Original Article

Imatinib-associated skin rash is related to treatment outcome in patients with unresectable and/or metastatic gastrointestinal stromal tumor

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Background: Imatinib-associated skin rash in gastrointestinal stromal tumor (GIST) patients is one of the most troublesome adverse effects, and can reduce imatinib adherence and persistence. However, the relationship between skin rash and adherence is unknown, and there are few published studies on the clinical outcomes of patients with severe skin rash.

Methods: Adult patients (≥18 years) who were treated with 400 mg/day imatinib for unresectable or metastatic GIST were enrolled in this retrospective study. The skin rash was graded by physicians according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Progression-free survival (PFS) was compared using the Kaplan-Meier method between groups with and without skin rash. The risk factors for GIST progression were investigated by Cox regression analysis.

Results: A total of 125 GIST patients were finally included. Among them, 43 (34.4%) patients developed skin rash during imatinib treatment. Serial blood eosinophil levels were associated with skin rash and severity (P<0.001). Patients with skin rash tended to have poorer PFS than patients with no rash (P=0.035). Moreover, patients with rash had a significantly higher prevalence of non-adherence compared with patients without rash [odds ratio (OR): 3.42, 95% confidence interval (CI): 1.36–8.61, P=0.009 for grades 1–2; OR: 6.07, 95% CI: 1.42–26.11, P=0.015 for grades 3–4). Cox regression analysis indicated that the independent risk factors for GIST progression were non-adherence (OR: 4.20, 95% CI: 1.57–11.25, P=0.004) and medium- and high-risk GIST (OR: 5.38, 95% CI: 1.15–25.09, P=0.032).

Conclusions: Non-adherence and medium- and high-risk GIST are independent risk factors for GIST progression. Skin rash can be associated with treatment adherence, which can in turn be associated with poor outcomes of GIST treatment. Measuring the blood eosinophil levels could be helpful in predicting risk of skin rash during imatinib treatment.

Keywords: Gastrointestinal stromal tumor (GIST); risk factors; rash; imatinib

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Introduction

Gastrointestinal stromal tumor (GIST) arises from the interstitial cells of Cajal, which are the most frequent malignant mesenchymal tumors in the digestive tract (1,2). The reported incidence of GIST ranges from 6 to 22 cases per million per year (1-4). The most primary GIST has a gain-of-function mutation in either KIT (70%) or PDGFRA (10–15%) and some other genes (about 15%), including BRAF and RAS family genes (4-8). Tyrosine kinase inhibitors (TKIs) are the standard therapy for metastatic/recurrent GIST, and have significantly improved the clinical outcomes of GIST patients (3,9,10). Imatinib mesylate is the first-line GIST treatment, although second- or third-line and other novel TKIs (e.g., sunitinib, regorafenib, ripretinib, and avapritinib) have demonstrated clinical benefits (11-14). Imatinib efficacy for GIST patients could be predicted by pathological examination and genetic testing in KIT and PDGFRA mutations (15-17). The response rate to imatinib is 83.5% in GIST patients with KIT exon 11 mutations, and 48% in GIST patients with KIT exon 9 mutations (17-20). Additionally, GIST patients with KIT-PDGFRA wild-type (WT) and exon 18 PDGFRA D842V mutations are primarily resistant to imatinib (17-20). Postoperative use of imatinib should be administered for >36 months for high-risk GIST patients (11). Current treatment guidelines suggest that advanced GIST patients should be given long-term imatinib if clinical benefits are sustained, because disease continues to progress in most cases after treatment is interrupted (21,22). For patients receiving long-term imatinib treatment, maintaining an adequate continuous dose is essential to maintain clinical effectiveness (23). For GIST patients on imatinib for prolonged periods, adequate management and close monitoring of imatinib-associated side-effects are important to maintain quality of life.

Imatinib is generally well tolerated in GIST patients, and most adverse effects do not need imatinib dose reduction or interruption (24,25). However, dose reduction is required by 40% of GIST patients, and the discontinuation rate of imatinib is as high as 49% in these patients (14,25-27). Imatinib dose reduction rate for early adverse effects has been reported to be 17%, and 29% for discontinuation (25). Maintaining a continuous and sufficient imatinib dose is important to achieve optimal clinical outcomes; therefore, adequate management of imatinib-associated adverse events is crucial (25,28). Skin rash commonly presenting as erythematous and maculopapular lesions occurs in up to 35% of GIST patients treated with imatinib, and approximately 10% of patients experience grades 3–4 skin rash (9,10,24). The underlying mechanism of imatinib-related skin rash is still unclear, but based on the high frequency, it is believed to be due to the blockade of the c-kit protein, which is normally present in the skin, rather than hypersensitivity (28). The blood eosinophil cells may be also involved in amplifying the underlying inflammatory and/or immune response in imatinib-induced rash (28); female sex and daily dose of imatinib have been reported to be independent risk factors for imatinib-related rashes (9). Skin rash is one of the most troublesome adverse effects, and can reduce imatinib adherence and persistence. However, the relationship between skin rash and adherence is unknown, and there are few published studies on the clinical outcomes of patients with severe skin rash among Chinese GIST patients. Therefore, we conducted this retrospective study to explore the relationship between rash and adherence to imatinib for the first time, and further evaluate the relationship between skin rash and treatment outcomes of imatinib in GIST patients among Chinese population.

We present the following article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-65/rc).

Methods

Patients

All adult patients (≥18 years) who were treated with 400 mg/day imatinib for unresectable or metastatic GIST between February 1, 2012 to December 31, 2018 at Chongqing University Cancer Hospital were enrolled in this retrospective study. Patients who received palliative imatinib treatment due to tumor perforation before or during surgery for local disease were excluded from the progression-free survival (PFS) analysis. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The present study was approved by the Ethics Committee of Chongqing University Cancer Hospital (No. CZLS2022021-A), and the requirement for informed consent was waived due to the retrospective nature of the study.

Data collection and follow up

Demographic and clinical data were collected by reviewing electronic medical records. The following information was carefully recorded: sex, gender, age, site of the primary

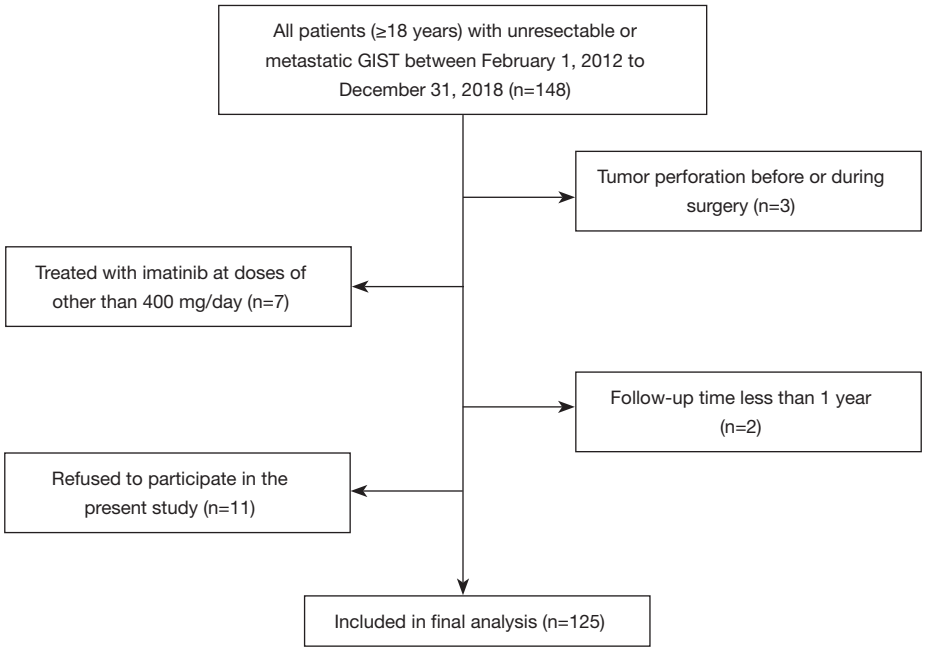

Figure 1 Patient enrollment and exclusion process. GIST, gastrointestinal stromal tumor.

tumor and metastasis, tumor size, tumor mutational status in c-KIT and PDGFRA, baseline laboratory values (e.g., serial eosinophil counts, white blood cell, bilirubin, hemoglobin, and albumin), CT examination records, adherence assessment results, skin rash records, and serial eosinophil counts when skin rash occurred. The skin rash was graded by physicians according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 on every visit (29). Adherence was assessed using the validated 8-item Morisky Medication Adherence Scale (MMAS-8); The MMAS-8 is composed of 7 items answered with "yes" or "no" alternatives and 1 item rated on a 5-point Likert scale. Patients with 8 points were classified as adherent, or otherwise non-adherent if patients had less than 8 points according to the MMAS-8 scoring system (30). Patients were divided into very low-risk, low-risk, medium-risk, and high-risk groups according to the Modified National Institutes of Health (M-NIH) risk classification (31). All data were collected and reviewed by two authors. All patients were followed up for at least 1 year until the end of the study, unless the patient died or refused to participate.

Statistical analysis

All continuous variables were described as median [interquartile range (IQR)] or mean ± standard deviation. Continuous data were tested for normality using the Kolmogorov-Smirnov test. Comparisons of two groups were performed with Student's *t*-test or the Mann-Whitney U-test; χ^2-test was used to compare differences of categorical variables, expressed as percentages or frequencies. PFS was compared using the Kaplan-Meier method between groups with and without skin rash. The risk factors for GIST progression were investigated by Cox regression analysis. Only covariates with $P<0.20$ in the univariate analysis were used in the multivariate Cox regression analysis. All reported P values were two-tailed, and $P<0.05$ was considered statistically significant. All statistical analyses were performed using the SPSS version 19.0 (SPSS, Chicago, IL, USA).

Results

Patient characteristics

A total of 125 GIST patients treated with 400 mg/day imatinib for unresectable or metastatic GIST were ultimately included. The process for patient enrollment and exclusion is shown in *Figure 1*. Of the 125 patients, 43 (34.4%) developed skin rash, 33 (26.4%) developed grades 1–2 skin rash, and 10 (8%) developed grades 3–4 skin rash

Table 1 Baseline characteristics of patients treated with imatinib for unresectable or metastatic GIST

Characteristics	Patients with rash (n=43)	Patients without rash (n=82)	P value
Sex, male, n (%)	20 (46.5)	40 (48.8)	0.809
Age (years), median (IQR)	58.0 (51.0–63.0)	53.5 (47.8–64.3)	0.138
Primary tumor site, n (%)			0.441
Small bowel	12 (27.9)	21 (25.6)	
Stomach	31 (72.1)	58 (70.7)	
Other	0 (0.0)	3 (3.7)	
Primary tumor size (cm)[a], median (IQR)	6.6 (4.0–11.3)	5.1 (3.9–8.0)	0.105
Liver metastasis, n (%)	10 (23.3)	7 (8.5)	0.023*
Peritoneal metastasis, n (%)	10 (23.3)	8 (9.8)	0.041*
Kinase mutation, n (%)			0.009*
KIT exon 11	10 (23.3)	5 (6.1)	
Wild or other mutation	8 (18.6)	11 (13.4)	
Unknown	25 (58.1)	66 (80.5)	
Blood eosinophil counts (/μL), median (IQR)	160 (60–900)	100 (50–210)	0.024*
White blood cell (/μL), median (IQR)	5,680 (3,800–8,880)	5,070 (3,680–8,212)	0.566
Bilirubin (μmol/L), median (IQR)	12.2 (8.9–18.4)	12.4 (8.3–18.0)	0.741
Hemoglobin (g/L), median (IQR)	120.0 (96.0–135.0)	118.0 (101.8–131.3)	0.702
Albumin (g/L), median (IQR)	70.7 (61.7–74.8)	67.3 (60.7–73.5)	0.276

*, indicate that these variables were statistically significant (P<0.05); [a], primary tumor size indicates the longest tumor diameter of the primary tumor present at the time of imatinib initiation. GIST, gastrointestinal stromal tumor; IQR, interquartile range.

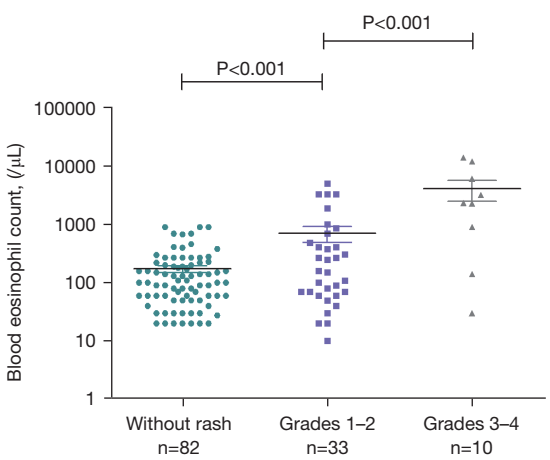

Figure 2 Association between rash severity and blood eosinophil counts with rash development.

after a median follow-up time of 640 (IQR: 303–900) days. The characteristics of the 125 patients are shown in *Table 1*. The proportion of patients with rash in the liver metastasis and peritoneal metastasis group was higher compared with patients without rash (P=0.023 and P=0.041, respectively). There was a significant difference in the number of patients with rash in the kinase mutation groups (P=0.009). The rash group had a greater blood eosinophil count than group without rash (P=0.024).

Incidence of skin rash and survival outcomes according to skin rash

Of the 43 (34.4%) patients with rash during follow up, 24 patients (55.8%) had grade 1 rash, 9 patients (20.9%) had grade 2 rash, 9 patients (20.9%) had grade 3 rash, and 1 patient (2.3%) had grade 4 rash. Blood eosinophil counts were associated with rash severity (*Figure 2*). Higher blood eosinophil counts when rash occurs were significantly

to be associated with higher severity of rash. Median eosinophil counts were 160/μL in the group with grades 1–2 rash compared with 100/μL in the group without rash (P<0.001). Median eosinophil counts were 2,320/μL in the group with grades 3–4 rash compared with 160/μL in the group with grades 1–2 rash (P<0.001). To determine the influence of skin rash on imatinib treatment outcomes, PFS was compared between patients with and without rash.

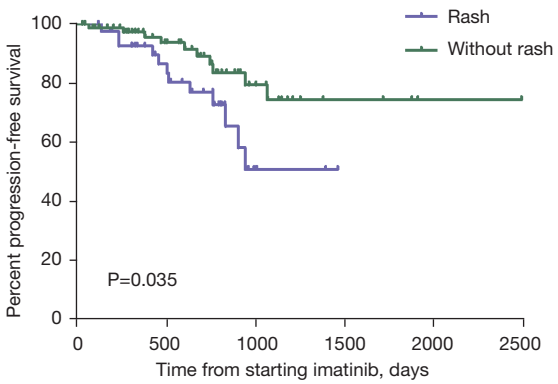

Figure 3 Comparison of PFS between patients with and without rash. PFS, progression-free survival.

The median follow-up period of rash group was 640 (IQR: 332–825) and 620 (IQR: 285–920) days, respectively. As shown in *Figure 3*, PFS in patients without rash was significantly longer than that in patients with rash (P=0.035).

The relationship between adherence and rash

Considering that skin rash is one of the most troublesome adverse effects, and can reduce imatinib adherence and persistence, we investigated the relationship between adherence and rash. Results are shown in *Table 2*. A total of 40 (32%) patients were identified as non-adherent among the 125 GIST patients. Patients with rash had a significantly higher prevalence of non-adherence compared with patients without rash [odds ratio (OR): 3.42, 95% confidence interval (CI): 1.36–8.61, P=0.009 for grades 1–2; OR: 6.07, 95% CI: 1.42–26.11, P=0.015 for grades 3–4].

The risk factors related to progression of GIST

To verify whether eosinophil counts are related to imatinib treatment outcome, we analyzed the risk factors related to the progression of GIST by multivariate Cox regression. The results are shown in *Table 3*. Interestingly, rash (OR: 0.36, 95% CI: 0.14–0.98, P=0.032) was found to be

Table 2 Non-adherence incidence in different rash grades

Rash grade	All patients (n=125), n (%)	Non-adherent (n=40), n (%)	Univariate		Multivariate	
			OR (95% CI)	P value	OR (95% CI)	P value
No rash	82 (65.6)	17 (20.7)	–	–	–	–
1–2	33 (26.4)	17 (51.5)	4.06 (1.71–9.67)	0.002*	3.42 (1.36–8.61)	0.009*
3–4	10 (0.08)	6 (60.0)	5.74 (1.45–22.64)	0.013*	6.07 (1.42–26.11)	0.015*

*, indicate that these variables were statistically significant (P<0.05). Grades 1–2 and grade 3–4 groups were compared with "no rash" group. OR, odds ratio; CI, confidence interval.

Table 3 Cox regression model for the risk factors for GIST progression

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Non-adherence	4.07 (1.56–10.58)	0.004	4.20 (1.57–11.25)	0.004*
Medium- and high-risk GIST	5.15 (1.14–23.29)	0.033	5.38 (1.15–25.09)	0.032*
Rash	0.36 (0.14–0.98)	0.032	–	–
Primary tumor size ≥6 cm	0.44 (0.17–1.15)	0.094	–	–

*, indicate that these variables were statistically significant (P<0.05). Only variables with P≤0.20 in the univariate analysis were included in the multivariate analysis. GIST, gastrointestinal stromal tumor; OR, odds ratio; CI, confidence interval.

associated with GIST progression in the univariate analysis but not in the multivariable model. The independent risk factors for GIST progression were non-adherence (OR: 4.20, 95% CI: 1.57–11.25, P=0.004) and medium- and high-risk GIST (OR: 5.38, 95% CI: 1.15–25.09, P=0.032).

Discussion

Skin rash is one of the most common side-effects for GIST patients taking imatinib. In the present study, we found that the incidence of skin rash was 34.4% for unresectable or metastatic GIST patients. PFS of patients with skin rash was significantly shortened, but was not an independent risk factor for GIST progression. The independent risk factors for GIST progression were non-adherence and medium- and high-risk GIST.

Skin rash incidence varies widely, affecting 11–67% of GIST patients. Approximately 10% of patients develop grade ≥3 rashes (32,33). In the present study, the overall incidence of skin rash was 34.4%; 26.4% for grades 1–2 skin rash and 8% for grades 3–4 skin rash.

This discrepancy in the wide range of incidence might be attributed to the following reasons. First, the inclusion criteria varied in studies; some studies included patients in the setting of neoadjuvant, adjuvant, and palliative treatment, including a report from Korea (28). Park *et al.* reported that the overall incidence of skin rash was 23.9%, and that 17.1% of patients developed grades 1–2 rash and 6.8% of patients developed grades 3–4 severe rash during imatinib treatment, which was lower than that reported in the present study (28). The current study only included unresectable or metastatic GIST patients. Second, the imatinib dose varied from 300 to 600 mg, but in the present study, we only included the patients on a dose of 400 mg. Skin rash severity might be associated with dose intensity (24). Third, the increased incidence could be due to the limited sample size in the present study.

Medium- and high-risk GIST were identified as prognostic factors, further supporting the concept that personalized risk assessment is important. Medium- and high-risk GIST patients should be given more clinical attention and more frequent follow up. In the present study, we divided patients into very low-risk, low-risk, medium-risk and high-risk groups according to the M-NIH risk classification mainly based on tumor size, mitotic index, and tumor site (31). There were other risk classification methods except M-NIH risk classification, which were validated to be more accurate in predicting the progression of GIST (34,35). However, these new assessments are not widely used because they are relatively complicated to use. In the future, risk assessments that are more accurate and easier to use in should be explored.

Non-adherence was found to be another risk factor for GIST progression. The non-adherent rate was 32% in the current study. Wang *et al.* reported that 58.2% of patients in their study were considered non-adherent, according to MMAS-8 (36). Chuah *et al.* found more than half of their patients (55.1%) were non-adherent based on the medication compliance questionnaire (MCQ) used for patients with metastatic and/or unresectable GIST (37). Other studies reported the non-adherence rate to range from 24% to 29% among GIST patients based on the Basel Assessment of Adherence Scale to Immunosuppressive Medication Scale, pharmacy records, and medication possession ratio (37,38). These differences might be attributed to variations in tools of adherence assessment and different disease stages of the recruited population.

Interestingly, in the present study we found that the PFS of patients with skin rash was significantly shortened and higher grades of rash were related to a higher prevalence of non-adherence. Non-adherence was found to be another risk factor for GIST progression, but skin rash was not found to be an independent prognostic factor for GIST. This finding indicated that skin rash might reduce the imatinib adherence and lead to poor treatment outcomes, which is in line with the results of a previously published study (28). Park *et al.* reported that imatinib dose reduction or interruption due to skin rash could lead to a significant reduction in overall dose intensity, which results in poor prognosis (28). It is important for GIST patients to maintain continuous imatinib administration at a sufficient dose to obtain optimal treatment outcomes (39,40). In patients with mild or moderate imatinib-associated skin rash, symptoms can be relieved with antihistamines, topical lotions, or topical steroids (24,41). However, 6.8% patients developed grade ≥3 skin rash, requiring dose reduction or interruption (32), which might lead to substantial decrease in overall dose intensity. Therefore, early recognition and effective management of imatinib-associated rash might help GIST patients maintain an adequate imatinib dose and ultimately achieve optimal clinical outcomes. In their study, Kim *et al.* demonstrated that imatinib-associated grade 2 skin rash with grade ≥2 pruritus or grade 3 rash could be effectively controlled by systemic steroid treatment without interruption or dose reduction of imatinib in patients with GIST, which is an important finding and should be

verified in a larger sample in the future (32). Moreover, imatinib plasma trough concentrations (C_{min} ≥1,100 ng/mL) were found to be associated with objective benefit rate and time to progression in advanced GIST patients, which has been suggested that clinicians could help patients maintain sufficient imatinib dose intensity by steady-state imatinib trough concentrations (33). Our finding indicated that skin rash might reduce the imatinib adherence, which could lead to imatinib dose reduction and overall dose intensity and eventually lead to poor treatment outcomes. To promote imatinib outcomes in patients with GIST, we suggest early recognition and effective management of imatinib-associated rash to avoid nonadherence to imatinib. Regular evaluation of adverse reactions for GIST patients is necessary. Meanwhile, finding effective treatment methods for skin rash without imatinib interruption or dose reduction is essential. Besides, it is also important to maintain good adherence in GIST patients. Imatinib concentration monitoring and regular adherence assessment can effectively assist clinicians in detecting non-adherence timely, which could help patients maintain sufficient imatinib dose intensity.

Our study has some limitations. First, it was a single-center study with a small sample size. GIST is a cancer with relatively lower prevalence. The sample size was still small although all patients who met the criteria were included in the present study. Second, our study only measured rash and adherence at a single time point. We will need to continue to monitor the changes in adherence and rash for a long period of time in the future. Additionally, the results were not directly verified in the present study. Despite these limitations, the findings of the present study demonstrated the prevalence of skin rash, the relationship between adherence to imatinib and rash, and the effect of rash and compliance on imatinib treatment outcome in GIST patients. We will replicate the results in studies with larger sample sizes and longer follow-up durations in the future.

Conclusions

The incidence of skin rash is 34.4% for unresectable or metastatic GIST patients. Patients with medium- and high-risk GIST and non-adherent patients are the most likely to progress. Imatinib-associated rash might decrease patients' adherence to imatinib and further reduce its benefits. Further research should focus on improving prevention and treatment methods for imatinib-associated rash, rather than reducing the dose of, or discontinuing, imatinib.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-65/rc

Data Sharing Statement: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-65/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-65/coif). All authors report that the study was supported by the Chongqing Clinical Pharmacy Key Specialties Construction Project. The authors have no other 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. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The present study was approved by the Ethics Committee of Chongqing University Cancer Hospital (No. CZLS2022021-A), and the requirement for informed consent was waived due to the retrospective nature of the study.

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