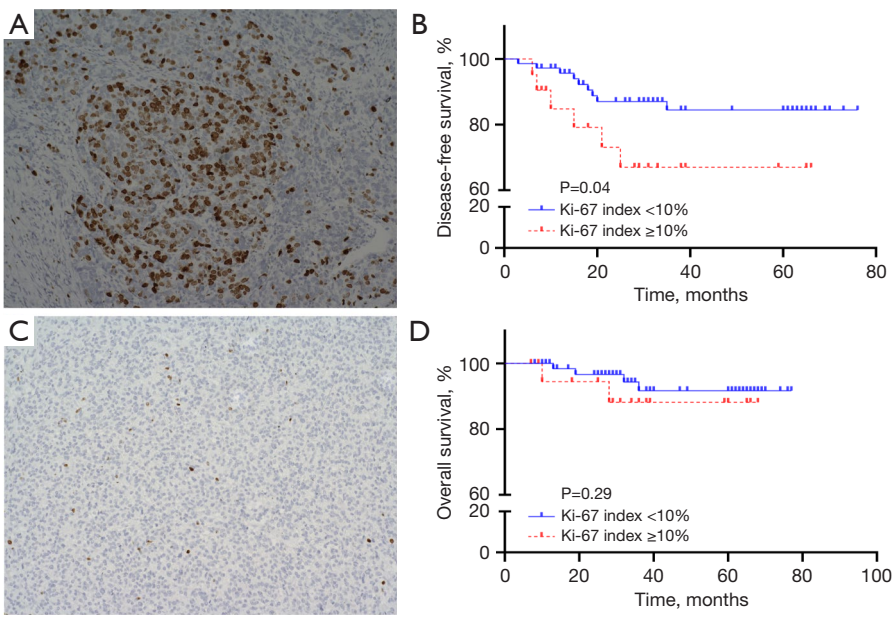

Figure 3 The immunohistochemistry staining analyses and the survival curves according to the expression of Ki-67. Immunohistochemistry staining of Ki-67 in gastric GIST tissues (A,C). High-expression of Ki-67 (A) and low-expression of Ki-67 (C) (×200). The disease-free survival and overall survival curves of Ki-67 (B,D) in gastric GIST patients. GIST, gastrointestinal stromal tumor.

(HR: 3.24, 95% CI: 1.04–10.11, P=0.04). Synchronous GC and age ≥60 years were also significant independent predictors of poor DFS (HR: 8.71, 95% CI: 1.89–40.16, P=0.006, and HR: 3.36, 95% CI: 1.04–10.84, P=0.04, respectively) (*Table 2*).

Discussion

GISTs are rare tumors of the GI tract that arise from primitive mesenchymal cells (24). GISTs tend to be infrequent before the age of 30 and are most common in

Table 2 Multivariate analysis of OS and DFS in 106 patients with gastric GISTs

Variable	DFS		OS	
	HR (95% CI)	P	HR (95% CI)	P
ABO blood type				
Non-A (B/AB/O)	1.00		1.00	
A	3.24 (1.04–10.11)	0.04*	7.09 (1.15–43.73)	0.04*
Age				
<60 years	1.00		1.00	
≥60 years	3.36 (1.04–10.84)	0.04*	3.20 (0.59–17.27)	0.18
Tumor invasion				
Mucosa + submucosa	1.00		1.00	
Muscular + serosa	2.88 (0.55–15.12)	0.21	3.46 (0.32–37.92)	0.31
Ki-67 index				
<10%	1.00		1.00	
≥10%	1.77 (0.56–5.60)	0.33	1.08 (0.18–6.54)	0.94
Synchronous GC				
No	1.00		1.00	
Yes	8.71 (1.89–40.16)	0.006*	3.02 (0.22–40.87)	0.41
Tumor necrosis				
No	1.00		1.00	
Yes	1.45 (0.45–4.67)	0.54	1.68 (0.33–8.70)	0.54
GI-bleeding				
No	1.00		1.00	
Yes	2.32 (0.46–11.67)	0.31	2.85 (0.33–24.43)	0.34

*, P<0.05. OS, overall survival; DFS, disease-free survival; GIST, gastrointestinal stromal tumor; HR, hazard ratio; CI, confidence interval; GC, gastric cancer; GI, gastrointestinal.

patients older than 60 years. The median age at diagnosis varies from 58–65 years, and the male to female ratio is 1:1 (25-29). Similarly, in this study, the median age of gastric GIST patients was about 61 years, ranging from 30–79 years, and the ratio of men to women was 1:1.79.

Comparing with several previous studies which mainly focused on the risk factors for DFS and/or OS in GISTs, such as mitotic count, Ki-67 index, or tumor necrosis (30,31), our study highlighted that the synchronous GC and blood type A were significant unfavorable predictors for DFS and/or OS. Interestingly, our study is the first to report that blood type A is a significant independent risk factor for both poor OS and DFS in gastric GIST patients. A study of 162 Turkish patients with GISTs showed that blood type had no relationship to clinicopathological features (32); however, the association of blood type with survival was not examined, and other reports about the role of blood type in GISTs are rare. The role of blood type A in cancer was originally suggested decades ago, with the clinical description that patients with blood type A were more likely to develop GC (33). Many large, prospective, population-based studies have since consistently documented that individual with blood type A have a sensitive immune system with an increased risk of gastric neoplasia (21,34-38). This is thought to be because of the structural similarity of the blood group antigen A to the Forssman antigen, which is expressed in GI cancers. Because of this similarity, individuals with other blood types have antibodies against

the blood group antigen A, and these antibodies may readily recognize the Forssman antigen and attack precancerous and cancerous cells expressing this antigen. Accordingly, people with blood type A are more susceptible to developing GI carcinomas than patients with other blood types (39). The effect of blood type A on GC risk may also be mediated by alterations in a few physiological processes, from systemic inflammation to antitumor immune surveillance. For instance, Sievers *et al.* indicated that individuals with blood type A had less free acid in their stomachs than those with blood type O (40). Further, blood type A was significantly associated with longer ovarian cancer survival in the largest such study to date (41). Similar results were also observed in nasopharyngeal carcinoma (42) and pancreatic cancer (43). Multiple studies have analyzed the link between character, personality, and compatibility based on blood type (44,45). Cattell *et al.* found that individuals with blood type A had significantly different levels of anxiety than individuals with other blood types (46). Accordingly, the unfavorable prognosis of GIST patients with blood type A may be influenced by mood.

Co-existence of different neoplasms in one patient is not a common phenomenon since the tumors can develop synchronously or asynchronously (47). Gastric GISTs combined with synchronous GC have some specific pathological features. For instance, Yan *et al.* found that the majority of gastric GISTs with synchronous GC (14/15) were <2 cm in size with very low or low risk (48), whereas most of the tumors in our study (4/12) were ≥3 cm with intermediate and high risk. However, the prognoses of gastric GIST patients with synchronous GC in both the study by Yan *et al.* and our study were worse than those of patients with gastric GIST alone (49). These findings, as well as our study, demonstrated that the clinicopathological features of gastric GISTs with synchronous GC may vary in different populations, but these patients tend to have a worse prognosis than patients with only gastric GIST. Further, several studies showed that necrosis is associated with increased tumor cell proliferation and reduced disease-specific survival (50-52). However, the mechanisms behind this phenomenon are still unexplained. One possible reason is that rapid cell proliferation may cause the tumor to outgrow the vasculature and lead to hypoxic conditions, promoting metastatic cascade and causing subsequent cell death (53,54).

Imatinib is the only tyrosine kinase inhibitor that has been studied as an adjuvant treatment for operable GIST (55). Long-term imatinib treatment is effective in preventing recurrence of GIST during treatment for patients with mutations sensitive to this drug (56). However, most patients with advanced GIST may experience disease progression after surgery and using imatinib, which may be attributed to discontinued therapy because of patient choice (56). In addition, wild-type GIST may be considered insensitive to imatinib, and mutation analysis may add prognostic information for patients suffering from GIST (57). Our data showed that neoadjuvant imatinib was an unfavorable prognostic factor for DFS in GIST patients (data not shown), but we thought that a group of factors make it difficult to establish benefit or the lack of benefit of adjuvant imatinib in this population. For example, only a small number of patients receiving imatinib (n=12, 11.3%). Besides, there were no mutational tests to identify patients likely to benefit from imatinib. Therefore, more patients and relevant evidences were needed to establish a reasonable conclusion for the effect of neoadjuvant imatinib in the future study.

There are some limitations to this study. Firstly, due to the limited information and the study design, information such as KIT mutation, environmental factors, clinicopathologic information of synchronous GCs, and detailed mutation information for imatinib treatment could not be collected. More information to explore these risk factors and prognostic factors are expected to be collected in future studies. Secondly, as a non-randomized retrospective single-center study, our findings could have been observed by chance. Therefore, large-scale, prospective multicenter studies are needed to evaluate whether blood type A could be an important supplementary or substituted index for the prognosis of gastric GIST.

Conclusions

In summary, our results suggested that the blood type A, age ≥60 years, and synchronous GC were unfavorable prognostic factors for patients with postoperative gastric GIST. The impact of these three factors on the malignant potential of gastric GIST and the prognosis of patients with gastric GIST remain an interesting area of research that warrants additional investigation.

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Footnote

Reporting Checklist: The authors have completed the REMARK reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-1042/rc

Data Sharing Statement: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-1042/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-1042/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of Ningxia Medical University (2014-032) and the Ethics Committee of Hainan Medical University (HYLL-2021-339) and individual consent for this retrospective analysis was waived.

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