Modified Clavien-Dindo Classification to Analyze the Risk Factors of Early Complications after Radical Gastrectomy and the Impact of Complications on Long-Term Prognosis

Jun Ma

Second Affiliated Hospital of Soochow University/Anqing municipal hospital

Ying Wang

Affiliated hospital of Yangzhou university

Shui-hong Yu

Anqing medical and phamaceutiacal college

Chao-pin Zhou

Anqing municipal hospital

Da-tian Wang

Anqing municipal hospital

Dai-bin Tang

Anqing municipal hospital

Guoqin Jiang (✉ guo_qinjiang@126.com)

Second Affiliated Hospital of Soochow University

Yaming Zhang

Anqing municipal hospital

Research

Keywords: Gastric cancer, Radical gastrectomy, Postoperative complications, Modified Clavien-Dindo classification, Risk factors, Prognosis

Posted Date: October 26th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-96107/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background The modified Clavien-Dindo classification system was employed to investigate the occurrence of early complications along with the related risk factors following a radical gastrectomy procedure, with the view of conducting an analysis into the impact of complications on long-term prognosis.

Methods The clinical data of 525 patients who had previously undergone a radical gastrectomy procedure for gastric cancer were analyzed in a retrospective fashion.

Results Postoperative hospital stay: Complication group (17.88 ± 8.472) days, severe complications group (23.10 ± 7.594) days, significantly higher than non-complication group (10.26 ± 1.973) days and non-severe complications group (11.47 ± 4.712) days ($P=0.000 < 0.05$). Multivariate analysis: age (OR = 1.781, $P = 0.013$), preoperative comorbidity (OR = 1.765, $P = 0.020$), blood loss (OR = 2.153, $P = 0.001$), surgical approach (OR = 3.137, $P = 0.000$) were identified as an independent risk factor associated with early complications. Blood loss (OR=13.053, $P=0.013$), type of resection (OR=7.936, $P=0.047$) and nerve involvement (OR=3.670, $P=0.009$) were identified to be independent risk factors for severe complications. Severe postoperative complications (HR=1.595, $P=0.107$) and postoperative complications (HR=1.078, $P=0.670$) were not independent risk factors affecting the 5-year over survival rate.

Conclusion Complications following radical gastrectomy were closely related to age, preoperative comorbidity, blood loss, and surgical approach; severe complications were closely related to blood loss, total gastrectomy, and nerve involvement; complications and severe complications were not found to be independent risk factors associated with long-term survival, that being said, they were significantly prolonged postoperative hospital stay.

Introduction

Surgery represents the first line therapeutic approach for gastric cancer, however postoperative complications, particularly early postoperative complications (such as gastrointestinal leakage, obstruction, bleeding, etc.) have long been earmarked as notable stumbling blocks for surgeons. The Clavien-Dindo classification system is widely used clinical approach¹⁻³. The grading of complications facilitates a more objective evaluation of the severity of the complications. Advantages associated with this method include its simplicity, understandable format, acceptability, as well as a high degree of reproducibility. However, this standard is only suitable for the classification of general adverse events. Surgical-related complications often lack a clear definition as well as a set of diagnostic principles. In 2015, the Japan Clinical Oncology Group (JCOG) established a special committee to revise the Clavien-Dindo standard aimed at providing a more precise evaluation of surgery-related complications, which led to the formation of the "JCOG postoperative complication standard", which is a modified version of the Clavien-Dindo classification system⁴. The current study set out to conduct a retrospective analysis with the objective of identifying the incidence of early complications and related risk factors in 525 cases of

radical gastric cancer via a modified version of the Clavien-Dindo classification system. The relationship between complications and rate of survival was further evaluated with the overall target of helping to improve prevention as well as early detection of postoperative complications which would ultimately benefit gastric cancer patients.

Materials And Methods

Patients

A retrospective investigation of 525 patients who underwent radical gastrectomy for gastric cancer between October 2010 to September 2015 in relation with the follow-up database of surgical oncology department at the Anqing Municipal Hospital. The study included 387 males and 138 females; mean age (62.5 ± 10.7) years old (range: 16 to 89 years old). Patients and their families signed informed and surgical consent documentation prior to the operation.

Case Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (1) Gastric cancer diagnosed by means of gastroscopy and pathological examination prior to surgery; (2) Patients underwent either laparoscopic operation or open operation. The type of resection included radical total gastrectomy, radical distal gastrectomy or radical proximal gastrectomy; (3) R0 resection and lymph nodes have reached D1 + or D2 dissection; (4) Postoperative complications occurred between the day of the operation to the date of discharge (excluding cases of re-hospitalization after discharge due to postoperative complications); (5) The patient's clinical pathology, complications and follow-up data were complete in nature, in addition to each operation performed by the same group of surgeons.

Exclusion criteria: (1) Preoperative examination and intraoperative exploration of distant tumor metastasis, which could not be achieved by radical resection; (2) Patients who had received neoadjuvant radiotherapy and chemotherapy and intraoperative chemotherapy (including intraperitoneal hyperthermic chemotherapy) prior to surgery; (3) Abdominal aortic lymph node dissection (PAND); (4) Pylorus-preserving gastrectomy (PPG); (5) Presence of other simultaneous malignant tumors; (6) Remnant gastric carcinoma; (7) Emergency surgery.

Observation Index

(1) The occurrence of early postoperative complications, and the application of the modified Clavien-Dindo standard for classification (2) General clinical indicators: gender, age, body mass index (BMI), smoking history, drinking history, previous abdominal surgery history, nutrition risk screening 2002(NRS2002), Charlson comorbidity index (CCI), American Association of Anesthesiologists (ASA) Score, preoperative comorbidities (heart disease, cerebrovascular disease, hypertension, diabetes, chronic obstructive pulmonary disease(COPD), cirrhosis, immune system diseases, history of previous malignant tumors, any of the aforementioned comorbidities); (3) Preoperative laboratory related indicators: albumin, hemoglobin (Hb), carcinoembryonic antigen level (CEA), CA199, alpha-fetoprotein (AFP); (4) surgical

related indicators: tumor location, intraoperative blood loss, Operation time, perioperative blood transfusion, surgical approach, type of resection, combined organ resection (intraoperative exploration considers sT4b combined with organ resection, concurrent cholecystectomy or abdominal benign tumor resection); (5) Pathology-related indicators: pathological T stage (pT), pathological N stage (pN), pathological TNM stage (pTNM), Number of retrieved Lymph node, tumor size, histological differentiation, intravascular embolus, nerve Involvement. (6) Survival after operation, calculation of the 5-year survival rate (OS, overall survival).

Judgement Standard

Nutrition risk screening 2002(NRS2002) ⁵ASA score ⁶modified Clavien-Dindo classification ⁴, Grade $\geq$ I is defined as postoperative complications, grade $\geq$ IIIa defined as severe postoperative complications, in the event of multiple complications in the same patient, the highest grade prevails, Charlson comorbidity index (CCI) ⁷TNM stage is based on the 8th edition of the International Union Against Cancer (UICC) ⁸.

Statistical Analysis

SPSS 17.0 software was employed for statistical analysis purposes. Measurement data were expressed as the mean $\pm$ standard deviation, the comparison of count data and single factor analysis were performed by χ^2 test or Fisher's exact probability test. The variables with statistical significance in univariate analysis were included in the multivariate logistic regression (backward stepwise regression method applied, entering the level of 0.05, excluding the level of 0.1) for data analysis. Kaplan-Meier method was used to analyze the survival status of patients, and COX model was used to analyze the prognostic factors (stepwise regression method, entering level 0.05, excluding level 0.1). A value of $P < 0.05$ was considered to be indicative of statistically significant difference.

Results

Case Characteristics

Patient characteristics are depicted in **Table 1**

Characteristics	Total = 525
Age(year)	62.5 ± 10.7
Gender(Male/Female)	387/138
BMI	21.3 ± 3.1
History of previous abdominal surgery (%)	51(9.7%)
Preoperative comorbidities (%)	123(23.4%)
Hypertension	88(16.8%)
Diabetes	19(3.6%)
Heart disease	12(2.2%)
Cerebrovascular disease	10(1.9%)
COPD	8(1.5%)
Immune system diseases	6(1.1%)
Cirrhosis	6(1.1%)
History of malignant tumor	4(0.8%)
Combination of 2 or more	29(5.5%)
Multiple organ resection (%)	39(7.4%)
Combined organectomy	12(2.2%)
Cholecystectomy	18(3.4%)
Abdominal benign tumor resection	9(1.7%)
ASA score(1/2/3/4/5)	365/124/36/0/0
Histological differentiation (high/middle/low)	35/97/393
Modified Clavien-Dindo classification (1/2/3a/3b/4a/4b/5)	25/69/15/4/1/0/0
Tstage (T1a/T1b/T2/T3/T4a/T4b)	56/37/60/2/350/20
Nstage (N0/N1/N2/N3a/N3b)	204/94/97/96/34
TNM stage (1a/1b/2a/2b/3a/3b/3c)	83/41/16/91/161/94/39
Tumor location (upper/middle/lower/two sites and above)	187/156/166/16
tpye of resection (total/proximal/distal)	330/186/9

Characteristics	Total = 525
Surgical approach (laparotomy/open)	404/121
Extent of Lymph node dissection(D1+/D2)	103/422
Number of retrieved Lymph node (pieces)	22.9 ± 9.8
Postoperative hospital stay (days)	11.9 ± 5.3
Operation time(min)	238.6 ± 51.9
Blood loss (ml)	187.3 ± 141.2
Days of first flatus	4.4 ± 1.4

Modified Clavien-Dindo Classification and Postoperative Hospital Stay for Early Postoperative Complications

525 cases of early complications after radical gastrectomy had 114 cases with Clavien-Dindo grade $\geq$ I grade, accounting for 21.7% (114/525) of the total cases. There were 20 cases of Clavien-Dindo grade $\geq$ IIIa in early postoperative severe complications, accounting for 17.5% (20/114) of postoperative complications and 3.8% (20/525) of the total cases. See Table 2 for details. Severe postoperative complications required 4 repeat procedures under general anesthesia (2 cases of abdominal bleeding, 1 case of intestinal obstruction, and 1 case of drainage tube incarceration). Postoperative hospital stay in the complication group was (17.88 ± 8.472) days, in severe complication group was (23.10 ± 7.594) days, significantly higher than the non-complication group (10.26 ± 1.973) days and non-severe complications group (11.47 ± 4.712) days ($P = 0.000 < 0.05$) (Fig. 1).

Table 2 Modified Clavien-Dindo classification

Complication	NO.of cases	Modified Clavien-Dindo classification						
		I	II	IIIa	IIIb	IVa	IVb	V
pneumonia	42	6	36					
Postoperative gastrointestinal symptoms (bloating and reflux)	12	11	1					
Duodenal stump leakage	10			10				
Abdominal bleeding	5		3		2			
Gastroparesis	4		4					
Chylous leakage	4	2	2					
Anastomotic stenosis	4	2	2					
Ascites	4	2	2					
Cholecystitis	3		3					
Fever	3		3					
Abdominal Infection	3		2	1				
Abnormal liver function	3		3					
Intestinal obstruction	2		1		1			
Anastomotic bleeding	2		2					
Arrhythmia	2		2					
Pleural effusion	2			2				
Liver abscess	1		1					
Urinary retention	1	1						
Pneumothorax				1				
Esophageal jejunum Anastomotic leakage	1			1				
Heart failure	1					1		
Thrombus	1		1					
Pancreatic leakage	1		1					
Drainage tube incarceration	1				1			
Fat liquefaction	1	1						
Total	114	25	69	15	4	1	0	0

Single Factor Analysis of Early Postoperative Complications

As shown in Table 3–6, age ($P = 0.002$), ASA score ($P = 0.003$), CCI ($P = 0.031$), preoperative comorbidity ($P = 0.005$), blood loss ($P = 0.003$), surgical approach ($P = 0.001$) are related to postoperative early complications. Gender ($P = 0.027$), blood loss($P = 0.001$), operation time ($P = 0.029$), type of resection ($P = 0.002$), pT stage ($P = 0.015$), pTNM stage ($P = 0.027$), nerve involvement ($P = 0.000$) is related to the occurrence of serious complications in the early postoperative period.

Table 3 General clinical indicators

gender, age, body mass index (BMI), smoking history, drinking history, previous abdominal surgery history, nutrition risk screening 2002(NRS2002), Charlson comorbidity index (CCI), American Association of Anesthesiologists (ASA) Score, preoperative comorbidity

Factors	Complications(%)	<i>P</i> value	Severe complications(%)	<i>P</i> Value
Gender		0.993		0.027
Male	21.7(84/387)		4.9(19/387)	
Female	21.7(30/138)		0.7(1/138)	
Age(year)		0.002		0.102
≥ 70	30.5(46/151)		6.0(9/151)	
< 70	18.2(68/374)		2.9(11/374)	
BMI(kg/m ²)		0.149		1.000
≥ 24	27.7(23/83)		3.6(3/83)	
< 24	20.6(91/442)		3.8(17/442)	
Smoking history		0.855		0.306
Yes	22.3(27/121)		5.8(7/121)	
No	21.5(87/404)		3.2(13/404)	
Drinking history		0.720		0.852
Yes	20.2(17/84)		4.8(4/84)	
No	22.0(97/441)		3.6(16/441)	
History of abdominal surgery		0.741		1.000
Yes	23.5(12/51)		3.9(2/51)	
No	21.5(102/474)		3.8(18/474)	
NRS2002 score		0.369		0.395
≥ 4	23.3(62/266)		4.5(12/266)	
< 4	20.1(52/259)		3.1(8/259)	
CCI		0.031		0.097
≥ 2	24.4(87/357)		4.8(17/357)	
< 2	16.1(27/168)		1.8(3/168)	
ASA score		0.003		0.908
≥ 3	41.7(15/36)		5.6(2/36)	

Factors	Complications(%)	<i>P</i> value	Severe complications(%)	<i>P</i> Value
1 or 2	20.2(99/489)		3.7(18/489)	
preoperative comorbidity		0.005		0.130
Yes	30.9(38/123)		6.5(8/123)	
No	18.9(76/402)		3.0(12/402)	

Table 4 Preoperative laboratory indicators

Albumin, hemoglobin (Hb), carcinoembryonic antigen level (CEA), CA199, alpha-fetoprotein (AFP);

Factors	Complications(%)	<i>P</i> value	Severe complications(%)	<i>P</i> value
Albumin		0.654		0.508
≥ 35	22.1(95/430)		4.2(18/430)	
< 35	20.0(19/95)		2.1(2/95)	
Hemoglobin		0.983		0.721
≥ 110	21.7(67/309)		3.6(11/309)	
< 110	21.8(47/216)		4.2(9/216)	
CEA		0.886		1.000
≥ 6.5	22.4(15/67)		4.5(3/67)	
< 6.5	21.6(99/458)		3.7(17/458)	
CA199		0.227		0.735
≥ 34	26.9(21/78)		5.1(4/78)	
< 34	20.8(93/447)		3.6(16/447)	
AFP		0.436		0.216
≥ 7	30.4(7/23)		8.7(2/23)	
< 7	21.3(107/502)		3.6(18/502)	

Table 5 Surgery-related indicators

tumor location, blood loss, operation time, perioperative blood transfusion, surgical approach, type of resection, multiple organ resection

Factors	Complications(%)	P value	Severe complications(%)	P value
Tumor location		0.214		1.000
≥ 2	6.3(1/16)		0.0(0/16)	
1	22.2(113/509)		3.9(20/509)	
blood loss (ml)		0.003		0.001
≥ 150	26.1(81/310)		6.1(19/310)	
< 150	15.3(33/215)		0.5(1/215)	
operation time(min)		0.098		0.029
≥ 235	24.6(66/268)		5.6(15/268)	
< 235	18.7(48/257)		1.9(5/257)	
Blood transfusion		0.575		0.911
Yes	24.3(17/70)		2.9(2/70)	
No	21.3(97/445)		4.0(18/445)	
Surgical approach		0.001		1.000
open	25.0(101/404)		3.7(15/404)	
Laparotomy	10.7(13/121)		4.1(5/121)	
Type of resection		0.608		0.002
Total gastrectomy	22.4(74/330)		5.8(19/330)	
Subtotal gastrectomy	20.5(40/195)		0.5(1/195)	
Multiple organ resection		0.154		0.990
Yes	30.8(12/39)		5.1(2/39)	
No	21.0(102/486)		3.7(18/486)	

Table 6 Pathology-related indicators

pathological T staging (pT), pathological N staging (pN), pathological TNM staging (pTNM), Number of retrieved Lymph node, tumor size, Histological type, intravascular emboli, nerve involvement..

Factors	Complications(%)	<i>P</i> value	Severe complications(%)	<i>P</i> value
pT stage		0.679		0.015
T1 + T2	22.9(35/153)		0.7(1/153)	
T3 + T4	21.2(79/372)		5.1(19/372)	
pN stage		0.482		0.123
N0 + N1	22.8(68/298)		2.7(8/298)	
N2 + N3	20.3(46/227)		5.3(12/227)	
pTNM stage		0.645		0.027
I stage + II stage	20.8(48/231)		1.7(4/231)	
III stage	22.4(66/294)		5.4(16/294)	
Number of retrieved Lymph node		0.101		0.776
≥ 15	20.2(85/420)		3.6(15/420)	
< 15	27.6(29/105)		4.8(5/105)	
Tumor size(cm)		0.944		0.146
≥ 4	21.8(62/284)		4.9(14/284)	
< 4	21.6(52/241)		2.5(6/241)	
Histological type		0.569		0.111
High or middle differentiation	23.5(31/132)		1.5(2/132)	
Poorly differentiated	21.1(83/393)		4.6(18/393)	
Intravascular tumor thrombus		0.345		0.141
Yes	20.1(57/283)		4.9(14/283)	
No	23.6(57/242)		2.5(6/242)	
Nerve involvement		0.141		0.000
Yes	25.8(40/155)		8.4(13/155)	
No	20.0(74/370)		1.9(74/370)	

Multi-Factor Analysis of Early Postoperative Complications

The statistically significant variables included in the univariate analysis were included in the multivariate logistic regression analysis (Table 7), age (OR = 1.781, $P = 0.013$), preoperative complications (OR = 1.765, $P = 0.020$), blood loss (OR = 2.153, $P = 0.001$), surgical approach (OR = 3.137, $P = 0.000$) were independent risk factors for early postoperative complications. Blood loss (OR = 13.053, $P = 0.013$), Type of resection (OR = 7.936, $P = 0.047$), and nervous system involvement (OR = 3.670, $P = 0.009$) were independent risk factors for early postoperative severe complications.

Table 7 Multi-factor analysis of early postoperative complications and severe complications.

Variables	Complications			Severe complications		
	P	OR	95%CI	P	OR	95%CI
Age(≥ 70 year)	0.013	1.781	1.132–2.802	-	-	-
Preoperative complications	0.02	1.765	1.094–2.846	-	-	-
Blood loss (150 ml)	0.001	2.153	1.354–3.423	0.013	13.053	1.712–99.497
Surgical approach	< 0.001	3.137	1.665–5.911	-	-	-
Type of resection	-	-	-	0.047	7.936	1.032–61.044
Nervous system involvement	-	-	-	0.009	3.67	1.392–9.676
Constant	< 0.001	0.048		< 0.001	< 0.001	

Analysis of 5-Year Survival Rate of Early Postoperative Complications Based on Modified Clavien-Dindo Classification

The end-point follow-up time was June 2020, with the overall 5-year survival rate found to be 60.6%. As shown in Fig. 2, the 5-year survival rate after Clavien-Dindo classification was grade I 59.3%, grade II 56.3%, grade III and above 35%, and the 5-year overall survival rates of the complication group and the non-complication group were 53.2% and 62.6%, respectively, with no difference ($p = 0.104 > 0.05$). As shown in Fig. 3, the 5-year overall survival rates of the postoperative severe complication group and the non-severe complication group were 35% and 61.8%, respectively ($p = 0.004 < 0.05$).

Analysis of the Relationship Between Complications and Prognosis with COX Multi-Factor Model

As shown in Table 8, TNM stage (HR = 3.115, P = 0.000), preoperative comorbidity (HR = 1.534, P = 0.004) are independent risk factors that affect the 5-year overall survival rate after surgery.

Severe postoperative early complications (HR = 1.595, P = 0.107) and postoperative early complications (HR = 1.078, P = 0.670) were not detected as independent risk factors affecting the 5-year overall survival rate after surgery.

Table 8 Analysis of the relationship between complications and prognosis with COX multi-factor model

Variables	P	OR	95%CI
TNM stage	< 0.001	2.917	2.122–4.011
Preoperative comorbidity	.016	1.448	1.073–1.956
Severe complications	0.107	1.595	0.904–2.815
Complications	0.670	1.078	0.764–1.520
Histology type	0.363	1.174	0.831–1.660
Age	0.177	1.217	0.915–1.620
Gender	0.659	1.073	0.785–1.468

Discussions

As the more commonly employed approach, the general Clavien-Dindo classification standard for postoperative complications was initially proposed by Professor Pierre-Alain Clavien of the University Hospital of Zurich in Switzerland in 1992 ¹, which was based on a survey of 6336 patients, predominantly based on "life-threatening" and "permanent disability" grades, divided into 4 grades according to postoperative adverse events. In 2004, Professors Dindo and Clavien of the University Hospital of Zurich, Switzerland revised the grading standards. This revision was essentially premised upon a "complication-based treatment" classification and was divided into 5 grades according to postoperative adverse events ². The advantages to this revision included added simplicity and ease of use, allowing for a wider use in the surgical clinical field ³. However, this classification lacks consistency in terms of its definition of postoperative adverse events of different surgical procedures, which may lead to bias in the classification of complications in specific work. Therefore, in 2015, the Japanese Clinical Oncology Collaboration Group created the "JCOG Postoperative Complication Standard" based on the Clavien-Dindo grading system and the National Cancer Institute CTCAE adverse event grading standard. ⁴ This standard was comprised of 72 surgical complications (emphasis includes 17 gastrointestinal-related complications, 13 infection-related complications, and 6 thoracic surgery-related complications), listing the common

adverse events associated with surgical procedures and optimizes them. The classification of the surgical complications is clearly defined, allowing for a more unified standard, suitable for the evaluation of early postoperative complications. For example, the placement of a gastric tube and a small intestinal decompression tube after intestinal obstruction after surgery are grade I and II complications, respectively, and the postoperative digestive tract leakage puncture or replacement of the drainage tube listed as grade IIIa complications. The current study adopted the JCOG postoperative complication standard, that is, the modified Clavien-Dindo classification as the standard for evaluating postoperative complications.

Our study highlighted 114 cases of early complications after radical gastrectomy (Clavien-Dindo $\geq$ I), 20 cases of which were early postoperative severe complications Clavien-Dindo grade $\geq$ IIIa. No postoperative deaths took place. Pneumonia, gastrointestinal symptoms (abdominal distension and reflux) after operation, duodenal stump leakage, abdominal hemorrhage, gastroparesis, chylous leakage, and ascites were still common early complications after radical gastrectomy. The most common complication associated with radical gastric cancer was pneumonia (42 cases), taking place at a rate of 8% (42/525), which is in line with existing literature results⁹. Reasons for analysis may include: 1. The average age of patients is (62.5 $\pm$ 10.7) years old, the proportion of patients $\geq$ 70 years old is 28.8%, the lung elasticity and chest wall compliance of elderly patients are naturally reduced, the amount of residual alveolar gas is increased, elderly patients tend to be more prone to respiratory muscle fatigue and upper respiratory tract obstruction¹⁰. 2. The proportion of males in this data set was 73.7% (387/525), which is essentially consistent with the data the geographical Cancer Registry¹¹; A greater proportion of male patients smoke (117/387), which heightens their chances of falling victim to postoperative pneumonia¹². 3. Approximately 76% (404/525) of our patients underwent open operations. The post-operative pain associated with this approach often prevents patients from clearing sputum effectively and can affect the process of deep breathing, ultimately affecting diaphragm activity, leading to a greater degree of difficulty in recruiting the lower lobes of the lung, all of which markedly elevates the chances of infection¹³. 4. The proportion of total gastrectomy in this study was high, accounting for approximately 62.9% (330/525). Previous studies have highlighted pneumonia as a notable post-operative risk associated with total gastrectomy¹⁴. 5. The author's institution often ensures the routine placement of gastric tube and jejunal nutrition tube after surgery, which may contribute to the occurrence of lung infection.

The most serious postoperative complications included duodenal stump leakage (10 cases), accounting for 8.8% (10/114) of the total postoperative complications and 50% (10/20) of the severe complications, consistent with existing literature¹⁵. Reasons: 1. Related to the age of preoperative patients, Filip B and others reviewed 189 cases of radical gastric cancer surgery through a single center and identified age as an independent risk factor for postoperative surgical complications¹⁶; 2. The preoperative comorbidity rate was 23.4% (123/525), while the preoperative multiple comorbidity rate was 5.5% (29/525). Paik et al. concluded that preoperative multiple comorbidity was the main reason of postoperative duodenal stump fistula.¹⁷; 3. In the past, the stump was only reinforced, but not embedded. Following a review and technical improvement, the stump was embedded, which allowed for a marked reduction in leakage from

the duodenal stump.^{18,19} Interestingly, all duodenal stump leakage took place after total gastrectomy in our institution, no duodenal stump leakage occurred after distal gastrectomy, which may relate to some patients with distal gastrectomy using of a double cannula for preventive irrigation. All duodenal stump leakage was treated by double cannula irrigation or puncture and drainage, with no additional surgery required.

In addition, no jejunum-jejunum anastomosis and stump leakage occurred after total gastrectomy, indicating that Roux-and-y jejunal anastomosis is not associated with certain complications such anastomotic leakage. It is worth noting that intra-abdominal hemorrhage should attract the attention of the surgeon, as 2 of the 5 cases of intra-abdominal hemorrhage resulted in the requirement of additional surgery, which may be associated with increased blood clots in the abdominal cavity after hemorrhage. This can lead to repeated exudation and consumption of platelets. Two cases of anastomotic hemorrhage were flushed through the stomach tube and injected locally with hemostatic drugs, suggesting that the prognosis of anastomotic hemorrhage was superior to intra-abdominal hemorrhage.

Through multi-factor analysis, it was identified that blood loss was a twofold independent risk factor for postoperative complications and severe postoperative complications, which was in line with existing literature reports^{20,21}. Reasons: 1. Excessive bleeding during surgery not only affects the stability of intraoperative hemodynamics, but also may affect the mood of the surgeon, which is not conducive for the high-quality completion of the operative procedure. 2. Postoperative anemia patients often display a poor general condition and a lesser threshold for stress, which is not conducive for the healing of an anastomosis or stump²². 3. Anemia can negatively influence the immune system, and lead to insufficient tissue oxygenation, low protein levels, and increase the risk of infection²³.

The current study identified age as an independent risk factor for postoperative complications. Firstly, elderly patients often have reduced lung function prior to surgery, poor sputum excretion after surgery, and it's worth noting that upper abdominal surgical wounds are likely to affect the diaphragm, resulting in an increased incidence of lung infections. Through retrospective analysis of 750 cases of gastric cancer surgery, Miki Y et al reported age as an independent risk factor for postoperative lung infection¹⁰. Second, elderly patients with gastric cancer were often accompanied by hypoproteinemia, prone to anastomosis and stump leakage¹⁶. Finally, elderly patients exhibited a high ASA score prior to surgery, which was closely linked with the occurrence of complications. Nelen SD et al. found through a gastric cancer cohort study that the ASA score of elderly patients was significantly higher than that of the younger group. In addition, patients over 70 years old were risk factors for postoperative complications²⁴.

Comorbidity prior to surgery represents an independent risk factor for postoperative complications. During the present study, the combination of complications and hypertension was up to 16.8% (88/525). Filip B et al. reviewed 189 cases of radical gastric cancer surgery through a single center and found that hypertension was a dual independent risk factor for postoperative complications and surgical complications¹⁶, Choudhuri AH et al. analyzed 137 cases of gastrointestinal leak after gastrointestinal

surgery and found that hypertension was also an independent risk factor for gastrointestinal leak ²². In addition, COPD as well as coronary heart disease contribute to an increased probability of postoperative complications. Coimbra FJF and others retrospective analyzed of 1223 patients with gastric cancer surgery, highlighting hypertension, COPD, and diabetes as the most common comorbidities before surgery, while COPD, coronary heart disease were independent risk factors for postoperative complications ²⁵. Finally, diabetic patients are often prone to triggering a greater stress response as well as an increase in insulin resistance, making it difficult to control blood glucose, which can easily lead to complications such as incision infection, poor healing, and anastomotic leakage. Wang JB and others retrospectively analyzed 1657 cases of laparoscopic-assisted total gastrectomy, this passage found that diabetes was closely related to the occurrence of postoperative anastomotic leakage, abdominal bleeding, and lung infection ²⁶.

Open surgery is an independent risk factor for postoperative complications, similar to the results of other literature ^{13,27}. Reasons behind this include: 1. Following laparoscopic, surgery patients recovery is faster, with a significantly less deal of pain experienced, which is conducive for deep breathing, effective sputum excretion, and a greater ability to use lung capacity in a postoperative state, reducing the probability of lung infection. After laparoscopic surgery, patients often quickly recover intestinal function. They can take food and get out of bed early, increase nutrition and immunity, reducing the chances of ascites occurring due to hypoproteinemia, and diminishes the probability of venous thrombosis and atelectasis taking place, both of which have been strongly associated with long-term bed rest.

In addition, total gastrectomy was an independent risk factor for severe postoperative complications. Compared with subtotal gastrectomy, the range of total gastrectomy is larger, and the number of anastomoses is increased ²⁴. 1. Our institution often performs routine gastrectomy for D2 lymph node dissection for advanced gastric cancer, so the incidence of postoperative chylus leak increases. 2. As per the Japanese Gastric Cancer Protocol, as part of the D2 dissection, the splenic hilar lymph nodes were routinely cleaned in my unit. When performing splenic hilar lymph node dissection, the blood vessels are easily damaged which can also lead to splenic bleeding; 3. Due to the anatomic position of the esophagus, it is difficult to reconstruct the digestive tract, particularly when performing anastomosis of the esophagus and jejunum. In certain instances the anastomosis cannot be strengthened, which can lead to anastomotic bleeding and anastomotic leakage; 4. When the splenic hilar and mediastinal lymph nodes are removed, the incidence of pleural effusion and pneumothorax increased (in this group, 1 case of pneumothorax and 2 cases of pleural effusion be performed pleural drainage after total gastrectomy).

Interestingly, the current study detected that pathological nerve involvement is related to the occurrence of serious postoperative complications. The specific reason is not clear and requires further investigation with a larger sample size.

The 5-year survival period of the severe complication group was only 35%, which was different from that of the non-severe complication group (61.8%), but the COX model suggested that severe complications were not independent risk factors affecting the prognosis, which was inconsistent with some literature

results.^{28,29} We believe that the reasons may be: 1. Our inclusion of variables that may affect prognosis (age, gender, histological type, TNM stage, preoperative comorbidity) into the COX model. The final preoperative comorbidity and TNM stage are independent risk factors that affect the prognosis, so they offset the risk of severe complications. 2. No deaths took place in the severe complication group, and the end event of OS was death, thus severe complications may not be the cause of an independent prognostic risk factors. 3. COX multivariate analysis showed that severe postoperative complications (HR = 1.595, P = 0.107), although P > 0.05, however the distance from clinical significance is small, which may be related to the small sample size of the group of severe complications (n = 20). 4. Gastrointestinal complications (such as nausea, gastrointestinal reflux, anastomotic stenosis) in the non-severe complications group may lead to poor postoperative nutritional status and potentially affect long-term prognosis.

The advantages of our study include: The document database was registered by a special person since October 2010, and someone regularly checked to ensure the authenticity and correctness of the data, 2. Strictly grade the complications in accordance with the improved Clavien-Dindo complication standard. All staff in the department participate in the follow-up of patients and centrally register and update the data, further enhancing the quality of the database.

There were certain limitations faced during the investigation: 1. Due to the high population mobility in China and the fact that some rural areas have are not conducive for timely follow up, (by telephone, correspondence, household registration, internet, etc.). Additionally, the time and location of tumor recurrence and metastasis in some patients are difficult to record, so only the overall survival OS was recorded. 2. The aim of the current study was to investigate the occurrence of early postoperative complications, and to minimize the confounding factors via inclusion and exclusion criteria through the use of a retrospective descriptive study, which by nature has its own limitations. The research evidence is low, and it needs to be further confirmed by a multi-center, large-sample prospective cohort study. 3. The study showed that there was no difference in survival between the early postoperative severe complications group and the non-severe complications group, which may be related to the small sample size of the severe complications group (n = 20), which needs to be confirmed in a larger sample size. 4. This study utilized the definition of 'early postoperative' from surgery until the initial hospital discharge time, with some patients having complications after discharge, thus were not included in the study.

Conclusion

Taken together, age, preoperative comorbidity, blood loss, and open surgery represent independent risk factors associated with early complications after radical gastrectomy. Total gastrectomy, blood loss, and nerve involvement are independent risk factors for early postoperative severe complications. Although early postoperative complications are not independent risk factors for poor prognosis, they can consequently lead to a significantly elongated postoperative hospital stay. We recommend that the surgeon aims to minimize the occurrence of early postoperative complications, which can help shorten

the length of hospital stay, increase bed turnover rate, reduce the economic burden of patients, and ultimately improve patient quality of life.

Declarations

Ethic approval and consent to participate

The study was approved by the medical ethical committee of The Affiliated AnQing Municipal Hospital of Anhui Medical University, China. All patients provided written informed consent.

The Medical Ethical Committee of AnQing Municipal Hospital

Item Demonstrate Report

(Original)

Approval number: Medical ethic (2020) 86th

Item Reporter: Jun Ma

Item Title: **Modified Clavien-Dindo Classification to Analyze the Risk Factors of Early Complications after Radical Gastrectomy and the Impact of Complications on Long-Term Prognosis**

Department: Surgical Oncology

1, The medical ethical committees of AnQing municipal hospital demonstrate this item, and especially discuss the three points seriously, as follows:

- The rights and benefits of participators
- Ensure all participators write informed consent
- Tell all participators the risks and benefits

2, The medical ethical committees of AnQing municipal hospital approve to executive this item. Please use those materials approved by medical ethical committees, such as informed consent, questionnaire and introduction letters.

3, If the item need revise, please inform the medical ethical committees, the revise item can executive after the new item approved by the medical ethical committees, the revise contents and reasons are serve as a record.

4, If find some side effects during executive this item, please report the medical ethical committees immediately.

Date: July, 29, 2020

The Medical Ethical Committee of

AnQing Municipal Hospital

Chariman of committee:

Date:Aug,4,2020

Consent for publication

In cases where images are entirely unidentifiable and there are no details on individuals reported within the manuscript, consent for publication of images may not be required.

Availability of data and materials

All data generated or analysed during this study are included in this published article [and its supplementary information files]

Acknowledgments

The authors would like to acknowledge the helpful comments on this paper received from the reviewers.

Author Contributions

J.M. and Y.W. conceived and designed research; J.M., Y.W. and S.H.Y. performed experiments; S.H.Y., C.P.Z. and D.T.W. analyzed data; D.B.T. and G.Q.J. interpreted results of experiments; Y.M.Z. prepared figures; J.M., Y.W. and S.H.Y. drafted manuscript; H.Z. edited and revised manuscript; J.M., Y.W., S.H.Y., C.P.Z., D.T.W., D.B.T., G.Q.J. and Y.M.Z. approved final version of manuscript.

Funding

This work was supported by grants from the Suzhou Health Planning Commission's Key Clinical Diagnosis and Treatment Program (LCZX201606), National Natural Science Foundation of China (81873730) and the Jiangsu Women and Children Health Key Discipline Program (FXK201758).

Compliance with Ethical Standards

Conflict of Interest

The authors declare that they have no conflict of interests.

References

1. Clavien PA, Sanabria JR, Strasberg SM. Proposed classification of complications of surgery with examples of utility in cholecystectomy. *Surgery*. 1992;111:518-526.

2. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg.* 2004;240:205-213.
3. Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo classification of surgical complications: five-year experience. *Ann Surg.* 2009;250:187-196.
4. Katayama H, Kurokawa Y, Nakamura K, et al. Extended Clavien-Dindo classification of surgical complications: Japan Clinical Oncology Group postoperative complications criteria. *Surg Today.* 2016;46:668-685.
5. Kondrup J, Allison SP, Elia M, et al. ESPEN guidelines for nutrition screening 2002. *Clin Nutr.* 2003;22:415-421.
6. ASo A. ASA physical status classification system. *ASA House of Delegates.* 2014.
7. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. *J Clin Epidemiol.* 1994;47:1245-1251.
8. NCCN. The NCCN gastric cancer clinical practice guidelines in oncology(version 3.2018)[EB/OL]. *Fort Washington NCCN.* 2018;2018.
9. Gertsen EC, Brenkman HJF, Seesing MFJ, et al. Introduction of minimally invasive surgery for distal and total gastrectomy: a population-based study. *Eur J Surg Oncol.* 2019;45:403-409.
10. Miki Y, Makuuchi R, Tokunaga M, et al. Risk factors for postoperative pneumonia after gastrectomy for gastric cancer. *Surg Today.* 2016;46:552-556.
11. Chen W, Zheng R, Zeng H, Zhang S. The incidence and mortality of major cancers in China, 2012. *Chin J Cancer.* 2016;35:73.
12. Rei J, Lareiro S, Fernandes P, et al. Uniportal Video-assisted Thoracic Surgery Anatomical Resections - Does Previous Tobacco Exposure Adversely Influence Post-Operative Outcomes? *Rev Port Cir Cardiorac Vasc.* 2019;26:121-125.
13. Berlth F, Plum PS, Chon SH, et al. Total minimally invasive esophagectomy for esophageal adenocarcinoma reduces postoperative pain and pneumonia compared to hybrid esophagectomy. *Surg Endosc.* 2018;32:4957-4965.
14. Ntutumu R, Liu H, Zhen L, et al. Risk factors for pulmonary complications following laparoscopic gastrectomy: A single-center study. *Medicine (Baltimore).* 2016;95:e4567.
15. Ramos M, Pereira MA, Barchi LC, et al. Duodenal fistula: The most lethal surgical complication in a case series of radical gastrectomy. *Int J Surg.* 2018;53:366-370.
16. Filip B, Toma C, Buna-Arvinte M, et al. Impact of Surgery and Early Postoperative Outcomes After Radical Gastrectomy for Cancer. *Chirurgia (Bucur).* 2018;113:478-485.
17. Paik HJ, Lee SH, Choi CI, et al. Duodenal stump fistula after gastrectomy for gastric cancer: risk factors, prevention, and management. *Ann Surg Treat Res.* 2016;90:157-163.
18. Orsenigo E, Bissolati M, Socci C, et al. Duodenal stump fistula after gastric surgery for malignancies: a retrospective analysis of risk factors in a single centre experience. *Gastric Cancer.* 2014;17:733-744.

19. Kim MC, Kim SY, Kim KW. Laparoscopic Reinforcement Suture (LARS) on Staple Line of Duodenal Stump Using Barbed Suture in Laparoscopic Gastrectomy for Gastric Cancer: a Prospective Single Arm Phase II Study. *J Gastric Cancer*. 2017;17:354-362.
20. Wakahara T, Ueno N, Maeda T, et al. Postoperative morbidity in elderly patients after gastric cancer surgery. *Ann Gastroenterol*. 2018;31:621-627.
21. Ishino Y, Saigusa S, Ohi M, et al. Preoperative C-reactive protein and operative blood loss predict poor prognosis in patients with gastric cancer after laparoscopy-assisted gastrectomy. *Asian J Endosc Surg*. 2014;7:287-294.
22. Choudhuri AH, Uppal R, Kumar M. Influence of non-surgical risk factors on anastomotic leakage after major gastrointestinal surgery: Audit from a tertiary care teaching institute. *Int J Crit Illn Inj Sci*. 2013;3:246-249.
23. Lv H, Yin P, Long A, et al. Clinical characteristics and risk factors of postoperative pneumonia after hip fracture surgery: a prospective cohort study. *Osteoporos Int*. 2016;27:3001-3009.
24. Nelen SD, Bosscha K, Lemmens V, et al. Morbidity and mortality according to age following gastrectomy for gastric cancer. *Br J Surg*. 2018;105:1163-1170.
25. Coimbra FJF, de Jesus VHF, Franco CP, et al. Predicting overall and major postoperative morbidity in gastric cancer patients. *J Surg Oncol*. 2019;120:1371-1378.
26. Wang JB, Zheng CH, Li P, et al. Effect of comorbidities on postoperative complications in patients with gastric cancer after laparoscopy-assisted total gastrectomy: results from an 8-year experience at a large-scale single center. *Surg Endosc*. 2017;31:2651-2660.
27. Yang SY, Roh KH, Kim YN, et al. Surgical Outcomes After Open, Laparoscopic, and Robotic Gastrectomy for Gastric Cancer. *Ann Surg Oncol*. 2017;24:1770-1777.
28. Li Z, Bai B, Ji G, et al. Relationship between Clavien-Dindo classification and long-term survival outcomes after curative resection for gastric cancer: A propensity score-matched analysis. *Int J Surg*. 2018;60:67-73.
29. Powell A, Coxon AH, Patel N, et al. Prognostic Significance of Post-Operative Morbidity Severity Score After Potentially Curative D2 Gastrectomy for Carcinoma. *J Gastrointest Surg*. 2018;22:1516-1527.

Figures

Figure 1

Comparison of the length of postoperative hospital stay between complication and no-complication groups (A), between severe complication and non-severe complication groups. **** $P < 0.0001$.

Figure 2

The Kaplan-meier curves were plotted to estimate patient overall five-year survival (A) or according to Clavien-Dindo classification (B).

Figure 3

The Kaplan-meier curves were plotted to estimate patient overall five-year survival according to the presence of complications (A) and according to severe complications and non-severe complications (B).