Gastrointestinal Stromal Tumours of the Small Intestine

Hakan Uzunoglu, Yasin Tosun, Ozan Akinci and Baver Baris

Department of General Surgery, Kartal Dr. Lütfi Kırdar City Hospital, Istanbul, Turkey

ABSTRACT

Objectives: To describe the spectrum of small intestine gastrointestinal stromal tumour (GIST) cases; and to analyse prognostic factors.

Study Design: Descriptive study.

Place and Duration of Study: Kartal Dr. Lütfi Kirdar City Hospital, Istanbul, Turkey, from 2010 to 2020.

Methodology: Forty patients with small intestine GIST followed up between 2010-2020 were included in this study. The demographic information and clinical laboratory, histopathology, and radiology findings of all patients were analysed and compared. Five-year overall survival (OS) rate and five-year disease-free survival (DFS)were calculated.

Results: The mean patient age at diagnosis was 58.9 ± 12.6 years (34–79 years). Thirty-seven (92.5%) tumours were in the jejunum and ileum, and three (7.5%) were in the duodenum. The most common symptoms were bleeding (50%) and pain (37.5%). A total of 5% of the patients were asymptomatic, and 67.5% were in the high-risk group. Two patients (5%) died within a 30-day postoperative period, and 13 (32.5%) died during the follow-up period. The five-year overall survival (OS) rate was 54.2%. The mean five-year OS and five-year disease-free survival (DFS) were 47.5 ± 16.8 months and 40.9 ± 25.0 months, respectively. The mortality risk was calculated as 4.5-fold increased in the patients aged over 60 years and as 3.556-fold increased in those with recurrence/metastasis detected in their follow-ups.

Conclusion: The OS ratio and OS duration were not as high as expected for small intestine GIST cases. Tumour diameter, mitotic index, and risk classification may not provide sufficient information for prognosis prediction in some cases. The frequency of recurrence and/or metastasis was higher than expected — although complete resection was achieved.

Key Words: *Gastrointestinal stromal tumours, Small intestine, Tumour diameter, Mitotic index.*

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INTRODUCTION

Gastrointestinal stromal tumours (GIST) are the most common mesenchymal tumours. GISTs originate from the precursors of the interstitial cells of cajal. The incidence of GIST is between 4.3-15 per million. GISTs most commonly involve the stomach followed by the small intestine.[1-3] In most GIST cases, diagnosis is made *via* the histopathological examination of the resection material removed during the operation. In some cases, diagnosis is made *via* the pathological examination of the pre-op biopsy sample collected with aspiration, under the guidance of endoscopic ultrasonography. However, this method may cause complications, such as perforation or bleeding.[1-5]

The most common treatment performed in small intestine GIST cases is the surgical resection of the tumour, which is the aim of removing the tumour completely.

Correspondence to: Dr. Hakan Uzunoglu, Department of General Surgery, Kartal Dr. Lutfi Kırdar City Hospital, Istanbul, Turkey
E-mail: drhakanuzunoglu@gmail.com

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However, despite complete resection, recurrences can be seen frequently in the first two years after surgery. However, in some cases featuring a large tumour or with high risk of recurrence, adjuvant chemotherapy consisting tyrosine kinase inhibitors (*i.e.*, imatinib) is given to the patient to facilitate a better outcome. The prognosis is very variable in GIST cases. Some small intestine GIST cases may have a very good clinical course. However, in many cases, the clinical picture can deteriorate rapidly, and morbidity and mortality can occur despite surgical treatment.[3-6] Therefore, predicting prognosis is critical in small intestine GISTs. In order to determine the prognosis, various risk classifications have been made, in which the localisation, diameter, and mitotic activity of the primary tumour are evaluated together.[3,7,8]

In small intestine GIST cases, early diagnosis and follow-up are critical. Recurrence or metastasis can be most commonly seen in the liver, periton, or resection area in small intestine GIST cases. In order to avoid complications, morbidity, recurrence and metastasis during follow-up, the patient should be followed closely for a long time after surgery.[9-12]

There have only been a few studies conducted specifically on small intestine GIST cases.[13-19] In this study, the aim was to analyse the clinical, laboratory, pathological and radiological

findings of small intestine GIST cases, followed up for ten years at this hospital as well as to analyse the prognostic factors.

METHODOLOGY

This study was performed in line with the principles of the Declaration of Helsinki. Ethical approval was waived by the local Ethics Committee in view of the retrospective nature of the study and all the procedures being performed were part of the routine care (Date: 08/07/2020; No. 2020/514/181/12).

A total of 40 patients who were operated upon due to small intestine GISTs in the General Surgery Department, Kartal Dr. Lütfi Kirdar City Hospital, Istanbul, Turkey within the 10-year period between May 2010 and May 2020, were included in this study. The demographic information and clinical, laboratory, pathology, and radiology findings of all the patients were recorded. Those who refused to participate, those under the age of 18 years, and those who died due to a cause other than the small intestine GIST tumour, were not included in this study. Risk classification of the patients was grouped, based on the National Institute of Health (NIH) prognostic criteria developed according to the tumour diameters and mitotic indexes.[3,7,8]

The tumours were excised and the biopsy samples were collected with aspiration under the guidance of endoscopic ultrasonography.

All statistical analyses were done using SPSS version 25.0 software (IBM SPSS, Chicago, IL, USA). Qualitative data are given as numbers and percentages; while, quantitative as mean ± standard deviation. In terms of categorical variables, comparisons between groups were made with Pearson's Chi-square, likelihood ratio or Fisher's Exact test. Whether continuous variables are suitable for normal distribution was confirmed by the Shapiro-Wilk test. A kurtosis value ± 1.0 was considered excellent and a value between ± 2.0 was also acceptable, The differences between the groups in terms of continuous variables were analysed using Student's t-test, and the comparison of mean values was done between multiple groups by variance analysis. The relationship between continuous variables was tested using Pearson's correlation analysis. Risk coefficient of categorical variables was evaluated by logistic regression analysis and given as odds ratio. The results were evaluated within the 95% confidence interval, and $p < 0.05$ values were considered significant. Bonferroni correction was made wherever appropriate.

RESULTS

Twenty-one (52.5%) patients were males. A total of 37 (92.5%) of the tumours were in the jejunum and ileum, and three (7.5%) were in the duodenum. The most common symptoms were bleeding (50%) and pain (37.5%). The tumour diameter was 10 cm and greater in 37.5% of the patients, the mitotic index was 5 /50 high power field (HPF) and below in 62.5%. A total of 67.5% patients were in the high-risk group. CD117 and DOG1 were detected in all patients, and CD34 in 77.5% (Table I).

Table I: Distribution of symptoms, risk, tumour diameter, mitotic index groups and marker detection rates.

	n	%
Gender		
Men	21	52.5
Women	19	47.5
Localization		
Jejunum and ileum	37	92.5
Duodenum	3	7.5
Symptoms		
Bleeding	20	50.0
Pain	15	37.5
Palpable mass	2	5.0
Asymptomatic	2	5.0
Other	1	2.5
Diagnosis type		
Resection material	39	97.5
Pre-op biopsy	1	2.5
Additional disease	19	47.5
HT	9	22.5
DM	8	20.0
DM + HT	1	2.5
Other	1	2.5
NIH risk category		
Very Low	0	0
Low	9	22.5
Intermediate	4	10.0
High	27	67.5
Tumour diameter (cm)		
≤2	1	2.5
2.01-5	12	30.0
5.01-9.99	12	30.0
≥10	15	37.5
≤5	13	32.5
>5	27	67.5
Mitotic index (/50HPF)		
≤5	25	62.5
5.01-9.99	2	5.0
≥10	13	32.5
≤5	25	62.5
>5	15	37.5
CD117	40	100.0
CD34	31	77.5
DOG 1	25	100*
S100	2	5.0
Desmin	1	2.5
Necrosis	24	60.0
Rupture	8	20.0

Shows the ratio of the number of the tests performed. DM: Diabetes mellitus, HT: Hypertension, HPF: High power field.

The mortality rate was significantly higher in the patients over 60 years ($p=0.033$). Comparisons between the patients and survivors, as well as risk analyses of the patients, are shown in Table II.

The mean DFS was significantly lower in the patients with a tumour diameter >5 cm (32.3±35.5 months) than those with a tumour diameter of ≤5 cm (60.9 ± 37.8 months) ($p=0.024$). In addition, the mean DFS in those in the high-risk category (32 ± 35.8 months) was significantly lower compared to that of the patients in the non-high--risk groups (61.5 ± 36.6 months) ($p=0.02$) (Table III).

Seven (17.5%) patients had metastases at the time of diagnosis, and 12 (30%) had metastasis or recurrence detected during follow-up.

Table II: Comparison and risk analysis in terms of mortality.

	Died		Alive		Total	p*	OR**	(95% CI)
	n=13	%	n=27	%	n=40			
Gender (male)	4	30.8	17	63.0	21	0.056	0.261	0.064-1.074
Age at diagnosis (>60 years)	9	69.2	9	33.3	18	0.033	4.5	1.084-18.689
Necrosis	9	69.2	15	55.6	24	0.408	1.8	0.443-7.308
Rupture	2	15.4	6	22.2	8	>0.999	0.636	0.11-3.694
R0 resection	10	76.9	21	77.8	31	>0.999	0.952	0.197-4.611
Second primary tumour	2	15.4	1	3.7	3	0.242	4.727	0.387-57.696
Recurrence-metastasis during follow-up	4	30.8	3	11.1	7	0.187	3.556	0.662-19.108
NIH risk category						0.674		
Very Low	0	0	0	0	0			
Low	2	15.4	7	25.9	9			
Intermediate	1	7.7	3	11.1	4			
High	10	76.9	17	63.0	27			
Not High	3	23.1	10	37.0	13			
High	10	76.9	17	63.0	27	0.484	1.961	0.434-8.86
Tumour diameter (cm)						0.163		
≤2	0	0.0	1	3.7	1			
2.01-5	3	23.1	9	33.3	12			
5.01-9.99	2	15.4	10	37.0	12			
≥10	8	61.5	7	25.9	15			
≤5	3	23.1	10	37.0	13	0.484	1.961	0.434-8.86
>5	10	76.9	17	63.0	27			
Mitotic Index (/50HPF)						0.555		
≤5	8	61.5	17	63.0	25			
5.01-9.99	0	0.0	2	7.4	2			
≥10	5	38.5	8	29.6	13			
≤5	8	61.5	17	63.0	25			
>5	5	38.5	10	37.0	15	>0.999	1.063	0.272-4.153

**Pearson's Chi-square test was used. **Risk coefficient of categorical variables was evaluated by logistic regression analysis and given as "odds ratio''. OR: Odds ratio, NIH: The National Institute of Health, HPF: High power field.*

Two patients (5%) died within the post-op 30-day period, and 13 (32.5%) died during the follow-up period. Five-year OS and 5-year DFS rates were both 54.2% in the patients.

The mean of the patients age at diagnosis was 58.9 ± 12.6 years (age range: 34-79 years). The mean follow-up period of the patients was 46.03 ± 35.8 months. The mean tumour diameter was 8.3 ± 4.6 cm (range: 2.0-19.5 cm), and the mean mitotic index was 11.9 ± 20.8 /50HPF (range: 1-115 /50HPF). The mean 5-year OS of the patients was 47.5 ± 16.8 months, and the mean 5-year DFS was 40.9 ± 25.0 months. The mean OS of the patients was 47.4 ± 34.4 months, and the mean overall DFS was 41.6 ± 38.3 months.

The five-year OS decreased as the patient age increased (p=0.027; r=-0.45). Risk levels were significantly correlated with tumour diameter (p<0.001; r=0.664) and inversely correlated with overall DFS (p=0.041; r=-0.325). Tumour diameter was inversely correlated with overall DFS (p=0.026; r=-0.352).

DISCUSSION

Gastric and small intestine GIST cases are known to be similar in terms of their clinical features and prognosis. However, it has been stated that there may be differences between gastric and small intestine GISTs in terms of tumour diameter, mitotic index, prognosis, OS, and DFS.[3-8] Therefore, separately reviewing small intestine GIST cases can provide useful information in terms of determination of the prognosis. In the present study, only small intestine GIST cases were examined, and the effects of symptoms and findings on prognosis were evaluated.

The most common symptoms in small intestine GIST cases are bleeding, abdominal pain, and anemia.[13,14] In the present study, most of the patients (87.5%) presented with bleeding and/or pain, and 5% of the patients were found to be asymptomatic. It has been reported that small intestine GISTs are seen more frequently in those aged 60 and older.[13,15]

Table III: Comparison of mean survival duration by tumour diameter, mitotic index and risk groups.

	5-year OS rate		5-Year-Overall survival (months)		5-Year-DFS survival (months)		Overall survival (months)		Disease-free survival (months)	
	n=13 (%)	p*	Mean±SD	p**	Mean±SD	p**	Mean±SD	p**	Mean±SD	p**
Gender		0.219		0.073		0.35		0.235		0.344

Men	8(61.5)		53.8±11.1		45.8±24.6		53.6±32.5		47.1±37.9	
Women	5(38.5)		41.3±19.6		36±25.4		40.5±36		35.5±38.7	
Age at diagnosis		0.107		0.105		0.127		0.258		0.242
≤60 years	9(69.2)		52.7±14.4		48.1±21.6		53±32.3		48±36.4	
>60 years	4(30.8)		41.5±18.1		32.4±27.0		40.5±36.5		33.7±40	
Tumour diameter (cm)		0.022		0.343		0.149		0.139		0.077
≤2	1(7.7)		60±0		60±0		109±0		109±0	
2.01-5	5(38.5)		44.3±21.9		44.3±21.9		56.9±36.5		56.9±36.5	
5.01-9.99	4(30.8)		60±0		60±0		36.6±37.1		34.1±39	
≥10	3(23.1)		44.3±14.8		29.7±27.7		44.3±26.5		30.8±33.7	
Tumour diameter (cm)		0.423		0.762		0.448		0.083		0.024
≤5	6(46.2)		46±21.2		46±21.2		60.9±37.8		60.9±37.8	
>5	7(53.8)		48.5±14.4		37.8±27.2		40.9±31.2		32.3±35.5	
Mitotic index (/50HPF)		0.526		0.708		0.587		0.891		0.967
≤5	8(61.5)		48.1±17.6		42.8±24.2		46.8±33.5		42.8±36.3	
5.01-9.99	1(7.7)		60±0		60±0		37.5±48.8		37.5±48.8	
≥10	4(30.8)		45±16.7		34.9±27.9		49.9±37		39.9±43.8	
Mitotic index (/50HPF)		>0.999		0.849		0.636		0.901		0.804
≤5	8(61.5		48.1±17.6		42.8±24.2		46.8±33.5		42.8±36.3	
>5	5(38.5)		46.7±16.4		37.7±27.4		48.3±36.9		39.6±42.6	
NIH risk category		0.397		0.972		0.57		0.173		0.062
Very Low	-		-		-		-		-	
Low	4(30.8)		46.3±21.4		46.3±21.4		58.3±38.2		58.3±38.2	
Intermediate	3(23.1)		49±22		49±22		68.8±36.9		68.8±36.9	
High	6(46.2)		47.6±14.6		36.2±27.5		40.6±31.7		32±35.8	
NIH risk category		0.24		0.973		0.266		0.07		0.02
Not High	7(53.8)		47.4±20.4		47.4±20.4		61.5±36.6		61.5±36.6	
High	6(46.2)		47.6±14.6		36.2±27.5		40.6±31.7		32±35.8	
Necrosis		0.423		0.945		0.438		0.832		0.825
Present	7(53.8)		47.7±15.8		37.7±27.3		48.3±36.2		40.5±41.5	
Absent	6(46.2)		47.2±19.5		46.1±21		45.9±32.6		43.3±34.1	
Rupture		0.458		0.109		0.095		0.053		0.074
Present	0.0		21±0		0±0		26.5±21.1		20±25.5	
Absent	13(100.0)		48.7±16.2		42.7±23.9		52.6±35.3		47±39.3	
R0 Resection		>0.999		0.822		0.924		0.294		0.247
Yes	11(84.6)		47.9±17.3		41.1±25.8		50.5±35.2		45.4±38.7	
No	2(15.4		45.8±16.9		39.8±23.5		36.7±30.8		28.4±35.8	
Additional disease		>0.999		0.836		0.564		0.247		0.531
Absent	9(69.2)		48.1±16.6		38.9±27.5		54.1±35.1		45.6±41.5	
Present	4(30.8)		46.5±18.4		44.8±20.1		41.3±33.4		37.9±35.7	

*Pearson's Chi-square test was used. **Independent samples' t-test was used for analysis of the diffferences between two groups, and one way ANOVA test was used for the analysis of the diffferences among three or more groups. OS: Overall survival, SD: Standard deviation, NIH: The National Institute of Health.

In the present study, it was observed that the number of the cases were found to be slightly higher in those of the 6th and 7th decades and the males. It should also be kept in mind that patients of an advanced age who have complaints of pain and bleeding may have small intestine GIST.

The purpose of GIST surgery is to provide complete resection to reduce the possibility of recurrence and the development of metastasis. It has been reported that complete resection affects prognosis in GIST cases.[5,6,10] Crosby *et al.* reported that complete resection was achieved in 70% of the patients.[15] Complete resection rate was 77.5% in this study. These findings show that the rate of complete resection is not very high in small intestine GIST cases. Additionally, Crosby *et al.* detected metastases in 18% of their patients at the time of diagnosis.[15] These researchers showed that 11% of the patients who underwent complete resection developed metastasis and that complete resection significantly affected their prognosis. In their meta-analysis, Machairas *et al.* determined that the rate of recurrence in patients undergoing complete resection varied between 20-50%.[20] In the literature, recurrence and/or metastasis rates were reported to be between 22-48%.[13-15] In the present study, metastasis was detected in 17.5% of the patients at the time of diagnosis, and metastasis or recurrence was detected in 30% of the patients during the follow-up period. Complete resection rates were similar between the patients who died and those who survived during the follow-up period. In addition, the five-year OS rate, five-year OS duration, five-year DFS rate, and overall DFS values were all similar among the patients who underwent complete resection and those for whom the tumour could not be resected completely. All these data show that complete resection cannot be achieved in all small intestine GIST cases, and the rate of recurrence or metastasis development is not very low in patients who underwent complete resection.

In the present study, no significant difference was found

between the patients who died during the follow-up period and those who survived in terms of recurrence/metastasis rates. However, in the present study, it was determined that those who had recurrence/metastasis in their follow-ups had a 3.556-fold increased risk of mortality. This finding shows the importance of close follow-up with patients in terms of the development of recurrence or metastasis.

The mortality rate for small intestine GIST cases has been reported to be between 11.8–72%.[13,15,16,21] The five-year OS rate has been reported to be between 41–87.5%.[13-15,21] In their review, Machairas *et al.* determined that the five-year OS rate varied between 30–65% in patients who underwent complete resection.[20] Crosby *et al.* reported that the mean OS duration was significantly higher in those who underwent complete resection.[15] In the present study, the mean five-year OS of the patients was 47.5 ± 16.8 months, and the five-year DFS was 40.9 ± 25.0 months. The mean OS of the patients was 47.4 ± 34.4 months, and the mean DFS was 41.6 ± 38.3 months. These findings show that the mortality rate can be high and the overall survival and five-year OS rates not very high despite complete resection in small intestine GIST cases.

Fan *et al.* and Wu *et al.* found that the mean DFS values were similar between patients over 60 years-old and those under 60.[17,18] In the present study, the patients over 60 years and those below 60 years also had similar mean OS and five-year OS values. However, in the present study, the five-year OS was significantly correlated with age. In addition, mortality was significantly higher among the patients over 60 years of age. In the risk analysis, the mortality risk was calculated as 4.5-fold increased in those over 60 years of age. This data shows that age has an effect on prognosis, but taking a different threshold for age may be more decisive in terms of prognosis.

The determination of the tumour diameter in small intestine GIST cases is valuable in terms of predicting the clinical course and prognosis of the disease and making a risk classification.[7,8] Liao *et al.* and Crosby *et al.* reported a mean tumour diameter of 4.7 cm and 11 cm, respectively in small intestine GIST cases.[13,15] In the present study, the mean tumour diameter was found to be 8.3±4.6 cm. In the literature, a significant number of patients (30–51%) have been reported as having a tumour over 10 cm in diameter. [14,15] Similarly, in the present study, the rate of patients with a tumour diameter over 10 cm was found to be high (61.5%). Crosby *et al.* reported that tumour diameter did not affect prognosis in their analysis.[15] Similarly, Wu *et al.* could not find a relationship between tumour diameter and mean OS and DFS.[18] However, Liao *et al.* reported that a tumour diameter over 7 cm increased the recurrence rate in small intestine GIST cases.[13] On the other hand, Huang *et al.* also found that the rate of recurrence was higher in patients with a tumour diameter of 10 cm or above.[14] In the present study, the distribution rates of the tumour diameters were found to be similar between the patients who died and those survived.

In the correlation analysis performed in the present study, no significant correlation was found between tumour diameter and OS, five-year OS, and five-year DFS values; however, it was found that the DFS duration decreased as the tumour diameter increased. In the present study, the OS rate, five-year OS rate, and the mean five-year OS and DFS values were all found to be similar between the tumour diameter groups. However, the DFS was significantly lower in the patients with a tumour diameter >5 cm. In addition, it was determined that those with a tumour diameter >5 cm had a 1.961-fold increased mortality risk. These findings show that tumour diameter is important in terms of prognosis in small intestine GIST cases but that tumour diameter alone may not provide accurate and sufficient data for predicting a prognosis.

The determination of mitotic activity in the primary tumour in small intestine GIST cases is also valuable in terms of predicting the clinical course and prognosis of the disease and making a risk classification.[7,8] Liao *et al.* reported the rate of the patients with a mitotic index of 5/50 HPF and below as 69.5%.[13] In the present study, 61.5% of the patients had a mitotic index of 5/50 HPF and below. Crosby *et al.* reported that the mitotic index did not affect prognosis;[15] however, Liao *et al.* and Huang *et al.* reported that the recurrence rate of those with a mitotic index above 5/50 HPF was significantly higher than those with an index of 5/50 HPF or below. [13,14] Huang *et al.* reported that those with a mitotic index higher than 5/50 HPF had a 5.2-fold increased risk of recurrence and that there was a significant relationship between the mitotic index and mortality.[14] In the present study, the mitotic index distributions were similar between the patients who died and those who survived. Correlation analysis of the patients did not reveal any significant correlations between the mitotic index value and the OS, DFS, five-year OS, and five-year DFS values. Wu *et al.* reported that the mitotic index significantly affected the mean OS and DFS durations.[18] In the present study, the OS rate, DFS rate, five-year OS rate, and the mean five-year OS and DFS durations were all similar among the mitotic index groups. All these findings show that the mitotic activity level in the primary tumour is important in terms of prognosis and mortality but that the mitotic index alone may not be sufficient in predicting prognosis.

When the tumour location, tumour diameter, and mitotic index are evaluated together, a risk classification can be made to predict the development of metastasis or recurrence in GIST cases.[3,7,8] In the present study, 67.5% of the patients were in the high-risk group. Huang *et al.* determined that the rate of recurrence was higher in the high-risk group patients in their study.[14] In the present study, the

levels of risk between the groups were found to be similar between the patients who died and those who survived. However, it was determined that the patients in the high-risk group had a 1.961-fold increased risk of mortality. In the present study, the OS rate, five-year OS rate, and mean five-year OS and DFS durations were all similar among the risk groups, but the mean DFS duration was found to be significantly lower in those in the high-risk category. In the present study, it was also found that the risk level category and the DFS were significantly inversely correlated. These findings show that risk classification is critical in small intestine GIST cases and that high-risk group patients should be closely monitored in terms of the development of recurrence or metastasis.

There were some limitations in the present study. Firstly, it is a single-centred and retrospective nature. Secondly, the inclusion of patients in the study whose five-year follow-up period was not completed might have caused low mean OS and DFS durations. So, the five-year OS and five-year DFS were also used in addition to general OS and DFS to reduce the effect of this situation.

CONCLUSION

The OS ratio and OS duration were not as high as expected in small intestine GIST cases. In addition, tumour diameter, mitotic index and risk classification may not provide sufficient information in terms of predicting the prognosis in some cases. Finally, the frequency of recurrence and/or metastasis is higher than expected — although complete resection is achieved, and its negative effect on survival indicated the importance of close follow-up.

ETHICAL APPROVAL:
This study was performed in line with the principles of the Declaration of Helsinki. Ethical approval was waived by the local Ethics Committee in view of the retrospective nature of the study and all the procedures being performed were part of the routine care (Date: 08/07/2020; No. 2020/514/181/12).

PATIENTS' CONSENT:
No informed consents were taken from the patients since the data were collected from the hospital records retrospectively and since no private information was given in the paper.

CONFLICT OF INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
HU: Conception and design, analysis and interpretation of data, drafting of the manuscript, advices and final approval.
YT: Analysis and interpretation of data, conception and design, reviewing the paper, and final approval.
OA: Acquisition of data, analysis and interpretation of data, reviewing the paper, and final approval.
BB: Analysis and interpretation of data, reviewing the paper, and final approval.

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