Original Article

A retrospective analysis of the risk factors affecting recurrence time in patients with recurrent glioblastoma

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Background: This study explored the related factors that influence the recurrence time of glioblastomas (GBM).

Methods: A retrospective study of recurrent GBM patients with surgical resection was performed. Recurrence time was analyzed using Kaplan–Meier survival curves. The Cox regression model was used to investigate the possible factors associated with recurrence time.

Results: A total of 176 patients (113 males and 63 females) were enrolled in the study, with a median age of 57 years (range, 19–76 years). From this cohort, 18 patients (10.2%) had gross total resection (GTR), 53 patients (30.1%) had subtotal resection (STR), and 105 patients (59.7%) had partial resection (PR). Postoperatively, all patients received radiotherapy (RT), with 55.1% administered concurrent chemotherapy (CTh) and 59.7% administered adjuvant CTh. The median recurrence time was 10.0 months (range, 1.0–75.0 months). Patients with PR (P=0.004), gliomas that contacted the subventricular zone (SVZ) (P=0.004), isocitrate dehydrogenase 1 (IDH1) wild-type (P=0.048), telomerase reverse transcriptase (TERT) C228T wild-type (P=0.012), and positive glial fibrillary acidic protein (GFAP) expression (P=0.044) had a shortened time to recurrence. Cox regression analysis revealed that PR (P=0.036), SVZ contact (P=0.008), and TERT C228T wild type (P=0.023) were significantly associated with a shortened recurrence time.

Conclusions: PR, tumor contacting the SVZ, and TERT C228T wild type were independent risk factors for tumor recurrence in patients with GBM.

Keywords: Recurrent glioblastoma; recurrence; subventricular zone (SVZ); isocitrate dehydrogenase 1 (IDH1); surgical resection.

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Introduction

Glioblastoma (GBM) is the most frequent malignancy and the most aggressive type of primary brain tumor (1). It accounts for approximately 48% of all primary malignant central nervous system tumors (2,3). At present, comprehensive therapies for the management of GBM include surgery, chemoradiotherapy, and immunotherapy (4). Although there are many treatment options for GBM

patients, the outcome is dismal, and GBM typically recurs during the first year (5,6). In this study, a correlation analysis was conducted to determine the prognostic risk factors affecting the time to recurrence in GBM patients. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/apm-21-823).

Methods

Patient selection

A retrospective study was conducted on patients who were histologically diagnosed with GBM and underwent surgery at the Department of Radiotherapy of Renji Hospital, Shanghai Jiao Tong University School of Medicine between June 2008 and August 2020. Data for 426 patients were extracted from the database archives. The following inclusion criteria were applied: adult patients with newly diagnosed intracranial lesion who underwent surgical resection of the tumor; the pathological diagnosis of GBM was confirmed by at least two pathologists; and all basic data (including clinical characteristics, medical records, preoperative and tumor recurrence neuroimaging, molecular markers) and follow-up data were readily available. The following patients were excluded: patients less than 18 years old; patients who underwent biopsy; patients with other organic tumors; and patients in whom the tumor recurrence time was unavailable. Ultimately, 176 patients were enrolled in this study. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of Renji Hospital, Shanghai Jiaotong University School of Medicine (No. RA-2020-056). Individual consent for this retrospective analysis was waived.

Data extraction

Patient demographic data (including gender and age), clinical characteristics [including Karnofsky performance status (KPS), tumor diameter, tumor volume, location, tumor contact with the subventricular zone (SVZ), and enhanced features], extent of resection (EOR), management after surgery [such as radiotherapy (RT), chemotherapy (CTh), or concurrent RT and CTh], and time to recurrence were collated. For data analysis, patients were divided into the following 2 groups according to the median age: ≤57 years and >57 years. The KPS was categorized into 2 groups according to the median value, namely, <90 and ≥90. The proliferation of Ki-67 was classified into the following 2 groups: Ki-67 <0.3 and Ki-67 ≥0.3. The tumor diameter and volume were classified into 2 groups, namely, ≤4.7 cm and >4.7 cm for diameter and ≤33 and >33 cm^3 for volume. The tumor sites were obtained from preoperative magnetic resonance imaging (MRI), and EOR was evaluated through postoperative MRI or computed tomography by experienced neurosurgeons and radiologists. Gross total resection (GTR) was defined as >90% removal, subtotal resection (STR) was defined as 80–90% removal, and partial resection (PR) was defined as <80% removal. The EOR was classified into 2 groups, namely GTR/STR and PR. Postoperative adjuvant therapies included RT and CTh. Pathologic immunohistochemistry data were confirmed by two senior pathologists, with particular focus on the expression of the following biomarkers: isocitrate dehydrogenase (IDH) 1, telomerase reverse transcriptase (TERT) T228C, Ki-67, glial fibrillary acidic protein (GFAP), O6-methylguanine-DNA methyltransferase (MGMT), tumor protein P53 (TP53), ATRX (alpha-thalassemia/mental retardation, X-linked gene), and the B-Raf gene mutation BRAF V600E. The time to recurrence was calculated from diagnosis to tumor recurrence.

Statistical analysis

All statistical analyses were performed using IBM SPSS Version 23.0 software (IBM Corporation, Armonk, New York, USA). Descriptive statistics were used to characterize the study cohort. The cut off points of factors were set by the median number for both continuous variables and categorical variables. The prognostic factors for recurrence time was compared to establish subgroups of the factors. Kaplan-Meier analysis was used to study survival, and the factors with statistical significance were included in the Cox regression analysis. Hazard ratios (HR) with 95% confidence intervals (CI) were reported. A P value <0.05 was considered statistically significant.

Results

A total of 176 adult patients with recurrent GBM diagnosed between 2008 and 2020 were identified. The patient characteristics are summarized in *Table 1*. The median recurrence time was 10.0 months (range, 1–75 months). The median age at diagnosis was 57 years (range: 19–76 years), and

Table 1 A summary of patient demographics, and clinical and radiological features

Characteristics	N (%)
Age <57 years	88 (50.0)
Gender (male)	113 (64.2)
Pre-KPS (≥90)	101 (57.4)
Location of tumor	
Frontal lobe	96 (54.5)
Temporal lobe	47 (26.7)
Parietal lobe	21 (11.9)
Occipital lobe	11 (6.3)
Tumor volume (>33 cm^3)	20 (45.5)
Tumor diameter (≥4.7 cm)	23 (52.3)
Contact with SVZ	22 (64.7)
Enhanced feature	
Ring	5 (16.7)
Heterogeneity	30 (83.6)

SVZ, subventricular zone.

Table 2 A summary of the surgical and adjuvant therapies administered to the patients

Variable	N (%)
Extent of resection	
GTR	18 (10.2)
STR	53 (30.1)
PR	105 (59.7)
Adjuvant therapies	
RT	176 (100.0)
RT + concurrent CTh	97 (55.1)
RT + adjuvant CTh	105 (59.7)
RT + concurrent and adjuvant CTh	69 (39.2)
Duration of CTh (4–6 weeks)	64 (37.0)
Radiation interval (≥28 days)	82 (50.0)

GTR, gross total resection; STR, subtotal resection; PR, partial resection; RT, radiotherapy; CTh, chemotherapy.

males represented 113 (64.2%) cases. The median KPS before treatment was 90 (range, 40–100). Tumors were detected in the frontal lobe (n=96, 54.5%), the temporal lobe (n=47, 26.7%), the parietal lobe (n=21, 11.9%), and the occipital lobe (n=11, 6.3%). The median tumor diameter and volume were 4.5 cm and 33.0 cm^3, respectively. Heterogeneous enhancement and ring-enhancement were observed in 30 patients and 5 patients, respectively. Twenty-two patients presented with GBM that had contact with the SVZ.

Immunohistochemistry showed positive staining for IDH1 in 6.9% of cases (4/58), GFAP in 95.8% (46/48), TP53 in 78.6% (33/42), Ki67 ≥0.3 in 82.0% (41/50), TERT C228T in 33.3% (7/21), MGMT promoter methylation in 60.6% (20/33), ATRX in 16.0% (4/25), and BRAF V600E in 90.5% (19/21) of patients.

Surgical and adjuvant therapies for all patients are summarized in *Table 2*. Surgery consisted of GTR in 18 patients (10.2%), STR in 53 patients (30.1%), and PR in 105 patients (59.7%). Postoperatively, all patients received RT and the median time from diagnosis to RT after surgery was 28.0 days (range, 1–333 days). A total of 97 patients received concurrent CTh, adjuvant CTh was administered to 105 patients (59.7%), and 69 patients received RT with concurrent and adjuvant CTh.

Univariate analysis of the whole cohort (*Tables 3*,*4*) demonstrated that age, gender, KPS, location, enhancement features, tumor diameter, tumor volume, radiation interval time, concurrent CTh, adjuvant CTh, and duration of CTh were not correlated with recurrence time (P>0.05). However, PR (P=0.004), contact with the SVZ (P=0.004), IDH1 wild-type (P=0.048), TERT C228T wild-type (P=0.012), and positive GFAP expression (P=0.044) were all associated with a shorter recurrence time. Multivariate analysis demonstrated that PR (HR 1.440, 95% CI: 1.025–2.024, P=0.036), contact with the SVZ (HR 3.523, 95% CI: 1.380–8.990, P=0.008), and TERT C228T wild-type (HR 0.296, 95% CI: 0.104–0.896, P=0.023) were independent unfavorable risk factors for short-term tumor recurrence (*Table 5*).

Discussion

GBM is a type of intracranial malignant tumor, among which supratentorial GBM is the most common. Standard therapy includes tumor resection, RT, and CTh. Previous studies have suggested that age, extent of resection, CTh, Ki67 proliferative index, and IDH mutation were correlated with overall survival (5-10). However, few studies have examined the factors that influencing the short-term recurrence of GBM. In this current report, the data of 176 GBM patients with tumor recurrence were analyzed to determine the risk factors related to short-term recurrence

Table 3 Univariate analysis of the recurrence time in 176 recurrent glioblastoma patients

Variable	Number	χ^2	P
Age (<57/≥57 years)	88/88	1.472	0.225
EOR (GTR/STR/PR)	18/53/105	11.196	0.004
KPS (90/≥90)	64/101	2.169	0.141
Tumor diameter (<4.7/≥4.7 cm)	22/23	0.356	0.551
Concurrent CTh (yes/no)	97/79	0.061	0.806
RT+C-CTh+A-CTh (yes/no)	69/107	0.021	0.885
Radiation interval (<28/≥28 days)	81/82	0.739	0.390
Gender (male/female)	113/63	0.829	0.362
SVZ contacted (yes/no)	22/12	8.366	0.004
Enhanced (ring/heterogeneity)	5/30	0.322	0.570
Tumor volume (≤33/>33 cm^3)	19/20	2.178	0.140
Adjuvant CTh (yes/no)	105/71	0.666	0.414
Duration of CTh (1–3/4–6 weeks)	28/64	0.402	0.526
Location (frontal/temporal/parietal/occipital)	96/47/21/11	2.321	0.508

EOR, extent of resection; GTR, gross total resection; STR, subtotal resection; PR, partial resection; KPS, Karnofsky performance status; RT, radiotherapy; CTh, chemotherapy; C-CTh, concurrent chemotherapy; A-CTh, adjuvant chemotherapy.

Table 4 Univariate analysis of the recurrence time in glioblastoma patients

Variable	Number	χ^2	P
IDH1 (wild-type/mut)	54/4	3.904	0.048
TERT C228T (wild-type/mut)	14/7	6.360	0.012
GFAP (positive/negative)	46/2	4.048	0.044
Ki67 (<0.3/≥0.3)	9/41	1.252	0.263
TP53 (wild-type/mut)	8/33	0.013	0.910
ATRX (wild-type/mut)	21/4	0.003	0.959
BRAF V600E (wild-type/mut)	2/19	3.141	0.076
MGMT promoter (no/methylation)	20/13	0.012	0.913

IDH1, isocitrate dehydrogenase 1; GFAP, glial fibrillary acidic protein; TP53, tumor protein P53; BRAF, B-raf gene.

of GBM. Identifying these risk factors may provide novel insights into the recurrence of GBM.

Age and gender

In this study cohort, there were more males (64.2%) than females (35.8%). However, in agreement with previous reports (9,10), there were no significant differences in recurrence time between the genders. The median age at diagnosis was 57.0 years, and no differences were detected between patients ≤57 years and patients >57 years. This was inconsistent with previous studies (11) which suggested that younger patients have a better prognosis compared to elderly patients, and that age is an important factor affecting glioma recurrence (10,12-14). This may be due to the specific population in our cohort where all patients were diagnosed with GBM.

Neuroimaging characteristics

Table 5 Cox regression analysis of the recurrence time in patients with recurrent glioblastoma

Covariates	P value	HR	95% CI
EOR	0.002	1.429	1.140–1.793
Ventricle contacted	0.008	3.523	1.380–8.990
IDH1 mutation	0.071	2.957	0.911–9.598
TERT C228T mutation	0.023	0.296	0.104–0.896
GFAP positive	0.083	0.170	0.023–1.262

EOR, extent of resection; IDH1, isocitrate dehydrogenase 1, TERT, telomerase reverse transcriptase; GFAP, glial fibrillary acidic protein; HR, hazard ratio; CI, confidence interval.

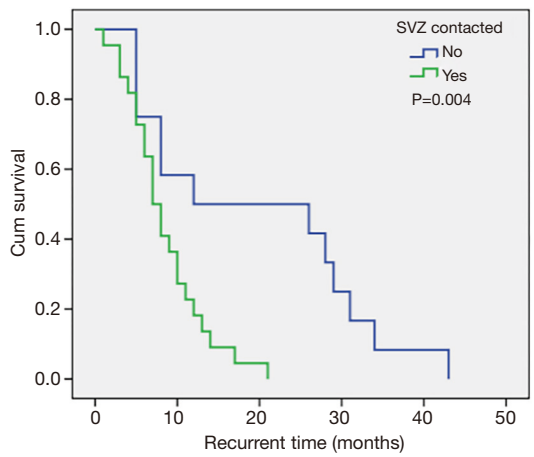

Figure 1 The tumor recurrence time was not significantly affected by whether the glioblastomas was in contact with the subventricular zone or not.

The most common sites of GBM were the frontal lobe, the temporal lobe, the parietal lobe, and the occipital lobe, successively from high to low. Approximately half of all GBMs were detected in the frontal lobe. However, there was no correlation between tumor location and recurrence time. Almost all GBMs had some degree of enhancement on contrast-enhanced MRI. In 67.4% of patients, imaging showed that the tumor had contact with the SVZ. These patients had a shortened recurrence time compared to patients without SVZ contact (median recurrence time: 12.0 *vs.* 7.0 months; *Figure 1*). Furthermore, SVZ contact was confirmed as an independent unfavorable risk factor to short-term tumor recurrence, and this was consistent with the observations by Comas *et al.* (15). Hallaert and colleagues (1) also analyzed the survival of 93 patients with GBM. In this latter study, 68% of patients had SVZ contact and the median progression free survival (PFS) was 5.9 months. This was significantly poorer compared to patient without SVZ contact. The SVZ contains multiple cell types with neural stem cells being the most abundant (16,17), and these are considered a source of cancer cells that are related to tumor formation and gliomagenesis (18). Numerous studies have suggested that GBMs that have contact with the SVZ have more aggressive patterns of relapse and poorer outcomes (19-24).

Molecular markers

Molecular biomarkers are used widely in the WHO 2016 classification of central nervous system tumors (25), and several molecular biomarkers have been identified to have significant relationships with the prognosis of patients (26). In this study cohort, 31.8% of patients showed the TERT C228T mutation, and the median recurrence times were 5.0 months and 11.0 months in patients with the TERT C228T wild-type and mutation, respectively (*Figure 2*), suggesting that the TERT C228T wild-type was an independent risk factor for shortened tumor recurrence time. This is contrary to previous studies (8) and may be due to the limited sample size in our investigation and thus, this conclusion should be interpreted with caution.

The IDH1 mutation rate in our cohort was 6.9%, and patients with the IDH1 mutation had a longer recurrence time compared to wild-type patients (median recurrence time: 18.0 *vs.* 8.0 months; *Tables 3*; *Figure 3*). However, the IDH1 mutation was not an independent risk factor for tumor recurrence. The IDH mutation is considered an independent predictor of good prognosis in all types of glioma patients, and patients with the IDH1 mutation generally have a prolonged PFS (27,28). However, Gülten *et al.* (29) summarized the IDH expression characteristics of 83 GBM patients and found that the IDH mutation rate

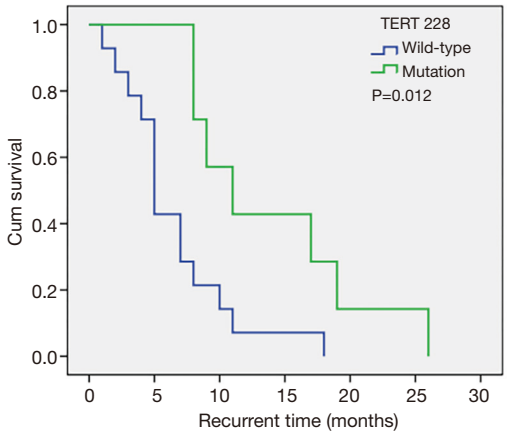

Figure 2 Patients with the telomerase reverse transcriptase (TERT) C228T mutation had a shortened recurrence time.

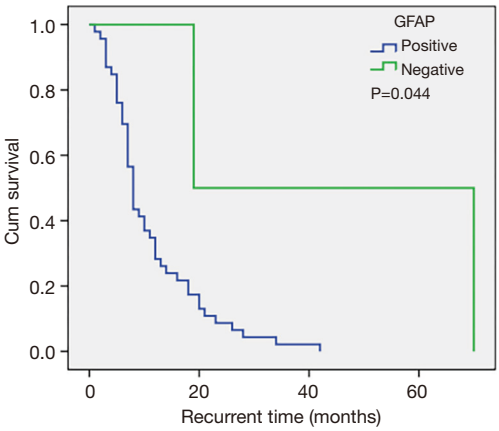

Figure 4 Patients with negative glial fibrillary acidic protein (GFAP) expression had a longer recurrence time.

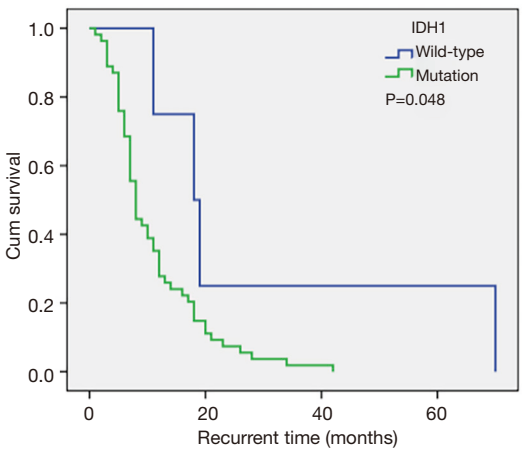

Figure 3 The isocitrate dehydrogenase 1 (IDH1) mutation was associated with a longer recurrence time.

was low and that it was not a factor affecting the recurrence time (29). In the study by Potharaju and colleagues (8), patients with the IDH mutation had a prolonged recurrence time, however, it was not an independent risk factor for tumor recurrence, and this is consistent with our results.

A total of 95.8% of our patients were positive for GFAP. The recurrence time in patients with negative GFAP was longer compared to patients who were positive for GFAP (*Figure 4*). However, GFAP was not an independent factor for tumor recurrence. In some studies (9,30,31), the Ki-67 proliferative index has been shown to be an independent prognostic factor for time to recurrence. In contrast, in the current study, the Ki-67 proliferative index was not related to recurrence time, and this may be due to the entire cohort being GBM patients GBM patients generally have a high Ki-67 proliferative index and in fact, 82% of the patient cohort showed a Ki-67 proliferative index ≥30%.

Extent of resection, RT, and CTh

The maximal feasible safe resection is the guiding principle for GBM surgery (2,32). The EOR partially depends on the size and location of the tumor. With advances in neuroimaging it is possible to assess the relationship between normal brain tissues and tumor tissues postoperatively. However, when the tumor invades important functional areas, it is difficult to perform GTR. In this current study, the median recurrence times for patients with GTR, STR, and PR were 14.0 months, 13.0 months, and 8.5 months, respectively (*Figure 5*). PR was confirmed as an independent risk factor for short-term tumor recurrence, which concurs with previously published studies. The extent of surgery is an independent factor for recurrence time and overall survival regardless of molecular status (2). Therefore, surgical resection is considered an important step in the management of GBM.

RT can improve both local control and outcome, and has long been used in the management of GBM (2). Indeed, RT was administered to all patients in this study and thus, the relationship between RT and recurrence time could not be determined. However, the median recurrence time (10.0 months) was longer than that reported in previous studies (33), suggesting that to some extent, our patients

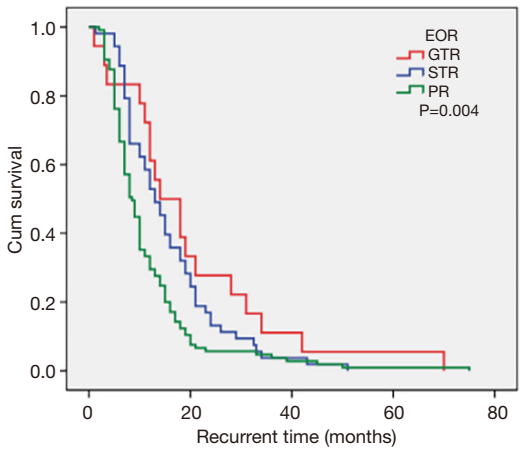

Figure 5 The extent of resection (EOR) had a statistically significant effect on recurrence time. GTR, gross total resection; STR, subtotal resection; PR, partial resection.

benefited from RT. Some reports have noted that delayed adjuvant chemoradiation (≥20 days) was an unfavorable factor for survival outcome (7). However, no relationship between RT interval time was observed in our results. This may due to most of our patients receiving RT more than 20 days after surgery. The first-line standard CTh includes temozolomide (TMZ) during RT followed by a further six cycles of TMZ (32). In this current report, 55.1% of patients received concurrent CTh during RT, adjuvant CTh was administered to 59.7% of patients, and RT combined with concurrent and adjuvant CTh was performed in 39.2% of cases. As most of our patients did not received 6 cycles of TMZ, the duration of CTh was divided into two groups, namely, 1–3 weeks and 4–6 weeks. The factors of concurrent CTh and adjuvant CTh had no effect on the recurrence time. In the majority of reports (31), completing 6 cycles of adjuvant TMZ is a favorable factor for PFS. In our study, 96.7% of our patients had less than 6 cycles of adjuvant TMZ, and this may explain the lack of effect of CTh on recurrence time. Although patients who received 6 or more cycles of adjuvant TMZ had a longer recurrence time, drug toxicity was also increased, and this can lead to decreased quality of life, especially in elderly patients (34). Therefore, the role of adjuvant CTh in survival outcome remains controversial.

Study strengths and limitations

This report identified the prognostic factors affecting the recurrence time in patients with GMB. However, the study has some limitations. First, the sample size of the molecular features is limited and the results may not reflect the actual situation in a larger population. Second, all our patients received RT and it was not possible to analyze the relationship between RT and recurrence time. Third, this study identified the TERT C228T wild-type as an independent unfavorable factor for recurrence time which was not consistent with previous studies and this conclusion should be interpreted with caution. Fourth, further studies are recommended to investigate the relationship among the status of Ki-67, TERT, the expression patterns of biomarkers, and time to relapse after surgery.

Conclusions

Patients with PR, SVZ contact, IDH1 wild-type, TERT C228T mutation, and positive GFAP had a shorter recurrence time compared with the corresponding control groups. The key factors affecting the recurrence time in GMB patients were EOR, SVZ contact, and TERT C228T status. The state of pathological molecular markers has guiding significance for adjuvant therapy. In addition, comprehensive therapy should be given regardless of molecular status, especially the maximum degree of safe surgical resection of the tumor.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/apm-21-823

Data Sharing Statement: Available at http://dx.doi.org/10.21037/apm-21-823

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apm-21-823). 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. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Renji Hospital, Shanghai Jiaotong University School of Medicine (No. RA-2020-056). Individual consent for this retrospective analysis was waived.

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