



# Analysis of Risk Factors and Clavien-Dindo Classification System for Complications after Total Gastrectomy

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## Abstract

**Purpose:** To investigate risk factors and Clavien-Dindo classification system for complications after radical total gastrectomy for gastric cancer.

**Methods and Materials:** Clinical data of 133 patients with gastric cancer who underwent radical total gastrectomy in our hospital from January 2012 to January 2017 were retrospectively analyzed. The complications after total gastrectomy was analyzed according to the Clavien-Dindo classification system and risk factors for postoperative complications were assessed by using the logistic regression model.

**Results:** According to the Clavien-Dindo classification system, grade II had the highest incidence. The multivariate logistic regression analysis revealed that perioperative blood transfusion (odds ratio (OR) =16.08, 95% Confidence Interval (CI): 4.80 to 53.81, P=0.001) and postoperative albumin level (OR=3.34, 95% CI: 1.13 to 9.87, P=0.029) were independent risk factors for postoperative complications. The TNM staging (OR=0.08, 95% CI: 0.01 to 0.63, P=0.016), N stage (OR=0.12, 95% CI: 0.01 to 1.28, P=0.017), and perioperative blood transfusion (OR=4.69, 95% CI: 1.58 to 13.92, P=0.023) were independent risk factors, influencing severe complications in the multivariate analysis.

**Conclusion:** The Clavien-Dindo classification system showed that grade II had the highest incidence, mainly including abdominal infection and abdominal hemorrhage. Furthermore, the majority of severe complications were related to anastomotic leakage. Postoperative blood transfusion and postoperative albumin level <30 g/l were identified as independent risk factors for postoperative complications. Moreover, TNM stage III, N3 stage, and postoperative blood transfusion were noted as independent risk factors for severe complications.

**Keywords:** Gastric cancer; Total gastrectomy; Postoperative complications; Clavien-Dindo classification; Risk factors

## Introduction

Gastric cancer is a common malignant tumor of the digestive tract. Radical total gastrectomy is extensively used as a surgical method for gastric cancer. With respect to advances in surgical techniques, development of surgical instruments, and refinement of perioperative management, safety of surgery has improved. However, there are still postoperative complications, influencing the patients' prognosis and quality of life. Therefore, a comprehensive analysis of the complications after radical total gastrectomy is indeed essential. It is necessary to analyze the risk factors of postoperative complications and standardize the classification of postoperative complications, so as to take appropriate preventive and intervention measures to reduce the occurrence of complications. In the present study, we collected the clinical data of patients who have gastric cancer, and underwent total gastrectomy. The complications after total gastrectomy were analyzed according to the Clavien-Dindo classification, and risk factors of the postoperative complications were analyzed by using the logistic regression model.

## Methods

### General information

From January 2012 to January 2017, 133 patients underwent radical total gastrectomy in Beijing Friendship Hospital Capital, Medical University, and Beijing, China. Among them, 100 patients were males and 33 patients were females, who aged 60.9+10.9 years. Each patient was diagnosed with gastric cancer preoperatively by Computed Tomography (CT), upper gastrointestinal

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Received Date: 02 Aug 2019

Accepted Date: 16 Sep 2019

Published Date: 20 Sep 2019

### Citation:

Huazhen T, Zhi Z, Jie Y, Jun C, Jun Z,  
Zhongtao Z. Analysis of Risk Factors  
and Clavien-Dindo Classification  
System for Complications after Total  
Gastrectomy. Clin Surg. 2019; 4: 2577.

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**Table 1:** Patients' characteristics (N=133).

Characteristic	Total (n=133)
Sex (male/female)	100/33
Age	60.9 ± 10.9
Charlson Comorbidity Index	3.5 ± 1.1
BMI	23.3 ± 3.6
NRS-2002 score	3.3 ± 1
Length of hospital stay	20.4 ± 11
Operation method (open/laparoscopic/ laparoscopy-assisted)	94/12/27
Digestive tract reconstruction (Roux-en-Y/ Hunt-Lawrence)	113/20
Extent of lymph node dissection (D1/D2)	3/130
Operation time (hour)	4.7 ± 1.5
Intraoperative blood loss (ml)	318.8 ± 246.6
Place intestinal feeding tube no/yes	46/87
Combined organ resection no/yes	118/15
Postoperative serum albumin(l)	28.4 ± 3.3
Blood transfusion (intraoperative/postoperative/no)	8/27/98
Histological type (G1/ G2/ G3/Undefined)	12/45/70/6
Tumor location Upper 1/3 /Middle 1/3/2/3 or more)	57/68/8
Tumor diameter (mm)	65 ± 40
Surgical margin (cm)	2.8 ± 1.4
T stage (T1/T2/T3/T4a/T4b)	17/13/47/50/6
N stage (N0/N1/N2/N3a/N3b)	51/19/20/24/19
TNM staging (IA/IB/IIA/IIIB/IIIA/IIIC)	15/10/23/14/26/26/19
Number of lymph node metastases	6 ± 8.7
Number of retrieved lymph nodes	28.7 ± 12.8
Intravascular tumor thrombus no/yes	70/63
Carcinoma nodule no/yes	121/12

radiography, gastroscopy, and confirmed by biopsy. Patients with incomplete or missing histologic or operative data were excluded from the analysis. In the present study, the perioperative hospital stay was 8 to 73 days, with a median of 17 days. Here, 94 patients underwent open total gastrectomy, 12 underwent totally laparoscopic surgery, and 27 underwent laparoscopic-assisted total gastrectomy. All operations were performed by experienced and skilled surgeons. Complications in this study included surgical complications associated with surgical-related reasons and systemic complications during perioperative period. Patients' basic data were collected through medical records as follows: age, sex, Charlson Comorbidity Index, Body Mass Index (BMI), nutritional risk screening 2002 (NRS-2002), method of operation, digestive tract reconstruction mode, operative time, bleeding volume, combined organ resection, scope of lymph node dissection, related pathological factors (pathological type, differentiation, location, size, histological type, T stage, N stage, TNM staging, and intravascular cancer embolus). Postoperative complications were recorded and graded as per C–D classification.

### Surgical procedures

In the current study, 94 patients underwent open total gastrectomy, 12 patients underwent totally laparoscopic surgery, and 27 patients underwent laparoscopic-assisted total gastrectomy. In our center, the majority of patients underwent total gastrectomy with D2 lymphadenectomy according to the rules of the Japanese Gastric

**Table 2:** Postoperative surgical complications.

Complication	Number
Overall complications (%)	51 (38.3%)
Grade I (%)	3 (2.3%)
Wound infection	1
Transient hepatic function abnormality	1
Pneumonia	1
Grade II (%)	25 (18.8%)
Abdominal infection	8
Abdominal hemorrhage	8
Pneumonia	3
Cardiac insufficiency	3
Pancreatic leakage	3
Grade IIIa (%)	16 (12.0%)
Anastomosis leakage	6
Pancreatic leakage	1
Intra-abdominal abscess	3
Wound problem	3
Intra-abdominal bleeding	1
Duodenal stump leakage	1
Anastomotic stenosis	1
Grade IIIb (%)	4 (3.0%)
Bowel obstruction	2
Intra-abdominal bleeding	1
Duodenal stump leakage	1
Grade IVa (%)	2 (1.5%)
Anastomosis leakage	1
Duodenal stump leakage	1
Grade V (%)	1 (0.8%)
Anastomosis leakage	1

Cancer Treatment Guidelines and the Japanese Classification of Gastric Carcinoma. However, we performed D1 lymphadenectomy in 3 patients with early gastric cancer and high surgical risk. Roux-en-Y anastomosis was often used for digestive tract reconstruction, and Hunt-Lawrence anastomosis was applied to 20 cases.

### Statistical analysis

All data are expressed as mean ± Standard Deviation (SD). Univariate and multivariate logistic regression analyses were undertaken to assess the risk factors that might affect postoperative complications. Univariate analysis was performed using Fisher's exact and chi-square tests. Variables that demonstrated association with complication frequency ( $P < 0.05$ ) were included in an initial multivariate logistic regression model.  $P < 0.05$  was considered statistically significant. All statistical calculations were carried out using SPSS 22.0 software (IBM, Armonk, NY, USA).

## Results

### Patients' characteristics

The patients' characteristics are summarized in Table 1. There were 15 cases that accompanied by multi-organ resection. Organs that were removed in whole or in part were as follows: spleen (9 cases), body and tail of pancreas (2 cases), left lateral lobe of liver (2

**Table 3:** University analysis of risk factors for postoperative complications after total gastrectomy.

Variable	Overall complication (%)	P-value	Severe complications (%)	p value
Sex		0.333		0.492
Male	36.0 (36/100)		15 (15/100)	
Female	45.5 (15/33)		24.2 (8/33)	
Age (years)		0.232		0.438
<65	34.1 (27/79)		12.7 (10/79)	
≥ 65	44.4 (24/54)		24.1 (13/54)	
Charlson Comorbidity Index		0.967		0.509
<3	38.9 (7/18)		33.3 (6/18)	
≥ 3	38.3 (44/115)		14.8 (17/115)	
BMI (kg/m <sup>2</sup> )		0.816		0.752
<18.5	46.2 (6/13)		38.5 (5/13)	
18.5–23.9	38.3 (23/60)		15 (9/60)	
≥ 24	36.7 (22/60)		15 (9/60)	
NRS-2002 score		0.223		0.845
<3	29.0 (9/31)		16.1 (5/31)	
≥ 3	41.2 (42/102)		17.6 (18/102)	
Operation method		0.247		0.387
Open	41.5 (39/94)		18.1 (17/94)	
Laparoscopy	16.7 (2/12)		50 (6/12)	
Laparoscopy-assisted	37.0 (10/27)		0 (0/27)	
Digestive tract reconstruction		0.739		0.999
Roux-en-Y	38.9 (44/113)		16.8 (19/113)	
Hunt-Lawrence	35 (7/20)		20 (4/20)	
Operation time (hour)		0.636		0.758
<4	35.1 (13/37)		18.9 (7/37)	
≥ 4	39.6 (38/96)		16.7 (16/96)	
Intraoperative blood loss (ml)		0.469		0.565
<200	32 (8/25)		16 (4/25)	
≥ 200	39.8 (43/108)		17.6 (19/108)	
Multi-organ resection		0.205		0.293
Yes	53.3 (8/15)		33.3 (5/15)	
No	36.4 (43/118)		15.3 (18/118)	
Postoperative serum albumin (g/l)		0.001		0.232
<30	48.9 (44/90)		20 (18/90)	
≥ 30	16.3 (7/43)		11.6 (5/43)	
Blood transfusion		0		0.016
Intraoperative	50 (4/8)		12.5 (1/8)	
Postoperative	85.2 (23/27)		37 (10/27)	
No	24.5 (24/98)		12.2 (12/98)	
Histological type		0.553		0.178
G1	25 (3/12)		8.3 (1/12)	
G2	42.2 (19/45)		24.4 (11/45)	
G3	40 (28/70)		15.7 (11/70)	
In defined	16.7 (1/6)		0 (0/6)	
Tumor location		0.041		0.4
Upper 1/3	33.3 (19/57)		19.3 (11/57)	
Middle 1/3	34 (27/68)		14 (11/68)	

2/3 or more	62.5 (5/8)		12.5 (1/8)	
Tumor diameter (mm)		0.172		0.983
<50	30.4 (14/46)		17.4 (8/46)	
≥ 50	42.5 (37/87)		17.2 (15/87)	
Surgical margin (cm)		0.321		0.429
<2	33.9 (21/62)		14.5 (9/62)	
≥ 2	42.2 (30/71)		19.7 (14/71)	
T stage		0.194		0.13
T1	29.4 (5/17)		11.8 (2/17)	
T2	33.3 (4/12)		0 (0/12)	
T3	41.7 (20/48)		18.8 (9/48)	
T4a	34 (17/50)		18.0 (9/50)	
T4b	83.3 (5/6)		50 (3/6)	
N stage		0.134		0.05
N0	27.4 (14/51)		9.8 (5/51)	
N1	47.4 (9/19)		26.3 (5/19)	
N2	55 (11/20)		35 (7/20)	
N3	39.5 (17/43)		14.0 (6/43)	
TNM stage		0.015		0.03
I+II	27.4 (17/62)		9.7 (6/62)	
III	47.9 (34/71)		23.9 (17/71)	
Intravascular tumor thrombus		0.955		0.681
Yes	38.1 (24/63)		14.3 (9/63)	
No	38.6 (27/70)		20 (14/70)	
Number of retrieved lymph nodes		0.742		0.488
<30	37.2 (29/78)		15.4 (12/78)	
≥ 30	40 (22/55)		20 (11/55)	

cases), and gallbladder (4 cases). According to the TNM staging, 25 cases (18.8%) were in stage I, 37 cases (27.8%) in stage II, and 71 cases (53.4%) in stage III. The majority of the patients who underwent total gastrectomy were in advanced stage, indicating a poor prognosis for these patients. Preoperative complications were assessed by Charlson Comorbidity Index, with an average score of  $3.5 \pm 1.1$ . The BMI was  $23.3 \pm 3.6 \text{ kg/m}^2$  and the NRS-2002 score was  $3.3 \pm 1$  (Table 1).

### Postoperative complications

In our study, all postoperative complications were classified by Clavien-Dindo classification. Of the 133 patients, 51 patients (38.3%) had overall complications, 37 patients (27.8%) had surgical complications, and 23 patients (17.3%) had severe complications (Table 2). The C-D classification for postoperative complication shows that grade II has the highest incidence, mainly including abdominal abscess and abdominal hemorrhage. Besides, the most frequent complications were anastomotic leakage in the severe complications.

### Univariate analysis of postoperative complications

The results of univariate analysis revealed that postoperative albumin level, perioperative blood transfusion, tumor location and TNM staging were identified as significant factors for overall complication ( $P < 0.05$ ), while perioperative blood transfusion, N stage, and TNM staging were significant factors, affecting the serious complications ( $P < 0.05$ ) (Table 3).

### Multivariate analysis of postoperative complications

The results of multivariate analysis showed that perioperative blood transfusion (OR=16.08, 95% CI: 4.80-53.81,  $P=0.001$ ) and postoperative albumin level (OR=3.34, 95% CI: 1.13-9.87,  $P=0.029$ ) were identified as independent risk factors for overall complications. The TNM staging (OR=0.08, 95% CI: 0.01 to 0.63,  $P=0.016$ ), N stage (OR=0.12, 95% CI: 0.01 to 1.28,  $P=0.017$ ), and perioperative blood transfusion (OR=4.69, 95% CI: 1.58 to 13.92,  $P=0.023$ ) were independent risk factors for severe complications (Table 4).

### Discussion

At present, a number of scholars recommended Clavien-Dindo classification system to standardize the definition and classification of complications. This system has been proved to be a reliable measure for quality assessment of surgery in different fields [1,2]. Using this standard system, we analyzed and classified the postoperative complications of total gastrectomy in gastric cancer. It has been reported that the incidence of complications after radical total gastrectomy for gastric cancer is about 7.0% to 39.8% and the incidence of severe complications is about 2.4% to 14%. The reported incidence of complications is quite different [3-10]. In the present study, the incidence of overall complications was 38.3%, and serious complications were 17.3%. The complications in our study not only included surgical complications, but also systemic complications, such as pneumonia and cardiac insufficiency, leading to the higher

**Table 4:** Multivariate analysis of risk factors for postoperative complications after total gastrectomy.

Variables	Overall complications (%)			Severe complications (%)		
	OR	95% CI	P-value	OR	95% CI	P-value
Postoperative serum albumin (g/l)						
≥ 30	Reference					
<30	3.34	(1.13, 9.87)	0.029			
Blood transfusion						
No	Reference					
Intraoperative	2.27	(0.56, 13.66)	0.658	0.57	(0.05, 6.67)	0.291
Postoperative	16.08	(4.80, 53.81)	0.001	4.69	(1.58, 13.92)	0.023
Tumor location						
2/3 or more	Reference					
Upper 1/3	0.28	(0.04, 1.98)	0.112			
Middle 1/3	0.53	(0.08, 3.63)	0.995			
TNM stage						
I+II	Reference					
III	0.51	(0.21, 1.26)	0.145	0.08	(0.01, 0.63)	0.016
N stage						
N0	Reference					
N1				0.99	(0.16, 6.41)	0.098
N2				0.31	(0.03, 3.60)	0.554
N3				0.12	(0.01, 1.28)	0.017

incidence rate. The C-D classification for overall complications shows that grade II has the highest incidence of 18.8%, mainly including intra-abdominal abscess and bleeding. The incidence of severe complications was 17.3%, mainly including anastomotic leakage. Previous studies have shown that the incidence of anastomotic leakage after total gastrectomy is 9.6%~14.0%, while that was 6.0% in our study [11-15]. Anastomotic leakage after total gastrectomy often leads to systemic inflammatory response syndrome, mediastinal abscess, persistent pleural effusion, anastomotic bleeding, etc., seriously endangering human life. The main reasons for anastomotic leakage are as follows: 1. There is no serosa covering the esophagus, that is easy to tear during anastomosis; 2. Excessive separation of the esophageal stump, injury of the esophageal vessels, or very close and tight suture, leading to insufficient blood supply of the anastomotic site; 3. Excessive tension of the anastomotic site during digestive tract reconstruction; 4. Improper placement of the drainage tube, causing mechanical injury when it is close to the anastomotic site. For anastomotic leakage, a series of treatment methods are mainly used, such as thoracic drainage, secondary operation, re-anastomosis, increased drainage or jejunostomy; simultaneously, enhanced antibiotic application and nutritional support are of great importance. Different risk factors for complications after total gastrectomy have been reported. It was previously reported that the complications after total gastrectomy are related to tumor stage, preoperative complications, postoperative serum albumin level, combined organ resection, operative time, BMI, perioperative blood transfusion, etc. [3-8,11,12]. Using multivariate analysis, we showed that perioperative blood transfusion and postoperative serum albumin level were independent risk factors for overall complications. In addition, TNM staging, perioperative blood transfusion, and N stage were independent risk factors for severe complications. It has been reported that perioperative blood transfusion increases the risk

of postoperative complications by 2.78 times, especially the risk of pneumonia and abdominal incision infection [16,17]. Mohri et al., [18] Reported that blood transfusion is a risk factor for pneumonia after gastric cancer surgery. In our study, post-operative blood transfusion was found as an independent risk factor for overall and severe complications ( $P < 0.05$ ). Postoperative blood transfusion is due to the continuous drainage of large amounts of blood, progressive decrease of hemoglobin, and instability of peripheral circulation, requiring blood transfusion for the treatment of anemia. The present study confirmed that blood transfusion increases the activity of regulatory T cells, inhibits the function of natural killer T cells and macrophages, attenuate the immune response, and increases the risk of infection [19-21]. Therefore, the indication of blood transfusion should be strictly mastered. In this study, 90 patients (67.7%) had low serum albumin level after operation. The mean serum albumin level 3 days after operation was  $28.4 \pm 3.3$  g/l. It is an independent risk factor for overall complications (Odds Ratio (OR) = 3.34, 95% confidence interval (CI): 1.13~9.87,  $P = 0.029$ ). Low serum albumin level increases the incidence of postoperative complications [22-25]. Nordberg et al., [23] found that serum albumin level is an important index for predicting the outcomes and complications of gastrectomy. Postoperative low serum albumin level may be caused by the following reasons. Firstly, long operative time and excessive bleeding during operation may lead to decrease of albumin. Secondly, inflammatory mediators may promote escape of albumin into the extra vascular space. Such mediators may also reprioritize synthesis of hepatic protein in favor of acute phase reactants at the expense of albumin production. Thirdly, Systemic Inflammatory Response Syndrome (SIRS) after surgery may cause increase of capillary endothelial permeability and pathological capillary leakage of serum albumin, especially in some malnourished patients [24]. Vincent et al., [25] believed that complications rates could be reduced when the

serum albumin level exceeded 30 g/l during albumin administration. Therefore, there are multiple factors leading to the decrease of albumin after surgery. It can be treated by strengthening perioperative care and an appropriate albumin administration. There were 71 patients (53.4%) with TNM III in this group. TNM staging was identified as another predictor for serious complications in multivariate analysis (OR=0.08, 95% CI: 0.01~0.63, P=0.016). Patients with advanced stage had reduced functional organ reserve and immunocompromisation. Malnutrition, anemia, weight loss, and hypoproteinemia frequently occurred. Therefore, the incidence of complications in patients with late TNM staging is high [4,8,26]. However, the association between TNM staging and complications needs to be further studied. However, our study has some limitations. Our study did not include long-term complications, influencing patients' quality of life. A retrospective study with small sample size and the presence of several confounding factors were other limitations of this study. Despite these limitations, we believe that the C-D classification is a significant indicator for evaluating complications. Further investigations should be performed with a large-sample, multicenter, randomized prospective cohort to assess the effects of C-D grading and the risk factors for complications.

## Conclusion

The Clavien-Dindo classification for postoperative complication after radical total gastrectomy showed that grade II had the highest incidence, mainly including abdominal infection and abdominal hemorrhage. Moreover, the majority of severe complications were related to anastomotic leakage. Postoperative blood transfusion and postoperative albumin level <30 g/l were identified as independent risk factors for postoperative complications. TNM stage III, N3 stage, and postoperative blood transfusion were independent risk factors for severe complications.

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