Original Article

Risk factors for metachronous adenoma in patients with stage I/II colorectal cancer after radical surgery

Wenli Song[1,2#], Zexian Chen[3,4#], Zheyu Zheng[1,4], Zongjin Zhang[1,4], Yongle Chen[1,4], Xiaosheng He[3,4], Ping Lan[1,4], Jiancong Hu[1,4], Xiaowen He[1,4]

[1]Department of Colorectal Surgery, the Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, China; [2]Department of Gastrointestinal Surgery, the Eighth Affiliated hospital, Sun Yat-sen University, Shenzhen, China; [3]Department of Gastrointestinal Surgery, the Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, China; [4]Guangdong Provincial Key Laboratory of Colorectal and Pelvic Floor Diseases, the Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, China

Contributions: (I) Conception and design: P Lan, J Hu, X He; (II) Administrative support: P Lan, J Hu, X He; (III) Provision of study materials or patients: W Song, Z Chen, Z Zheng; (IV) Collection and assembly of data: W Song, Z Chen, Z Zheng; (V) Data analysis and interpretation: Z Zhang, Y Chen, X He; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Ping Lan; Jiancong Hu; Xiaowen He. The Sixth Affiliated Hospital, Sun Yat-Sen University, 26 Yuancun Erheng Road, Guangzhou 510655, China. Email: sumslp@163.com; hujianc@mail.sysu.edu.cn; hexiaow3@mail.sysu.edu.cn.

Background: It is important to implement a preventive strategy for early detection and endoscopic removal of metachronous adenoma in patients with colorectal cancer (CRC). Here, we retrospectively explored the associated factors of metachronous adenoma in these patients.

Methods: This study recruited 551 patients with stage I and II CRC who underwent radical surgery between January 1, 2012 and July 1, 2017 with postoperative colonoscopic surveillance. Data on clinicopathological characteristics and surveillance colonoscopies were obtained from medical records. Univariate analysis by Kaplan-Meier method and multivariate analysis by Cox proportional hazards model were used to identify the factors associated with metachronous adenoma.

Results: Metachronous adenoma was detected in 110 (20.0%) patients. In these patients, 94.5% (104/110) had metachronous adenoma within 3 years postoperatively. Age, synchronous adenoma, hypertension, tumor stage, and surgical resection were correlated with metachronous adenoma in patients with stage I-II CRC after radical resection (log rank test, P<0.05). Multivariate analyses showed that synchronous adenoma (HR =2.515, 95% CI: 1.691–3.742, P<0.01); stage II (HR =2.066, 95% CI: 1.329–3.210, P<0.01); and left-side colorectal resection (HR =2.207, 95% CI: 1.292–3.772, P<0.01) were independent risk factors.

Conclusions: Synchronous adenoma, left-side colorectal resection, and stage II cancer are independent risk factors of metachronous adenoma in patients with previous stage I and II CRC. In patients with risk factors, an enhanced colonoscopic strategy might be needed for early detection and timely endoscopic removal of metachronous adenoma.

Keywords: Colorectal cancer (CRC); early stage; metachronous adenoma; risk factors; surveillance colonoscopy

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Introduction

Colorectal cancer (CRC) ranks third among the most commonly diagnosed malignancies and accounts for about 10% of all new cancer cases globally (1-3). With the economic development and westernization of developing countries, the incidence of new CRC cases is rapidly increasing (1). It is estimated that there will be more than 2.5 million new CRC cases worldwide every year by 2035 (4). Despite the ever increasing burden of CRC, the positive aspects are people's deeper understanding of CRC and the popularization of CRC screening that may ensure that more CRC patients will be diagnosed in stages I and II, which denotes good prognosis (5,6). Moreover, with the help of continuously improving treatment, the outcomes of CRC are better than ever. Especially in patients with stage I and II CRC, the 5-year relative survival rates have now reached 91% and 82%, respectively (7).

Understandably, the population with a history of stage I and II CRC is continuously expanding. Therefore, the implementation of prevention strategies requires more focus, because these patients with previous CRC are more likely to develop new CRC than the general population (8-10). As most CRCs are malignant from adenomas, early detection and resection of metachronous adenoma (MA) by surveillance colonoscopy has an irreplaceable status among the secondary prevention strategies for second CRC. The rate of MA ranged from about 20% to over 40% in patients with CRC, and risk factors for MA included elder age, synchronous adenoma, left-sided tumor, diabetes mellitus and so on, regardless of TNM stage (11-13). However, there are few studies on the incidence, occurrence regularity, and risk factors of MA in patients with stage I and II CRC, making it challenging to implement a more individualized follow-up prevention strategy.

To identify the patients with stage I and II CRC who have a higher risk of MA and implement a more targeted surveillance strategy, we conducted this retrospective study. By analyzing the relationship between the clinicopathological characteristics of stage I and II CRC patients and MA, we explored the incidences and risk factors of MA, hoping to provide references for doctors having to follow-up with these patients. We present the following article in accordance with the REMARK reporting checklist (available at http://dx.doi.org/10.21037/jgo-20-386).

Methods

This study was in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the institutional review board of the Sixth Affiliated Hospital of Sun Yat-sen University, Guangzhou, China (No. 2020-100), and individual consent for this retrospective analysis was waived.

Patient selection

In this retrospective cohort study, patients who underwent radical surgery between January 1, 2012 and July 1, 2017 were reviewed from the hospital's CRC database. The inclusion criteria were as follows: patients (I) diagnosed with stage I or stage II colorectal adenocarcinoma by pathology after surgery, (II) who underwent index colonoscopy before surgery or within 6 months (180 days) after radical surgery, and (III) with ≥1 surveillance colonoscopies after surgery. The exclusion criteria were as follows: patients (I) with neoadjuvant therapy, (III) with insufficient/missing data of surveillance colonoscopy and pathology, (III) with previous malignant tumor or with more than one cancer at the same time, and (IV) with familial adenomatous polyposis. The flow chart of case selection is presented in *Figure 1*.

Clinicopathological characteristics

The demographic and clinical characteristics of the eligible patients were gathered from the CRC database-including age, sex, surgical resection, height, weight, and comorbidities. Surgical resection was classified into left-sided colorectal resection (LCR) or right-sided colorectal resection (RCR) and defined as being distal (LCR) or proximal (RCR) to the splenic flexure (14). The body mass index (BMI) was calculated according to height and weight, and classified as thin (<18.5 kg/m^2), normal (18.5–23.9 kg/m^2), and overweight (>23.9 kg/m^2) according to the international BMI criteria.

In terms of pathology, both the specimens of radical surgery and colonoscopy were reviewed and the tumors were staged according to the 8th TNM classification criteria established by the American Joint Committee on Cancer. All pathological examination procedures were in line with international standards of colorectal lesions.

Colonoscopy

The index colonoscopy was defined as a colonoscopy that could confirm no polyps in the colorectum and which was performed between when CRC was diagnosed and 6 months

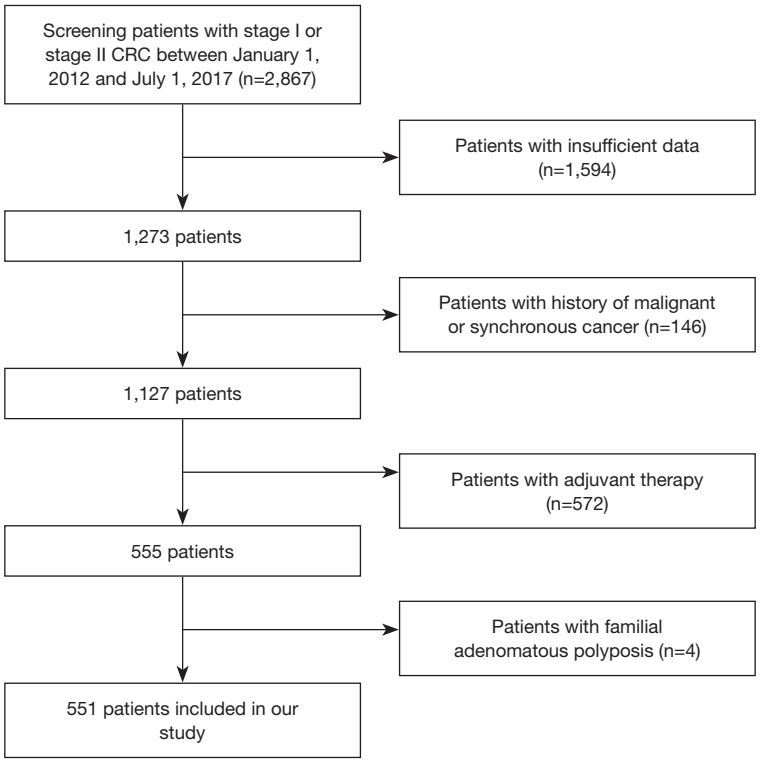

Figure 1 Flow chart of the patients enrolled in the study.

(180 days) after radical tumor resection (15). Surveillance colonoscopy was defined as colonoscopy performed 6 months or later after the curative surgery, while the frequency and timing of colonoscopy were determined by the follow-up physician based on CRC guidelines and clinical experience. Briefly, first surveillance colonoscopy was routinely recommended in one year after surgery, but in 3–6 months after surgery in case of obstructing CRC. If adenoma was found, colonoscopy was performed 1 year later, and if not, it was performed 3 years later. Synchronous adenoma (SA) was defined as those adenomas found when CRC was diagnosed or within 6 months after surgery, whereas MA were defined as those adenomas occurring more than 6 months after the radical resection of primary tumor. High-risk adenomas were defined as adenoma with villous histological feature, ≥10 mm in size, ≥3 in number, or with high-grade intraepithelial neoplasia or carcinoma (16-18). Other colorectal adenomas that did not meet the requirements of advanced adenomas were defined as low-risk adenomas.

To explore the effect of index colonoscopy on the detection of colorectal adenomas, we divided the preparation of index colonoscopy into *well* and *inadequate* according to whether there were factors (such as waste) affecting the detection. Furthermore, according to the examination performed before or after the surgery, we also divided the index colonoscopy into preoperative and postoperative groups.

Statistical analysis

In terms of descriptive data, statistics for categorical or continuous variables were calculated and reported as proportions and mean (standard deviation) or median (range), respectively. Student's *t*-test was used to compare continuous data which followed normal distribution, while Chi-square test or Fisher's exact test was used to compare dichotomous data.

The Kaplan-Meier method was used to calculate the cumulative probability of MA, while the log-rank test was used to test the intergroup differences. Cox proportional hazards model (enter stepwise method with an entry criterion of $P<0.05$ and a removal criterion of $P>0.10$) was performed to identify variables independently associated with the hazard of developing MA. In all statistical analyses, $P<0.05$ (two-sided) were considered to indicate statistical significance. All calculations were performed by using SPSS,

Table 1 Baseline clinicopathological characteristics of the patients recruited in the study

Variable	No. of patients	Percent (%)
Gender (male/female)	326/225	59.2/40.8
Age (years) (<50/≥50)	136/415	24.7/75.3
Average age ± SD (years)	57.04±11.583	
BMI (kg/m^2) (<18.5/18.5–23.9/≥24.0)	30/324/197	5.4/58.8/35.8
Diabetes mellitus (yes/no)	49/502	8.9/91.1
Hypertension (yes/no)	91/460	16.5/83.5
Adjuvant therapy (yes/no)	77/474	14.0/86.0
Surgical resection (RCR/LCR)	145/406	26.3/73.7
TNM stage (stage I/stage II)	194/357	35.2/64.8
Tumor differentiation (well + moderate/poor + others)	509/42	92.4/7.6
No. of retrieved lymph nodes (<12/≥12)	68/483	12.3/87.7
Mismatch repair (dMMR/pMMR)	60/469	10.9/85.1
Synchronous adenoma (no/low-risk/high-risk)	341/84/126	61.9/15.2/22.9
Preparation of index colonoscopy (well/inadequate)	323/228	58.6/41.4
Time of index colonoscopy (preoperative/preoperative)	235/316	42.6/57.4

BMI, body mass index; SD, standard deviations; RCR, right-sided colorectal resection; LCR, left-sided colorectal resection; dMMR, mismatch repair-deficient; pMMR, mismatch repair-proficient.

version 23 (IBM Corp. Armonk, New York, USA).

Results

Clinicopathological characteristics

According to the research standards, a total of 551 patients with a mean age of 57.04 (11.58) years were enrolled in the study. The number of patients in the RCR and LCR groups were 145 and 406, respectively. Overall, 210 of 551 (38.1%) patients were complicated with SA, including 84 (15.2%) low-risk SA and 126 (22.9%) high-risk SA. The clinicopathological characteristics of the patients are shown in *Table 1*.

Incidences of MA

During a median follow-up period of 19 (range: 6–60) months, 1142 surveillance colonoscopies were performed, 11.0% (126/1142) of which were MA diagnoses. MA was found in 110/551 (20.0%) patients; of these, 94 patients had MA only once, while the remaining 16 had a recurrence of MA. As shown in *Table 2*, MA was mainly found in patients that who has undergone previous colonoscopy in the first three years. Furthermore, in 104/110 (94.5%) patients, MA was first detected within 3 years after surgery, while in 52/110 (47.27%) patients, MA was first detected in the first year after surgery in 52/110 (47.27%) and in 3 years (*Table 2*).

Related factors of MA

The results of univariate analyses showed that the following basic clinicopathological characteristics were revealed as being associated with the development of MA (*Figure 2*): ≥50 years (log rank, P=0.04); associated with hypertension (log rank, P<0.01); LCR (log rank, P<0.01); stage II carcinoma (log rank, P=0.02); and associated with SA (log rank, P<0.01). With regard to the influence of SA, it was sound that no significant difference existed between patients with high-risk SA and patients with low-risk SA (log rank, P=0.40). The other factors such as diabetes mellitus, BMI, adjuvant therapy, and preparation of index colonoscopy were not related with the development of MA (*Table 3*).

The results of multivariate analysis by using Cox proportional hazards model, which incorporated the above five related factors, are shown in *Table 3*. SA was an independent risk factor for MA in patients with previous

Table 2 Time of first detection with metachronous adenoma

Time after radical surgery	Within 1 year	1–2 years	2–3 years	≥3 years
No. of patients with MA	52	32	20	6
Percent	9.4%	5.8%	3.6%	1.1%
Accumulated No. of patients with MA	52	84	104	110
Accumulated percent	9.4%	15.2%	18.9%	20%

MA, metachronous adenoma.

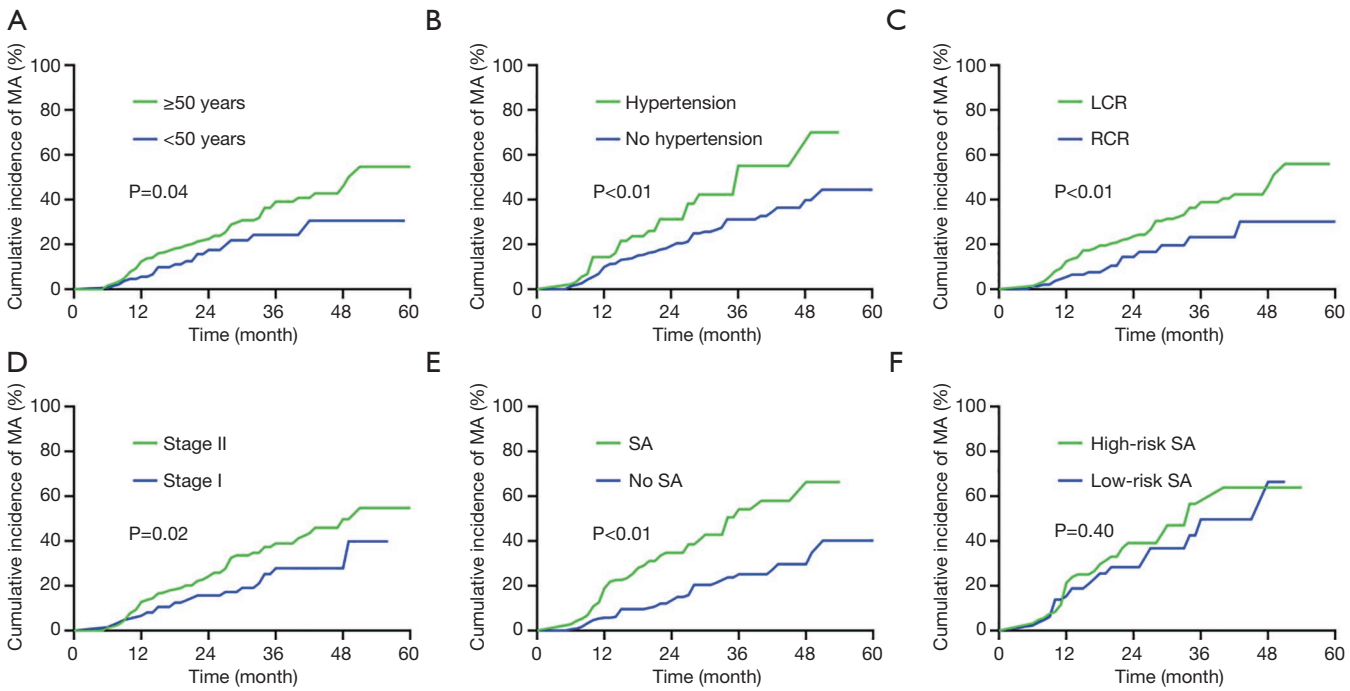

Figure 2 The cumulative incidence of MA was significantly different between the age <50 years and age ≥50 years groups (A). The cumulative incidence of MA was significantly different between patients with hypertension and without (B). The cumulative incidence of MA was significantly different between patients that accepted LCR and those that accepted RCR (C). The cumulative incidence of MA was significantly different between patients with stage I colorectal cancer and those with stage II colorectal cancer (D). The cumulative incidence of MA was significantly different between patients with synchronous adenoma and those without (E). The cumulative incidence of MA showed no difference between patients with high-risk synchronous adenoma and those with low-risk synchronous adenoma (F). MA, metachronous adenoma; SA, synchronous adenoma; RCR, right-sided colorectal resection; LCR, left-sided colorectal resection.

stage I/II CRC (HR =2.515; 95% CI: 1.691–3.742, P<0.01). LCR and stage II were also independent risk factors for MA. The results of multifactorial analysis indicate that the risk of MA in patients who underwent LCR is 2.207-times higher than in those that underwent RCR (95% CI: 1.292–2.772, P<0.01); patients with stage II CRC had 2.066-times higher risk of MA than those with stage I CRC (95% CI: 11.329–3.210, P<0.01).

Discussion

It is well known that people with previous CRC are more likely to have a recurrence of new CRC (8-10). Therefore, as an increasing number of patients are diagnosed with stage I/II CRC, it is crucial to adopt the colonoscopy surveillance strategy for early detection and resection of MA (19-21).

Table 3 Risk of metachronous adenoma in univariate and multivariate analyses

	Univariate analysis		Multivariate analysis		
	No. of patients [MA]	P value	HR	95% CI	P value
Gender (male/female)	326 [68]/225 [42]	0.09			
Age (years) (<50/≥50)	136 [20]/415 [90]	0.04*	1.056	0.630–1.769	0.84
BMI (kg/m^2) (<18.5/18.5–23.9/≥24.0)	30 [6]/324 [58]/197 [46]	0.41			
Diabetes mellitus	49 [10]/502 [100]	0.66			
Hypertension (yes/no)	91 [26]/460 [84]	<0.01*	1.262	0.796–2.000	0.32
Surgical resection (RCR/LCR)	145 [17]/406 [93]	<0.01*	2.207	1.292–3.772	<0.01*
Adjuvant therapy (yes/no)	77 [15]/474 [95]	0.94			
TNM stage (I/II)	194 [28]/357 [81]	0.02*	2.066	1.329–3.210	<0.01*
Tumor differentiation (well + moderate/poor + others)	509 [104]/42 [6]	0.16			
No. of retrieved lymph nodes (<12/≥12)	68 [14]/483 [96]	0.60			
Mismatch repair (dMMR/pMMR)	60 [12]/469 [96]	0.77			
Synchronous adenoma (yes/no)	210 [61]/341 [49]	<0.01*	2.515	1.691–3.742	<0.01*
(high-risk/low-risk)	126 [38]/84 [23]	0.40			
Preparation of index colonoscopy (well/inadequate)	323 [10]/228 [44]	0.88			
Time of index colonoscopy (preoperative/postoperative)	235 [40]/316 [70]	0.61			

*Results with statistical significance. BMI, body mass index; RCR, right-sided colorectal resection; LCR, left-sided colorectal resection; dMMR, mismatch repair-deficient; pMMR, mismatch repair-proficient.

In this study, 110 (20.0%) patients with previous stage I/II CRC were found to have MA; among them, MA was first detected in 94.5% patients within 3 years after surgery and in 47.3% in the first year after surgery. Univariate analyses found that age, SA, hypertension, tumor stage, and surgical resection were correlated with MA. Multivariate analysis showed that SA, LCR, and stage II were independent risk factors for MA. These results may help clinicians to better identify people with high risk of MA and implement more targeted strategies.

In patients with CRC, SA plays an important role in risk stratification of MA. It is generally believed that patients with colorectal adenoma are more likely to have a recurrence of colorectal adenoma (22-24). Lee *et al.* reported that SA was a risk factor for developing metachronous neoplasia in their study, which included 1,049 Korean patients who underwent curative resection of CRC. However, advanced-stage adenomas may have better prognostic value than early-stage disease in CRC (14,15). A study by Moon *et al.* showed that only advanced SA was associated with the risk of MA, while there was no significant difference in the incidence of MA between patients with low-risk SA and those without SA (15). Different from the research mentioned above, our study only included patients with stage I/II CRC, because most of them would be cured and have markedly better overall survival. After analysis, we found that both low-risk and advanced SA were associated with the risk of MA. Thus, in the follow-up of patients with stage I/II CRC, it may meaningful to pay more attention to people with SA, regardless of the type of SA.

Unlike SA, there is some controversy about the prognostic value of surgical resection. In most studies, patients who have accepted left-sided colectomy are more likely to have MA after treatment of CRC (25-27). For example, Yabuuchi *et al.* speculated that patients with synchronous advanced adenoma and after LCR had a potentially increased risk for metachronous advanced adenoma in a study of 1,731 CRC patients (14). In studies on patients with previous colon cancer, left-sided colectomy was still independently associated with MA (26,27). However, there are different ideas to the prognostic value of tumor location. Some researchers believe that patients

with proximal colon cancer were associated with a higher incidence of MA than those with distal colon cancer (11,28,29). Patel *et al.* concluded in a retrospective study that patients undergoing right-sided resection had a higher risk of MA in the long term after curative surgery for CRC. Our results suggest that patients who accepted LCR have a higher incidence of MA. Therefore, for patients with a history of LCR, higher vigilance may be needed to detect the MA located in the residual colorectum.

As for the TNM stage of the tumor, it may be an unanticipated factor that could influence the incidence of MA in stage I/II CRC patients. As our results showed, patients with stage II CRC have a higher incidence of both SA and MA. Hence, although other studies are needed to further confirm the prognostic value of stage II tumors, more attention should be focused on patients with stage II CRC, as this could still be helpful to detect the colorectal adenoma.

Although our study reasonably revealed the incidence and risk factors of MA in patients with previous stage I/II CRC, it has some limitations. First, because the median follow-up period was only 19 months, our results cannot fully reflect the long-term incidence of MA in a population with a history of stage I/II CRC, given that most of them may survive for many years. Second, because of the limitation of data in our retrospective research, some other possible relevant factors of MA such as aspirin and metformin use were not explored (30-32). Third, there could be selection bias as some patients did not receive index colonoscopy before surgery or a second surveillance colonoscopy after surgery. Therefore, to better serve the unique growing population with a history of stage I/II CRC, a series of studies on MA should be carried out in the future.

In conclusion, SA, LCR, and stage II are independent risk factors of MA in patients with previous stage I/II CRC. For early detection and timely endoscopic removal of MA, an enhanced colonoscopic strategy may be needed for these patients with risk factors.

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Footnote

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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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional review board of the Sixth Affiliated Hospital of Sun Yat-sen University (No. 2020-100) and individual consent for this retrospective analysis was waived.

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