

Retrospective Study

Onset and prognostic features of anastomotic leakage in patients undergoing radical surgery after neoadjuvant chemoradiation for rectal cancer

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Specialty type: Gastroenterology and hepatology**Provenance and peer review:** Unsolicited article; Externally peer reviewed.**Peer-review model:** Single blind**Peer-review report's classification****Scientific Quality:** Grade B**Novelty:** Grade B**Creativity or Innovation:** Grade B**Scientific Significance:** Grade B**P-Reviewer:** Akcil AM**Received:** June 5, 2024**Revised:** September 23, 2024**Accepted:** October 23, 2024**Published online:** December 27, 2024**Processing time:** 175 Days and 0.1 Hours

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Abstract

BACKGROUND

Anastomotic leakage (AL) is a significant complication of rectal cancer surgery, particularly in patients undergoing neoadjuvant chemoradiotherapy. This study aimed to evaluate the onset and prognostic factors influencing AL in these patients and provide insights for better postoperative management.

AIM

To explore AL incidence in patients who underwent neoadjuvant radiotherapy for rectal cancer and evaluate influencing factors and prognosis.

METHODS

We retrospectively analyzed data of patients with rectal cancer who underwent neoadjuvant chemoradiotherapy post-radical surgery admitted to our hospital from January 2020 to January 2023. Postoperative AL was recorded in all patients. Among 63 patients with AL initially enrolled, 2 were lost to follow-up; thus, 61 patients were included in the incident group. Another 59 patients without AL were included in the non-incident group. Clinical characteristics of both groups were analyzed to identify factors affecting postoperative AL and determine prognosis.

RESULTS

Multivariate analysis revealed that sex, operative time, bleeding, pelvic radiation injury, and intraoperative blood transfusion were independent risk factors for postoperative AL ($P < 0.05$). The Swiss Institute for Experimental Cancer Research (ISREC) grades for patients with postoperative AL were mainly A (49.18%) and B (40.98%), and most leakages occurred in the posterior wall (65.57%). Clinical manifestations included anal sacrococcygeal pain (29.51%), anal pus (26.23%), and other symptoms. Invasive interventions were performed < 2 times in 80.33% of

patients. Poor prognoses were mainly associated with chronic pressacral sinus formation (24.59%), anastomotic stenosis (29.51%), and long-term stoma (19.67%). Multivariate analysis revealed distance from the anal margin and ISREC grade as independent risk factors for poor prognosis following AL ($P < 0.05$).

CONCLUSION

Sex, operative time, bleeding loss, pelvic radiation damage, and intraoperative blood transfusion are independent risk factors for AL and the distance between tumor and ISREC grade potentially affect prognosis.

Key Words: Neoadjuvant chemoradiotherapy; Rectal cancer; Radical surgery; Anastomotic leakage; Prognosis

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Core Tip: This study identifies key risk factors and prognostic indicators for anastomotic leakage (AL) in rectal cancer patients post-neoadjuvant chemoradiotherapy and radical surgery. Independent risk factors for AL include male gender, longer operation time, significant blood loss, pelvic radiation injury, and intraoperative blood transfusion. The distance from the anal margin and the International Study Group of Rectal Cancer grade significantly affect prognosis. These findings underscore the need for careful surgical planning and management to mitigate AL risks and improve patient outcomes.

Citation: Wang L, Zhang WS, Huang GJ. Onset and prognostic features of anastomotic leakage in patients undergoing radical surgery after neoadjuvant chemoradiation for rectal cancer. *World J Gastrointest Surg* 2024; 16(12): 3710-3719

URL: <https://www.wjgnet.com/1948-9366/full/v16/i12/3710.htm>

DOI: <https://dx.doi.org/10.4240/wjgs.v16.i12.3710>

INTRODUCTION

Colorectal cancer (CRC) is a malignant tumor that occurs primarily in the colon and rectum. It usually originates from the cells lining the large intestine and initially manifests as polyps in the intestine[1]. Typical symptoms of CRC include rectal bleeding or blood in stool, persistent diarrhea or constipation, changes in stool shape, abdominal pain or discomfort, unexplained weight loss, and persistent fatigue. While the cause of CRC is not fully understood, various risk factors such as age, family history of cancer, adverse lifestyle, and specific genetic history are associated with an increased risk of CRC [2]. According to the 2012 global statistics, the incidence and mortality rates of CRC is increasing, with CRC ranked third in men and second in women among the newly diagnosed malignant tumors worldwide. The report also mentioned that more than 1.3 million new cases of CRC had been diagnosed, and approximately 700000 cases of death had been reported [3]. Surgery is a primary treatment option for early or middle-stage CRC. However, a common complication after rectal cancer surgery, anastomotic leakage (AL) considerably affects patient recovery, increasing medical costs and impairing quality of life. Reported incidence rates of AL vary between 3% and 20% depending on different diagnostic criteria and treatment methods[4]. Neoadjuvant chemoradiotherapy plays a key role in improving the success rate of radical resection for rectal cancer and enhancing the long-term prognosis of patients by promoting tumor shrinkage. However, chemoradiotherapy may also have negative effects, especially in terms of postoperative anastomotic healing. Tissue damage, such as edema and fibrosis, induced by pelvic radiotherapy has been identified as an important factor that increases the risk of AL. Several studies have reported that patients undergoing preoperative radiotherapy are more likely to develop AL after surgery[5,6]. In view of this finding, the present study aimed to investigate the incidence of AL and poor prognosis in patients with rectal cancer who underwent neoadjuvant chemoradiotherapy, analyze its influencing factors, and evaluate factors related to AL and poor prognosis to provide accurate risk assessment and management strategies for clinical treatment.

MATERIALS AND METHODS

Study design

Data of patients with rectal cancer admitted to our hospital between January 2020 and January 2023 were retrospectively analyzed. All patients underwent neoadjuvant chemoradiotherapy followed by radical surgery. The occurrence of postoperative AL was also recorded. Additionally, 59 patients without AL were included in the non-incident group.

Inclusion criteria: (1) Diagnosis of primary rectal cancer confirmed through pathological examination; (2) Treatment with neoadjuvant chemoradiotherapy and radical surgery at our hospital; (3) No other malignant tumors; and (4) Availability of complete clinical data.

Exclusion criteria: (1) Incomplete anastomosis; (2) Previous diagnosis and treatment history of CRC; (3) Emergency surgery for intestinal obstruction, perforation, or bleeding; and (4) Family history.

This study was approved by our ethics committee. Written informed consent was obtained from the patients and/or their guardians.

Management

Neoadjuvant chemotherapy: Intensity-modulated radiation therapy was delivered at a dose of 1.8 to 2.0 Gy per fraction in 25 to 28 fractions. Chemotherapy with fluorouracil or capecitabine alone or a combination of capecitabine plus oxaliplatin or fluorouracil plus oxaliplatin was administered before surgery for 2 to 12 cycles.

Radical surgery: After radiotherapy, the patients underwent radical anterior resection at a median of 8 weeks (range: 3–29 weeks), following the principle of total mesorectal excision. Surgical methods included laparoscopic transabdominal surgery, traditional open surgery, and combined laparoscopic and transanal endoscopic surgeries. During surgery, it is standard practice to transect the inferior mesenteric artery at its root and the inferior mesenteric vein at the lower edge of the pancreas. During surgery, the need to mobilize the splenic flexure of the colon was determined based on the bowel tension during anastomosis. Colorectal or coloanal anastomoses was typically performed with an end-to-end stapled anastomosis or through manual suture. Mechanical bowel cleansing was then performed, and an abdominal drainage tube was placed. The application of prophylactic enterostomy was selective, considering factors such as the location of the anastomosis and quality of anastomosis, complications, and patients' general nutritional status.

Data collection: Basic patient information, including sex, age, distance from tumor to the anus, interval between radiotherapy and surgery, colostomy, manual suture and anastomosis, operative time, intraoperative blood loss, pelvic radiation injury, smoking history, drinking history, hypertension, diabetes, preoperative anemia, preoperative hypoalbuminemia, intraoperative blood transfusion, tumor center location, and degree of differentiation, were collected from medical records.

Follow-up: Patients were followed up *via* telephone every 2 months after surgery. Follow-up assessments included the Swiss Institute for Experimental Cancer Research (ISREC) classification, fistula location, clinical manifestations, number of invasive interventions, and prognosis. The follow-up period was 6 months.

Observation

Clinical characteristics of the patients in the two groups were analyzed, and the factors affecting postoperative AL were investigated. Patients in the incident group were followed-up to record the occurrence of chronic presacral sinus formation, anastomotic stenosis, and long-term stoma. In total, 27 patients with the aforementioned conditions were included in the poor prognosis group, and 34 patients without these indicators were included in the good prognosis group. Additionally, factors affecting the prognosis of patients were investigated.

Statistical analysis

The Statistical Package for Social Science software (version 26.0; IBM, Armonk, NY, United States) was used for data analysis; enumeration data were expressed as *n* (%), and two tests were used for comparison between groups. Multivariate logistic regression analysis was used to analyze factors influencing postoperative AL and poor prognosis. Statistical significance was set at values of $P < 0.05$. significant.

RESULTS

Comparison of clinical data between the incident and non-incident groups

The proportion of male patients, operative time ≥ 180 minutes, intraoperative blood loss ≥ 150 mL, pelvic radiation injury, and intraoperative blood transfusion were higher in the incident group than in the non-incident group ($P < 0.05$; Table 1).

Multivariate analysis of the factors influencing postoperative AL

A binary logistic regression model was established including the presence or absence of AL after surgery as an independent variable (yes = 1, no = 0). Sex, operative time, intraoperative blood loss, pelvic radiation injury, and intraoperative blood transfusion were identified as independent risk factors for postoperative AL ($P < 0.05$; Table 2 and Table 3).

Analysis of clinical manifestations and prognosis of patients with postoperative AL

The ISREC grades for patients with postoperative AL was mainly grades A (49.18%) and B (40.98%). The leakage mostly occurred in the posterior wall (65.57%). The main clinical manifestations were anal sacrococcygeal pain (29.51%) and purulent discharges (26.23%). Less than two interventions were required in 80.33% of the patients. Poor prognosis was mainly associated with chronic presacral sinus formation (24.59%), anastomotic stenosis (29.51%), and long-term stoma (19.67; Table 4).

Univariate analysis of factors affecting poor prognosis in patients with postoperative AL

No significant differences between the good and poor prognosis groups were observed in terms of sex, age, prophylactic stoma, manual anastomosis, and leak location ($P > 0.05$). The proportion of poor prognosis was significantly higher in patients with distance from tumor to the anal verge < 5 cm than in patients with distance from tumor to the anal verge ≥ 5 cm; the proportion of good prognosis was higher in patients with ISREC grade A than in those with ISREC grade B.

Table 1 Comparison of clinical data between the incident and non-incident groups

Category	Incident group (n = 61)		Non-incident group (n = 59)		t/χ^2	P value
	Cases	Percentage (%)	Cases	Percentage (%)		
Sex						
Male	48	78.69	31	52.54	9.115	0.003
Female	13	21.31	28	47.46		
Age (years)						
< 55	33	54.10	38	64.41	1.319	0.251
≥ 55	28	45.90	21	35.59		
Tumor distance from anal margin (cm)						
< 5	29	47.54	35	59.32	1.672	0.196
≥ 5	32	52.46	24	40.68		
Interval between radiotherapy and surgery (weeks)						
≥ 8	15	24.59	18	30.51	0.527	0.468
< 8	46	75.41	41	69.49		
Stoma creation (preventive)						
Yes	27	44.26	22	37.29	0.604	0.437
No	34	55.74	37	62.71		
Hand-sewn anastomosis						
Yes	18	29.51	15	25.42	0.251	0.616
No	43	70.49	44	74.58		
Surgery time (minute)						
≥ 180	22	36.07	11	18.64	4.566	0.033
< 180	39	63.93	48	81.36		
Intraoperative bleeding (mL)						
≥ 150	23	37.70	11	18.64	5.366	0.021
< 150	38	62.30	48	81.36		
Pelvic radiation injury						
Yes	34	55.74	15	25.42	11.408	0.001
No	27	44.26	44	74.58		
Smoking history						
Yes	15	24.59	11	18.64	0.625	0.429
No	46	75.41	48	81.36		
Alcohol history						
Yes	16	26.23	13	22.03	0.288	0.591
No	45	73.77	46	77.97		
Hypertension						
Yes	11	18.03	15	25.42	0.965	0.326
No	50	81.97	44	74.58		
Diabetes						
Yes	8	13.11	9	15.25	0.113	0.737
No	53	86.89	50	84.75		
Preoperative anemia						

Yes	5	8.20	8	13.56	0.893	0.345
No	56	91.80	51	86.44		
Preoperative hypoalbuminemia (< 35 g/L)						
Yes	6	9.84	8	13.56	0.403	0.525
No	55	90.16	51	86.44		
Intraoperative blood transfusion						
Yes	25	40.98	13	22.03	4.977	0.026
No	36	59.02	46	77.97		
Tumor center location						
Below the peritoneal reflection	15	24.59	17	28.81	0.274	0.601
Above the peritoneal reflection	46	75.41	42	71.19		
Differentiation degree						
Moderately to well-differentiated	52	85.25	45	76.27	1.559	0.212
Poorly differentiated or undifferentiated	9	14.75	14	23.73		

Table 2 Assignments

Factor	Assignment
Sex	Male = 1, female = 0
Surgery time (minute)	≥ 180 = 1, < 180 = 0
Bleeding amount (mL)	≥ 150 = 1, < 150 = 0
Pelvic radiation injury	Yes = 1, No = 0
Intraoperative blood transfusion	Yes = 1, No = 0

Table 3 Multivariate analysis for factors influencing postoperative anastomotic leakage

Factor	B	SE	Wald	P value	OR	95%CI	
						Lower	Upper
Sex	1.204	0.407	8.754	0.003	3.335	1.502	7.407
Surgery time	0.901	0.428	4.438	0.035	2.462	1.065	5.691
Bleeding amount	0.899	0.408	4.856	0.028	1.407	1.183	1.905
Pelvic radiation injury	1.307	0.395	10.956	0.001	3.694	1.704	8.008
Intraoperative blood transfusion	0.899	0.408	4.856	0.028	2.457	1.105	5.467

OR: Odds ratio.

However, the proportion of poor prognosis was significantly higher in patients with grades B and C than in those with grade A ($P < 0.05$; Table 5).

Multivariate analysis of factors affecting poor prognosis in patients with postoperative AL

A binary logistic regression model was established including patient prognosis as the independent variable (good prognosis = 0, poor prognosis = 1). The results showed that the distance from tumor to the anal verge and ISREC grade were independent risk factors for poor prognosis in patients with postoperative AL ($P < 0.05$; Table 6).

DISCUSSION

As a common malignant tumor, the incidence of rectal cancer is increasing worldwide, substantially impacting the health

Table 4 Analysis of clinical manifestations and prognosis of patients with postoperative anastomotic leakage

Clinical feature	Cases	Percentage (%)
ISREC classification		
Grade A	30	49.18
Grade B	25	40.98
Grade C	6	9.84
Fistula location		
Anterior wall	9	14.75
Posterior wall	40	65.57
Lateral wall	8	13.11
Circumferential	4	6.56
Clinical manifestation		
Fever	6	9.84
Abdominal pain/bloating	7	11.48
Abnormal drainage	1	1.64
Anorectal pus discharge	16	26.23
Anorectal/coccygeal pain	18	29.51
Rectal irritation sign	11	18.03
Abnormal vaginal discharge	2	3.28
Necrosis of everted bowel	2	3.28
Number of invasive interventions (times)		
< 2	49	80.33
≥ 2	12	19.67
Prognosis		
Chronic sacrococcygeal fistula formation	15	24.59
Anastomotic stenosis	18	29.51
Long-term stoma	12	19.67

ISREC: Swiss Institute for Experimental Cancer Research.

and quality of life of patients[7]. In 2015, statistics from China reported approximately 376000 newly diagnosed cases of CRC, ranking fifth among all cancers in the country. Of these, the estimated number of rectal cancer cases exceeded 100000, presenting a major challenge to national health[8]. For patients with locally advanced rectal cancer (T3-T4 stage) with lymph node metastasis but without distant metastasis, the current standard treatment mainly includes radiotherapy-based neoadjuvant therapy combined with total mesorectal excision. Preoperative radiotherapy in such patients can effectively reduce the rate of positive circumferential and distal resection margins, reduce the risk of local tumor recurrence, and increase the likelihood of preserving anal function owing to tumor shrinkage[9]. AL is a common and serious complication following rectal cancer surgery, considerably affecting patient recovery and quality of life. The technical challenges associated with rectal cancer surgery are amplified in patients undergoing neoadjuvant chemoradiotherapy due to radiation-induced tissue damage. This damage, including fibrosis and edema, can hinder proper healing of the anastomosis, thereby increasing the risk of AL. Radiation-associated tissue changes complicate the creation of a secure anastomosis in the lower rectum, which may result in higher rates of AL. Thus, managing postoperative AL in patients undergoing neoadjuvant chemoradiotherapy is crucial to improve clinical outcomes.

Our study results indicated that sex, operative time, blood loss, pelvic radiation injury, and intraoperative blood transfusion were independent risk factors for postoperative AL ($P < 0.05$). The reason for this is that the technical requirements of rectal cancer surgery are higher in male patients because of narrower pelvis. In addition, preoperative radiotherapy usually leads to tissue edema and fibrosis, thereby changing the normal anatomical structure and further increasing complicating surgery and increasing the risk of AL post-surgery[10]. A prolonged duration of surgery leads to an extended duration of anesthesia and low temperatures in the operating room, which may increase the risk of postoperative coagulation disorders and infection and impair the healing of the anastomosis[11]. Arima *et al*[12] and Hu *et al*[13] suggested that an operative time exceeding 180 minutes increases these risks. In addition, some studies have

Table 5 Univariate analysis of factors affecting poor prognosis in patients with postoperative anastomotic leakage

Factor	Favorable prognosis group (n = 27)		Unfavorable prognosis group (n = 34)		t/ χ^2	P value
	Cases	Percentage (%)	Cases	Percentage (%)		
Sex						
Male	22	81.48	26	76.47	0.225	0.635
Female	5	18.52	8	23.53		
Age (years)						
< 55	15	55.56	18	52.94	0.041	0.839
≥ 55	12	44.44	16	47.06		
Tumor distance from the anus (cm)						
< 5	9	33.33	23	67.65	7.105	0.008
≥ 5	18	66.67	11	32.35		
Interval between radiotherapy and surgery (weeks)						
≥ 8	7	25.93	8	23.53	0.047	0.829
< 8	20	74.07	26	76.47		
Prophylactic stoma						
Yes	12	44.44	15	44.12	0.001	0.980
No	15	55.56	19	55.88		
Hand-sewn anastomosis						
Yes	9	33.33	9	26.47	0.341	0.559
No	18	66.67	25	73.53		
ISREC classification						
Grade A	19	70.37	11	32.35	10.468	0.005
Grade B	5	18.52	20	58.82		
Grade C	3	11.11	3	8.82		
Fistula location						
Anterior wall	4	14.81	5	14.71	7.507	0.057
Posterior wall	14	51.85	26	76.47		
Lateral wall	7	25.93	1	2.94		
Circumferential	2	7.41	2	5.88		

ISREC: Swiss Institute for Experimental Cancer Research.

indicated that intraoperative blood loss exceeding 70 mL increases the risk of AL[14], as massive bleeding can trigger the release of local inflammatory factors and reduce blood supply to the digestive tract, thereby impairing the healing process [15]. Therefore, efforts should be made to shorten operative time and surgery should be carefully performed to reduce side injuries and limit blood loss, thereby reducing the incidence of AL. Radiation enteritis is one of the most common side effects of pelvic radiotherapy and has been closely associated with the occurrence of AL after rectal cancer surgery [16]. The findings of this study further showed that radiation injury was a risk factor for postoperative AL. Blood transfusion, often necessitated by massive bleeding, not only reflects reduced circulating blood volume and poor blood flow at anastomosis, which can increase the risk of infection and impair healing of anastomosis, but may also trigger an immune inflammatory response, which adversely affects healing of anastomosis[17].

In terms of the clinical manifestations of AL, the ISREC grading for patients with postoperative AL was mainly grades A (49.18%) and B (40.98%), which was partially different from previous studies and may be related to differences in diagnostic criteria and methods. In this study, leakage mostly occurred in the posterior wall (65.57%), mainly due to excessive tension in the posterior wall, insufficient space in the presacral region, and inadequate drainage. Other clinical manifestations included sacrococcygeal pain (29.51%) and purulent anal discharge (26.23%). Less than two interventions

Table 6 Multivariate analysis of factors influencing poor prognosis in patients with postoperative anastomotic leakage

Factor	B	SE	Wald	P value	OR	95%CI	
						Lower	Upper
Distance of Tumor from the anal verge	1.431	0.549	6.800	0.009	4.182	1.427	12.258
ISREC Classification	0.890	0.436	4.167	0.041	2.435	1.036	5.723

The assignment was as follows: The distance between the tumor and the anal margin was < 5 cm = 1, 5 cm = 0; Swiss Institute for Experimental Cancer Research grade A = 1, grade B = 2, grade C = 3. ISREC: Swiss Institute for Experimental Cancer Research; OR: Odds ratio.

were required in 80.33% of the patients. Poor prognosis was mainly associated with chronic presacral sinus formation (24.59%), anastomotic stenosis (29.51%), and long-term stoma (19.67%). These findings suggest that although most AL in most cases can be controlled with limited intervention, some patients experience severe complications and poor long-term prognosis. Therefore, although AL is manageable in most cases, its long-term effects cannot be ignored. Multivariate analysis further revealed that the distance from tumor to the anal verge and ISREC grade were independent risk factors for poor prognosis in patients with postoperative AL ($P < 0.05$). This finding can be explained by the fact that the lower rectum is located in the extraperitoneal region; therefore, when the tumor is close to the anus, a large wound is created during surgical resection. In addition, the use of electrocoagulation during surgery to damage blood vessels may lead to more exudation and oozing of blood, which further compromises blood supply to the anastomotic area[18]. After resection of the intestinal segment, the presacral region becomes cavitated, and the protection of the serosal layer at the anastomosis is lost. In this case, the anastomosis was more susceptible to prolonged fluid accumulation, thereby increasing the risk of infection. Second, when the tumor is located closer to the anus, the surgical area penetrates deeper into the pelvic cavity, resulting in a narrow surgical space. This increases the risk of inadvertently pinching the surrounding tissues when closing the anastomosis or necessitating the use of stapler multiple times due to the presence of thick tissues on both sides of the anastomosis. The choice of an unsuitable stapler model may also affect healing of anastomosis. Furthermore, as the tumor moves closer to the anus, the pressure in the intestinal wall increases, which compromises blood supply and increases lateral tension on the anastomosis[19]. The ISREC classification is based on the clinical symptoms of AL. Grade A AL is clinically asymptomatic, and leakage is detected only *via* contrast imaging examination without the need of special treatment. Grade B AL are characterized by abdominal pain, fever, and fecal residues passing through the anus, which require conservative management. In addition to local symptoms, grade C AL may be accompanied by systemic symptoms such as peritonitis and sepsis, which require secondary abdominal surgery [20]. Therefore, the distance between the tumor and anal verge and the ISREC grade directly influence surgical difficulty, the risk of AL, and the complexity of its management, thus affecting the postoperative prognosis in patients. These findings highlight the importance of considering these factors in surgical planning and postoperative management to reduce the occurrence of AL and improve patient outcomes.

Although our study provides valuable insights into the onset and prognostic features of AL in patients undergoing radical surgery after neoadjuvant chemoradiation for rectal cancer, certain limitations must be acknowledged. First, the study was conducted at a single center, which may have limited the generalizability of the findings. The outcomes may be influenced by specific surgical practices, institutional protocols, or patient demographics unique to our hospital. Future studies involving multiple centers would help validate our results and provide more generalized conclusions. Second, the sample size was relatively small, which may have reduced the statistical power of our findings. Although we identified independent risk factors for postoperative AL, a larger sample size would allow for more robust statistical analyses and potentially reveal additional factors influencing prognosis. Future studies with a larger cohort will further enhance the reliability of our conclusions.

CONCLUSION

The analysis of the incidence and prognostic characteristics of AL after radical surgery for rectal cancer following neoadjuvant chemoradiotherapy showed that sex, operative time, blood loss, pelvic radiation injury, and intraoperative blood transfusion were identified as independent risk factors for AL. Additionally, the distance from tumor to the anal verge and ISREC grade affected the prognosis.

FOOTNOTES

Author contributions: Wang L and Huang GJ designed the study and performed the experiments; Wang L and Zhang WS collected the data; Huang GJ and Zhang WS analyzed the data; and Wang L and Huang GJ prepared the manuscript; All the authors have read and approved the final version of the manuscript.

Institutional review board statement: This study was approved by the ethics committee of The Second Hospital of Nanjing, No 2018-18.

Informed consent statement: Signed written informed consents were obtained from the patients and/or guardians.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: The data that support the findings of this study are available from the corresponding author upon reasonable request at 15951985466@163.com.

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S-Editor: Li L

L-Editor: A

P-Editor: Yuan YY

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