



Severity and incidence of complications assessed by the Clavien–Dindo classification following robotic and laparoscopic gastrectomy for advanced gastric cancer: a retrospective and propensity score-matched study

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Abstract

Background Robot-assisted gastrectomy (RAG) has been increasingly used for the treatment of advanced gastric cancer (AGC), and many advantages over laparoscopy-assisted gastrectomy (LAG) have been reported. However, its postgastrectomy complications still under investigation and the results remain controversial. This study aimed to objectively assess the incidence and severity of complications following RAG vs. LAG using Clavien–Dindo (C–D) classification and to identify risk factors related to complications. **Methods** Five hundred and twenty-seven patients with AGC who underwent RAG or LAG between January 2016 and May 2018 were enrolled in this study. Complications were categorized according to the C–D classification. The complications following RAG and LAG were compared using one-to-one propensity score matching (PSM) analysis and subgroup analyses. Logistic regression analyses were performed to identify risk factors related to complications.

Results RAG was performed in 251 patients (47.6%) and LAG in 276 patients (52.4%). Before PSM, the RAG group had a smaller tumour size (P = 0.004) and less patients with previous abdominal operation (P = 0.013). After PSM, a well-balanced cohort of 446 patients (223 in each group) was further analyzed. Of interest, the incidence of overall and severe complications (C–D grade \geq IIIa) following the RAG group were significantly fewer than the LAG group (overall, 24.5% vs. 18.8%, P < 0.001; severe, 8.9% vs. 17.5%, P = 0.002). Subgroup analyses showed statistically significant difference were also observed in most stratified parameters. Multivariable analysis identified age \geq 65 years, total gastrectomy, stage T3–T4a, stage II–III, and operation time \geq 250 min as independent predictors of overall complications. Additionally, age \geq 65 years, stage II–III, and operation time \geq 250 min were confirmed as independent risk factors for severe complications. **Conclusions** RAG with D2 lymphadenectomy is feasible and safe for the treatment of AGC in terms of the lower incidence and severity of complications.

Keywords Gastric cancer \cdot Robot-assisted gastrectomy \cdot Laparoscopy-assisted gastrectomy \cdot Postoperative complication \cdot Clavien–Dindo classification

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 Second Clinical Medical College, Lanzhou University, No. 82 Chuiying Gate, Chengguan District, Lanzhou 730030, Gansu, People's Republic of China Gastric cancer (GC) is one of the most common malignant tumors and ranks fourth in cancer incidence and second in cancer mortality around the world [1, 2]. For patients with

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primary advanced gastric cancer (AGC), surgical resection with D2 lymphadenectomy remains the current standard [3]. In recent decades, minimally invasive surgery (MIS), including robotic and laparoscopic surgery, has been rapidly developed and improved, providing a new alternative surgical method for the treatment of AGC and gradually becoming the mainstream surgical treatment for GC. To date, many studies have evaluated the safety and efficacy of robot-assisted gastrectomy (RAG) and laparoscopic-assisted gastrectomy (LAG) in the treatment of AGC and have demonstrated that RAG has many advantages over LAG [4–7]. However, only a few reports have assessed and compared the incidence of complications following RAG with that following LAG using their own subjective criteria, which can easily lead to bias and misjudgment, and it is difficult to compare the incidence of complications between these studies.

In 1992, Clavien et al. [8] established a novel approach for grading the severity and incidence of postoperative complications based on the management of the complications. Dindo et al. [9] revised and improved this grading system in 2004, introducing a new five-scale classification with the aim of presenting an objective, simple, reliable, reproducible, flexible, and applicable way of evaluating postoperative complications irrespective of cultural background. This grading system was more widely applicable after being revised and improved, and it was eventually named the Clavien–Dindo (C–D) classification [8–10]. The C–D classification was subsequently validated and was widely used to systematically evaluate the severity and incidence of complications in many surgical disciplines [11-14]. Although several studies [15–19] evaluated complications following LAG using the C-D classification, complications assessed by the C-D classification in RAG have rarely been well described. Therefore, it is necessary to systematically evaluate the applicability of the C–D classification in RAG.

The aim of the present study was to grade and compare the severity and incidence of complications following RAG with those following LAG using the C–D classification in a propensity score matching (PSM) cohort and to identify the risk factors associated with complications after MIS for AGC.

Materials and methods

Patients and data collection

The study was approved by the institutional review board of Lanzhou General Hospital of Chinese People's Liberation Army, and written informed consent was obtained from all the patients in the study.

We retrospectively collected data from a prospective database of Western China Gastric Cancer Collaboration (WCGCC) group participated by the Department of General Surgery, Lanzhou General Hospital of Chinese People's Liberation Army. Inclusion criteria for the study were: (i) All patients were diagnosed with GC by biopsy; (ii) All patients with pT2-4aN0-3M0 GC were eligible; (iii) All patients were conducted gastrectomy with D2 lymphadenectomy; (iv) The physical status of all patients was evaluated as American Society of Anesthesiology (ASA) Classes I, II, or III; (v) All patients did not undergo radiotherapy or chemotherapy before surgery. (vi) All patients did not undergo splenectomy during surgery. However, patients with benign gastric tumors, gastrointestinal stromal tumors, or combined with other organ malignancies, and residual GC were excluded from this study (Fig. 1). In this study, the pathological stages were classified according to the eighth edition of the American Joint Committee on Cancer TNM Staging System for GC [20, 21]. The division of tumor sites was based on the guidelines of Japanese classification for GC [22]. The work of this study has been reported in accordance with the Strengthening the Reporting of Cohort Studies in Surgery (STROCSS) statement [23].

Operative procedures

The extent of gastrectomy and lymph node (LN) dissection was carried out based on the Japanese gastric



Fig. 1 CONSORT diagram for case enrollment in the present study. *RAG* robot-assisted gastrectomy, *LAG* laparoscopy-assisted gastrectomy, *ASA* American Society of Anesthesiologist

cancer treatment guidelines [3]. The extent of resection was decided according to the tumor location and extent. When the marginal state is suspicious, we performed an intraoperative frozen section to confirm the negative proximal resection margin to ensure R0 resection. The type of reconstruction was determined by the surgeon's experience. Roux-en-Y oesophago-jejunal anastomosis was performed to reconstruct the digestive tract for total gastrectomy, and Billroth II or Roux-en-Y gastro-jejunal anastomosis was applied to distal gastrectomy. The Da Vinci Surgical System (Intuitive Surgical Inc., Sunnyvale, CA) was used for RAG. The surgical procedures for RAG and LAG have been described as before in detail elsewhere [24, 25].

Perioperative management

All patients underwent preoperative evaluation through chest X-rays, electrocardiogram, lung function tests and laboratory tests, etc. Prophylactic use of antibiotics was routinely performed 1 h before surgery and every 3 h during surgery. Blood biochemical tests were routinely performed every 2–3 days after surgery. Patients were given sipping water after the first gastrointestinal ventilation after surgery, and were given liquid diet on the 3rd or 4th day after surgery. Once the patient tolerated a liquid diet for 2 days, a soft diet was given next. When the patient's soft diet is satisfactory and there are no complications, the patient is advised to be discharged. Patients without chemotherapy contraindications were given first adjuvant chemotherapy at the 4th week or 5th week after surgery.

Definition and assessment of complications

The C-D classification was adopted to grade the severity of the postoperative complications for each patient [9, 10, 26]. According to the C-D classification system, the severity of complications was assessed from Grade I to V. The complications assessed in our study mainly included wound problem, bleeding, anastomotic leakage or stenosis, remnant gastric infarction, postoperative ileus, and other complications within 2 months of the initial operation. These complications were divided into overall complications (Grade I–V), serious complications (Grade \geq IIIa) and mortality (Grade V). If the patient had multiple complications, the most serious complication was used for grading. Three independent attending surgeons assessed C–D grade for each patient, and any divergences were solved by discussion. Table 1 shows the details of the complications recorded in our center according to the C-D classification.

Propensity score matching analysis

PSM analysis was used to limit confounders and overcome possible patient selection bias. Propensity scores for all patients were calculated using a logistic regression model based on the following variables: age, gender, BMI, ASA, tumor size, and stage of primary tumor, etc. Variables with p values less than 0.05 between groups were included in the PSM analysis. Calculating the propensity scores also require that any potential clinical confounders be included as covariates regardless of their statistical range [27]. A 1:1 nearest neighbour matching algorithm with an optimal calliper width of 0.2 without replacement was used to match the propensity scores [28–30]. Standardized mean differences (SMD) were assessed to determine whether a sufficient balance was achieved after matching (SMD < 0.1) [31]. This procedure was conducted using the SPSS-R plugin developed by felixthoemmes, wliao229 (https://sourceforge.net/ projects/psmspss/files/).

Statistical analysis

Statistical Package for Social Science version 22.0 (SPSS, Chicago, IL, USA) was used for the calculation of the correlation coefficients. Continuous variables were assessed for normality of distribution using the one-sample Kolmogorov-Smirnov test. Continuous variables with a normal distribution are reported as mean (standard deviations, SD) and compared using Student's t test. Continuous variables that were not normally distributed are expressed as median (inter quartile range, IQR) and analyzed using Mann–Whitney Utest. Categorical variables are expressed as absolute numbers and percentages and compared using Pearson's χ^2 test or Fisher's exact test as appropriate. Multivariable binary logistic regression analysis was performed to identify independent risk factors for complications and odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. A two-sided P value < 0.05 was considered to be statistically significant.

Results

Demographics and surgical outcomes

Among 527 patients with AGC, 251 (47.6%) received RAG and 276 (52.4%) LAG (Fig. 1). The mean age was 57.7 years in the RAG group and 56.8 years in the LAG group (P=0.374). Patient characteristics and surgical outcomes of the two groups are provided in Table 2. RAG patients presented with a smaller tumor size compared to LAG patients (4.5 ± 2.3 vs. 5.1 ± 2.1 , P=0.004). In the RAG group, there were significantly less patients with previous abdominal operation compared to the LAG group (8.8% vs.

Table 1 Classification of the common complications following gastrectomy for AGC according to C-D classification system

Grade	Definition	Examples
I	Any deviation from the normal postoperative course without the need for surgery, endoscopic and radiological interventions, or pharmacologic treatment, excluding antiemetics, antipyretics, analgetics, and diuretics, and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside	Postoperative fever (> 38 °C) Wound problem treated at the bedside Atelectasis requiring physiotherapy Postoperative delayed recovery of bowel movement Transient hepatic function abnormality (total bilirubin≥1.3 mg/dl or/and AST/ALT levels > 100 IU/L) Transient elevation of serum creatinine Vomiting due to gastroesophageal reflux Small amount of ascites not requiring therapy Postoperative subcutaneous emphysema
Π	Pharmacologic treatment with drugs other than those allowed for grade I complications, TPN, and BT	 Infection requiring antibiotic therapy (wound infection, fluid collection, pneumonia, pancreatitis, urinary tract infection, etc) Postoperative bleeding or severe anemia without a relaparotomy but requiring BT Leakage of lymphatics requiring TPN Prolonged postoperative requiring TPN Anastomosis stenosis and leakage not requiring relaparotomy, but requiring TPN Intra-abdominal infection requiring therapy Remnant gastric infarction without a relaparotomy but requiring conservative therapy Transient ischemic attack requiring treatment with anticoagulants Transient postoperative psychological problem
IIIa	Surgical, endoscopic, or radiological intervention (not under general anesthesia)	Closure of wound under local anesthesia Anastomotic stenosis requiring endoscopic treatment Intra-abdominal abscess, anastomosis leakage, duodenal stump fistula, fluid collection, and leakage of lymphatics requiring percu- taneous drainage Pleural effusion requiring percutaneous drainage Intra-abdominal bleeding requiring radiologic and endoscopic intervention
IIIb	Surgical, endoscopic, or radiological intervention (under general anesthesia)	Closure of wound under general anesthesia Intra-abdominal/intra-luminal bleeding and anastomosis leakage requiring relaparotomy Small-bowel perforation requiring relaparotomy Remnant gastric infarction requiring relaparotomy Postoperative ileus requiring relaparotomy
IVa	IC/ICU management (single organ dysfunction)	Anastomosis leakage and intra-abdominal infection treated by relaparotomy requiring IC/ICU management Ischemic stroke requiring IC/ICU management Lung failure due to pneumonia requiring IC/ICU management Postoperative heart failure requiring IC/ICU management Postoperative renal failure requiring IC/ICU management
IVb	IC/ICU management (multiple organ dysfunction)	Multi-organ failure due to anastomosis leakage, intra-abdominal infection, and pneumonia requiring IC/ICU management
V	Death	Death as a result of postoperative complications

AGC advanced gastric cancer, C–D Clavien–Dindo, AST aspartate aminotransferase, ALT alanine aminotransferase, TPN total parenteral nutrition, BT blood transfusion, IC intermediate care, ICU intensive care unit

15.9%, P = 0.013). No significant differences between the two groups were noted in gender, body mass index (BMI), ASA, tumor location, extent of resection, histologic type, or pathological stage (Table 2).

The mean number of retrieved LNs for the RAG group was significantly larger than that for the LAG group $(41.2 \pm 15.1 \text{ vs. } 36.3 \pm 14.8, P < 0.001)$. The time to ambulation $(2.1 \pm 0.6 \text{ vs. } 2.2 \pm 0.4 \text{ days}, P = 0.024)$ and time to

first flatus $(2.6 \pm 0.7 \text{ vs. } 2.9 \pm 0.6 \text{ days}, P < 0.001)$ were significantly shorter in the RAG group. The postoperative hospital stay for patients who underwent RAG was significantly shorter than who underwent LAG $(10.9 \pm 2.8 \text{ vs. } 12.3 \pm 3.2 \text{ days}, P < 0.001)$. The difference between two groups in the operating time, estimated blood loss, and time to first liquid and soft intake was not significant (all P > 0.05, Table 2).

Table 2 Demographics and surgical outcomes of the entire cohort and PSM cohort

Variables	Entire cohort $(n = 527)$		P value	PSM cohort ($n = 446$)		P value
	RAG $(n=251)$	RAG $(n=251)$ LAG $(n=276)$		RAG $(n = 223)$	LAG $(n = 223)$	
Age (years)	57.7±11.2	56.8 ± 11.5	0.374 ^b	57.7 ± 10.9	57.4±11.1	0.774 ^b
Gender			0.114 ^c			0.715 ^c
Male	201 (80.1)	205 (74.3)		183 (82.1)	180 (80.7)	
Female	50 (19.9)	71 (25.7)		40 (17.9)	43 (19.3)	
BMI (kg/m ²)	22.1 ± 3.5	22.4 ± 3.4	0.325 ^b	22.1 ± 3.5	22.2 ± 3.4	0.901 ^b
ASA			0.788°			0.960 ^c
Ι	121 (48.2)	125 (45.3)		115 (51.6)	112 (50.2)	
П	89 (35.5)	102 (37.0)		77 (34.5)	79 (35.4)	
III	41 (16.3)	49 (17.8)		31 (13.9)	32 (14.3)	
Tumor size (cm)	4.5 ± 2.3	5.1 ± 2.1	0.004 ^b	5.0 ± 1.9	5.1 ± 2.2	0.608 ^b
Previous abdominal operation	_	_	0.013 ^c	_	_	0.576 ^c
No	229 (91.2)	232 (84.1)		206 (92.4)	209 (93.7)	
Yes	22 (8.8)	44 (15.9)		17 (7.6)	14 (6.3)	
Tumor location	(0.0)	(0.566 ^c	()	- ((()))	0.930 ^c
Upper third	40 (15.9)	51 (18.5)		38 (17.0)	41 (18.4)	
Middle third	79 (31 5)	92 (33 3)		78 (35 0)	76 (34.1)	
Lower third	132 (52.6)	133 (48 2)		107 (48 0)	106 (47 5)	
Extent of resection	152 (52.6)	155 (10.2)	0.088°	107 (10.0)	100 (17.5)	0 774 ^c
Distal gastrectomy	145 (57.8)	139 (50.4)	0.000	128 (57.4)	125 (56.4)	0.774
Total gastrectomy	145(37.3) 106(42.2)	137 (49.6)		95 (42.6)	98 (43 9)	
Histologic type	100 (42.2)	157 (49.0)	0 134 ^c	<i>))(</i> 42.0 <i>)</i>	90 (4 5.9)	0.645 ^c
Well differentiated	18 (7 2)	21 (7.6)	0.154	17 (7.6)	15 (67)	0.045
Moderately differentiated	75 (29.9)	78 (28 3)		70(314)	68 (30 5)	
Poorly differentiated	135 (53.8)	165 (59.8)		123 (55 2)	132 (59.2)	
Mucinous or signet ring cell carcinoma	23 (9 2)	105 (39.8)		13 (5.8)	8 (3 6)	
nT stage ^a	25 (9.2)	12 (4.5)	0.585°	15 (5.6)	8 (5.0)	0.771°
T2	72 (28 7)	90 (32.6)	0.505	66 (29 6)	68 (30 5)	0.771
T2	12(20.7)	134 (48.6)		111 (49.8)	115 (51.6)	
T4a	53 (21.1)	52 (18.8)		46 (20.6)	40 (17 9)	
nN stage ^a	55 (21.1)	52 (18.8)	0.637°	40 (20.0)	40 (17.9)	0.077 ^c
NO	00(304)	04(341)	0.057	78 (34 8)	80 (25 0)	0.977
NU NI	48 (10.1)	54 (54.1) 52 (10.2)		78 (34.8) 42 (19.8)	80 (33.9) 46 (20.6)	
NI N2	40 (19.1)	51 (19.2)		42 (16.5)	40 (20.0)	
N2	41 (10.5)	JI (16.3)		37 (10.3)	33(13.7)	
N2h	32(12.7)	43(10.3)		34(13.2)	32(14.3)	
nou	51 (12.4)	33 (12.0)	0.0050	33 (14.7)	50 (15.5)	0.000°
ID DIAM stage	65 (25.0)	62 (22.8)	0.895	52 (22.8)	54 (24.2)	0.999
	03 (23.9)	61 (22.8)		33 (23.8) 46 (20.6)	34 (24.2) 48 (21.5)	
	47 (18.7)	01(22.1)		40(20.0)	48 (21.3)	
	43 (17.9)	44 (13.9)		37 (10.0)	30 (10.1)	
	37 (14.7)	43 (13.0)		32 (14.3)	30 (13.3)	
	33 (13.1)	38 (13.8)		31 (13.9)	30 (13.5)	
	24 (9.6)	27 (9.8)	o o coh	24 (10.8)	25 (11.2)	o o tch
Operating time (min)	243.8 ± 32.9	237.9 ± 37.1	0.059 ⁸	242.3 ± 33.5	238.4 ± 37.8	0.246°
Estimated blood loss (ml)	145.2 ± 47.6	139.8 ± 50.4	0.208°	148.6 ± 51.2	143.5 ± 54.9	0.311°
Number of retrieved LNs	41.2 ± 15.1	30.3 ± 14.8	< 0.001°	40.8 ± 14.5	$3/.1 \pm 14.3$	0.007°
Time to ambulation (day)	2.1 ± 0.6	2.2 ± 0.4	0.024°	2.0 ± 0.3	2.1 ± 0.6	0.027 ⁶
Time to first flatus (day)	2.6 ± 0.7	2.9 ± 0.6	< 0.001°	2.7 ± 0.6	2.9 ± 0.9	0.006 ^b
Time to first liquid intake (day)	3.9 ± 1.2	4.1 ± 1.3	0.068	3.9 ± 0.8	4.0 ± 1.1	0.273
Time to first soft intake (day)	5.3 ± 1.1	5.4 ± 1.3	0.343	5.2 ± 1.2	5.3 ± 1.4	0.418
Postoperative hospital stay (day)	10.9 ± 2.8	12.3±3.2	< 0.001 ^b	10.2 ± 2.6	11.6 ± 3.4	< 0.001 ^b

PSM propensity score matched, RAG robot-assisted gastrectomy, LAG laparoscopy-assisted gastrectomy, BMI body mass index, ASA American Society of Anesthesiologist

Table 2 (continued)

^aBased on the Eighth American Joint Committee on Cancer classification

^bStudent's *t* test

^cPearson's χ^2 test



Fig. 2 Density distributions of standardized differences before and after matching in the present study

Propensity score matching analysis

After PSM analysis, 446 patients (223 patients in each group) were enrolled into further analysis. Standardized difference analysis demonstrated a successful match between all baseline characteristics (SMD = 0.006, Fig. 2). The baseline characteristics of the matched cohort were similar between the two groups (Table 2). Regarding surgical outcomes in the matched cohort, the time to ambulation, time to first flatus, and postoperative hospital stay were still significantly shorter in the RAG group than those in the LAG group (all P < 0.05; Table 2).

Postoperative morbidity and mortality

Morbidities and mortalities for all patients in the matched cohort are summarized in Table 3. After PSM, we analyzed overall and severe complications classified by C–D classification for the patients. In all, 42 patients (24.5%) incurred complications after RAG, compared with 78 patients (34.9%) presented complications after LAG (OR 0.43, 95% CI 0.28–0.67, P < 0.001). There were fewer major

complications experienced following RAG than the following LAG (8.9% vs. 17.5%; OR 0.39, 95% CI 0.21–0.71, P = 0.002).

RAG patients had fewer grade I complications compared to LAG and there was no statistically significant difference (P=0.848, Fig. 3). The most frequent grade I complications in both groups were fever followed by wound problem, delayed recovery of bowel movement, and atelectasis. We found a significant difference between the two groups in the rate of grade II complications, such as wound infection, fluid collection, pneumonia, postoperative ileus, and anastomosis leakage (4.9% vs. 10.8%, P = 0.022, Fig. 3). The incidence of grade IIIa complications was significantly lower in the RAG group (3.1% vs. 8.1%, P=0.024, Fig. 3). Among grade IIIa complications, anastomosis stenosis and leakage, pleural effusion, leakage of lymphatics, and fluid collection were relatively common. Grade IIIa complications occurred in five patients (anastomosis leakage in two patients, intra-abdominal bleeding in one, small-bowel perforation in one, and postoperative ileus in one) in the RAG group and 14 patients (anastomosis leakage in five patients, intra-abdominal bleeding in three, postoperative ileus in three, and other complications in three) in the LAG group (2.2% vs. 6.3%, P=0.035, Fig. 3). Moreover, no significant differences were noted in grade IVa and grade IVb complications rates between the two groups (grade IVa: 0.9% vs. 1.8%, P = 0.407; grade IVb: 0.4% vs. 0.9%, P = 0.559, Fig. 3). There were three deaths (2 in RAG and one in LAG) due to anastomosis leakage during hospitalization. Five patients experienced more than two complications before and after, and the most severe complication was used as a reference for final grading in the present study.

Subgroup analysis

Subgroup analyses were further performed for overall and severe complications in the matched cohort, respectively. In this study, we converted the clinicopathological parameters into dichotomous variables and selected the median of these parameters as the threshold.

Within the overall complications alone, there were significant differences between the two groups in all stratified parameters except age < 65 years (P=0.064), female (P=0.082), and previous abdominal operation (P=0.132), as shown in Fig. 4. Regarding the severe complications alone, subgroup analyses revealed that the statistical differences between the RAG and LAG groups were present Table 3Comparison ofcomplications following roboticand laparoscopic gastrectomyfor AGC using the Clavien–Dindo classification in the PSMcohort

Grades	RAG (<i>n</i> =223)	LAG (<i>n</i> =223)	P value
Grade I (%)	14 (6.3)	15 (6.7)	0.848 ^b
Fever	4	3	
Wound problem ^a	2	4	
Atelectasis	3	2	
Delayed recovery of bowel movement	2	4	
Transient hepatic function abnormality	1	0	
Transient elevation of serum creatinine	0	1	
Vomiting	1	0	
Ascites	0	1	
Subcutaneous emphysema	1	0	
Grade II (%)	11 (4.9)	24 (10.8)	0.022 ^b
Wound infection	3	5	
Fluid collection	2	3	
Pneumonia	1	1	
Pancreatitis	0	2	
Urinary tract infection	0	0	
Postoperative bleeding	1	1	
Leakage of lymphatics	0	2	
Postoperative ileus	2	2	
Anastomosis leakage	1	3	
Anastomosis stenosis	1	2	
Intra-abdominal infection	0	1	
Remnant gastric infarction	0	2	
Transient ischemic attack	0	0	
Postoperative psychological problem	0	0	
Grade IIIa (%)	7 (3.1)	18 (8.1)	0.024 ^b
Wound problem	0	1	
Anastomosis stenosis	1	3	
Intra-abdominal abscess	1	1	
Anastomosis leakage	2	5	
Duodenal stump fistula	0	2	
Fluid collection	1	-	
Leakage of lymphatics	0	2	
Pleural effusion	1	2	
Intra-abdominal bleeding	0	1	
Intra-luminal bleeding	1	0	
Grade IIIb (%)	5(22)	14 (6 3)	0.035 ^b
Wound problem	0	0	0.055
Intra abdominal bleeding	1	3	
Intra-luminal bleeding	0	1	
A nestomosis loskago	0	1	
Small bowel perforation	2	1	
Bernant gestric inference	1	1	
Remnant gastric marchon	0	1	
Crade We (%)	1 2 (0, 0)	5	0.407°
Anastomosis laskage	2 (0.9)	4 (1.0)	0.407
Anastomosis leakage	1	1	
Intra-abdominal infection	1	ے 1	
Stroke	0	1	
Lung failure	0	0	
Heart failure	U	0	
Renal failure	0	0	

Table 3 (continued)

Grades	RAG (n=223)	LAG (<i>n</i> =223)	P value
Grade IVb (%)	1 (0.4)	2 (0.9)	0.559 ^c
Multiorgan dysfunction	1	2	
Grade V (%)	2 (0.9)	1 (0.4)	0.559 ^c
Anastomosis leakage	2	1	
Hepatic failure	0	0	
Myocardial infarction	0	0	
Overall complications (%)	42 (24.5)	78 (34.9)	< 0.001 ^b
Clavien–Dindo grade≥IIIa (%)	17 (8.9)	39 (17.5)	0.002 ^b

AGC advanced gastric cancer, PSM propensity score matched, RAG robot-assisted gastrectomy, LAG lapa-roscopy-assisted gastrectomy

^aWound infection or poor healing

^bPearson's χ^2 test

^cContinuity correction



Fig. 3 Overall distributions of complications following robotic and laparoscopic gastrectomy for AGC using the Clavien–Dindo classification in PSM cohort. *RAG* robot-assisted gastrectomy, *LAG* laparoscopy-assisted gastrectomy, *AGC* advanced gastric cancer, *PSM* propensity score matched

in these stratifications, such as BMI, tumor size, histologic type, operating time, and estimated blood loss (all P < 0.05, Fig. 5), whereas no differences were observed in these stratified parameters including age ≥ 65 years (P = 0.147), female (P = 0.272), ASA class III (P = 0.121), upper third tumor (P = 0.231), total gastrectomy (P = 0.062), stage I (P = 0.183), and retrieved LNs < 30 (P = 0.129) (Fig. 5).

Risk factors for overall complications

Logistic regression was performed to determine factors associated with overall complications following RAG and LAG for AGC in the matched cohort. Univariate analysis revealed that age \geq 65 years, BMI \geq 30 kg/m², total gastrectomy, stage T3–T4a, stage N1–N3b, stage II–III, laparoscopic operation, and operation time \geq 250 min were significantly associated with higher risk of overall complications (all P < 0.05, Table 4). In multivariate analysis, age ≥ 65 years, total gastrectomy, stage T3–T4a, stage II–III, and operation time ≥ 250 min were significant independent risk factors for overall complications (all P < 0.05, Table 4).

Risk factors for severe complications

Regarding severe complications, higher complication rates correlated with age \geq 65 years, BMI \geq 30 kg/m², ASA class III, previous abdominal operation, total gastrectomy, stage T3–T4a, stage N1–N3b, stage II–III, laparoscopic operation, operation time \geq 250 min and retrieved LNs \geq 30 in univariate analysis (all *P* < 0.05, Table 4). Furthermore, the multivariate analysis showed that age \geq 65 years, stage II–III, and operation time \geq 250 min were independent risk factors for severe complications following RAG and LAG (all *P* < 0.05, Table 4).

Discussion

Accumulating evidence has demonstrated that RAG has been increasingly used in the treatment of AGC, and many advantages over LAG have been reported [5, 6, 24]. However, there is still no consensus on the definition and classification criteria of complications following RAG and LAG, which greatly hampers the assessment and comparison of different surgical procedures. Therefore, we have adopted the C–D classification system, which has proven to be a standard for surgical safety assessment in many fields [11–14, 32–34]. This study aimed to compare the severity and incidence of complications following RAG vs. those following LAG using C–D classification and to identify risk factors related to complications.

To date, complication reports assessed complications following RAG and LAG using the C–D classification are



Fig. 4 Subgroup analyses of overall complications following robotic and laparoscopic gastrectomy for AGC using the Clavien–Dindo classification in PSM cohort. *RAG* robot-assisted gastrectomy, *LAG* lapa-

roscopy-assisted gastrectomy, OR odds ratio, BMI body mass index, PAS previous abdominal operation, LNs lymph nodes, AGC advanced gastric cancer, PSM propensity score matched

quite limited and the results are still controversial [4, 35-37]. Obama et al. [4] and Kim et al. [35] reported no differences in the incidence of overall and major complications between RAG and LAG. However, a retrospective cohort study from a Japanese institution reported a higher incidence of overall complications (C–D grade \geq III), local complications, and pancreatic fistula in the LAG group than in the RAG group [36]. Seo et al. [37] also reported that the frequency of pancreatic fistula was higher in the LAG group. Using C-D classification to grade the severity of complications, we observed significant reduction in the overall and major complication rates of RAG compared with LAG, respectively. However, the incidence of complications appears to be slightly higher than those reported in previous studies, which may be due to the fact that our study included all complications from grade I to V, while most of the previous studies did not assess grade I complications.

Besides, we evaluated specific subgroups of the matched cohort to further test the independent relationship between the clinicopathological parameters and overall and severe complications, respectively. In the present study, we focused on the advantages of RAG in terms of the complications. Interestingly, subsequent subgroup analyses of overall complications supported RAG except age <65 years, female, and previous abdominal operation. We also performed subgroup analyses testing the effect of the stratified parameters on severe complications and again obtained similar results as in the overall complications, whereas no differences were observed in these stratified parameters including age \geq 65 years, female, ASA class III, upper third tumor, total gastrectomy, stage I, and retrieved LNs < 30. This difference may be caused by a limited number of cases in the above subgroup, so the above results also require greater data validation.

Understanding the relevant risk factors is important to minimize the incidence of complications. We then performed univariate and multivariate analyses in the mathed cohort to identify risk factors associated with overall and severe complications following RAG and LAG. The results showed that age, extent of resection, pTNM stage, and operation time were independent risk factors for overall complications, while age, pTNM stage, and operation time were associated with severe complications.

Age was identified as an independent risk factor for overall and severe complications following RAG and LAG



Fig. 5 Subgroup analyses of severe complications following robotic and laparoscopic gastrectomy for AGC using the Clavien–Dindo classification in PSM cohort. *RAG* robot-assisted gastrectomy, *LAG* lapa-

roscopy-assisted gastrectomy, OR odds ratio, BMI body mass index, PAS previous abdominal operation, LNs lymph nodes, AGC advanced gastric cancer, PSM propensity score matched

in our study, and this result was consistent with many previous reports [38, 39]. This may be due to the poor tolerance of elderly patients to surgical stress leading to an increased incidence of complications. However, there are still studies reporting no correlation between patient age and complications [40, 41]. Therefore, more prospective randomized clinical trials are needed to confirm the effect of age on surgical outcomes.

Extent of resection was also identified as an independent risk factor related to overall complications. The incidence of the overall complications following total gastrectomy was significantly higher than distal gastrectomy, and the major complications following total gastrectomy was an anastomosis complication. These results were consistent with Lee et al. [39] and Ji et al. [42]. This could be explained by the difference in blood supply around the anastomosis. The other possible cause is that the number of retrieved LNs following total gastrectomy is greater, which may compromise the vascular supply around the duodenal stump. Therefore, surgeons should always be more careful when removing LNs around the blood vessels, especially in total gastrectomy. As expected, our study showed that pTNM stage to be an independent risk factor for overall and severe complications. Zhou et al. reported [38] that patients with higher stage often have anemia, weight loss and hypoproteinemia, which may affect the vulnerability of surgical stress and the occurrence of complications. Some studies [43–45] also suggested that surgical resection for higher-stage AGC patients requires more complicated surgical procedures and longer operative time, resulting in excessive surgical stress and a high incidence of complications.

The current study also demonstrated a close link between the operation time and a higher incidence of overall and severe complications. This result is inconsistent with that reported by Watanabe et al. [46] and Lin et al. [47]. This may be because the surgical procedure with a long operation time is more technically complicated. For example, total gastrectomy needs to resect more areas of LNs, and the oesophago-jejunal anastomosis is more complicated and requires more time than the gastro-jejunal anastomosis.

Nevertheless, our study has certain limitations to be acknowledged. First, this study is limited by its retrospective nature, which places the study at risk for possible selection Table 4 Risk factors for overall and severe complications following robotic and laparoscopic gastrectomy for AGC in the PSM cohort

	Overall complications (I–V)				Severe complications (IIIa–V)			
Variables	Univariate		Multivariate		Univariate		Multivariate	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Age								
<65 years	Ref.				Ref.			
\geq 65 years	1.581 (1.106– 2.261)	0.012	2.165 (1.185– 3.955)	0.027	1.294 (1.069– 1.566)	0.008	2.167 (1.014– 4.632)	0.046
Gender								
Male	Ref.				Ref.			
Female	1.435 (0.892– 2.309)	0.137			1.952 (0.459– 8.298)	0.365		
BMI								
$< 30 \text{ kg/m}^2$	Ref.				Ref.			
\geq 30 kg/m ²	1.763 (1.056– 2.942)	0.030	1.527 (0.783– 2.977)	0.214	1.151 (1.002– 1.322)	0.047	1.813 (0.503– 6.533)	0.363
ASA								
I–II	Ref.				Ref.			
III	1.943 (0.908– 4.158)	0.087			1.451 (1.119– 1.882)	0.005	2.147 (0.784– 5.878)	0.137
Tumor size								
<5 cm	Ref.				Ref.			
\geq 5 cm	2.037 (0.542– 7.651)	0.292			2.810 (0.577– 13.692)	0.201		
Previous abdominal operation								
No	Ref.				Ref.			
Yes	1.056 (0.987– 1.129)	0.114			1.530 (1.026– 2.282)	0.037	2.014 (0.856– 4.741)	0.109
Tumor location								
Upper third	Ref.				Ref.			
Middle or lower third	0.761 (0.579– 1.002)	0.053			0.612 (0.226– 1.118)	0.067		
Extent of resec- tion								
Distal	Ref.				Ref.			
Total	2.238 (1.385– 3.616)	0.001	2.891 (1.150– 7.268)	0.024	2.108 (1.119– 3.971)	0.021	3.102 (0.990– 9.717)	0.052
Histologic type								
Well/moderately differentiated	Ref.				Ref.			
Poorly/undifferen- tiated	1.803 (0.911– 3.572)	0.091			1.974 (0.927– 4.205)	0.078		
pT stage ^a								
T2	Ref.				Ref.			
T3–T4a	1.298 (1.093– 1.542)	0.003	1.531 (1.076– 2.179)	0.018	1.520 (1.013– 2.281)	0.043	1.607 (0.978– 2.639)	0.061
pN stage ^a								
N0	Ref.				Ref.			
N1–N3b	1.013 (1.001– 1.025)	0.037	2.009 (0.822– 4.910)	0.126	1.501 (0.928– 2.428)	0.098		
pTNM stage ^a								
I	Ref.				Ref.			

Table 4 (continued)

	Overall complications (I–V)				Severe complications (IIIa–V)			
Variables	Univariate		Multivariate		Univariate		Multivariate	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
II–III	1.753 (1.255– 2.449)	0.001	2.402 (1.049– 5.496)	0.038	1.683 (1.102– 2.571)	0.016	2.539 (1.044– 6.178)	0.040
Operation method								
Robotic	Ref.				Ref.			
Laparoscopic	1.409 (1.046– 1.898)	0.024	1.682 (0.958– 2.952)	0.070	2.098 (1.001– 4.359)	0.047	2.265 (0.858– 5.983)	0.099
Operation time								
<250 min	Ref.				Ref.			
\geq 250 min	1.807 (1.107– 2.950)	0.018	1.445 (1.003– 2.081)	0.048	1.009 (1.001– 1.018)	0.037	1.765 (1.024– 3.044)	0.041
Estimated blood loss								
<150 ml	Ref.				Ref.			
\geq 150 ml	1.905 (0.706– 5.138)	0.203			2.016 (0.796– 5.103)	0.139		
Retrieved LNs								
< 30	Ref.				Ref.			
≥30	1.548 (0.239– 10.046)	0.647			1.901 (1.046– 3.454)	0.035	2.949 (0.882– 9.857)	0.079

AGC advanced gastric cancer, PSM propensity score matched, RAG robot-assisted gastrectomy, LAG laparoscopy-assisted gastrectomy, BMI body mass index, ASA American Society of Anesthesiologist, LNs lymph nodes

^aBased on the Eighth American Joint Committee on Cancer classification

and information bias and limits the evidence level of our conclusions. Although PSM was used to mitigate these biases, some residual confounders may persist. Second, this is a single-center study regarding Chinese populations and this demographic condition may limit the applicability of our results to other populations. Third, our study does not assess long-term complications owing to the relatively short follow-up period. Fourth, postoperative complications in this research did not include pancreatic fistula, which may affect the assessment of the overall and severe complications. Next, we will continue to follow-up these patients to further investigate these issues. Finally, some factors such as patients' preoperative hematologic parameters and surgeon's proficiency which may affect postoperative morbidity and mortality are not fully incorporated into our study.

Conclusions

In conclusion, the present study demonstrated RAG with D2 lymphadenectomy is feasible and safe for the treatment of AGC in terms of the lower incidence and severity of complications. In our opinion, the C–D classification facilitates to objectively assess the incidence and severity of specific complications and is an important vehicle for comprehensive comparison and evaluation of the safety of different types of gastrectomy. However, more large-scaled, multicenter, and prospective randomized control studies using the C–D classification are still warranted to fully evaluate the complications following robotic and laparoscopic gastrectomy for AGC.

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Author contributions The original study design was undertaken by HBL, WJW, and HTL. Data collection was undertaken by JPY, LS, PC, LW, CAG, and WH. The Clavien–Dindo grade for each patient was assessed by LY, KL, and YWM, and any divergences on grade were solved by discussion. Data were analysed by WJW, and appraised by HTL, JPY, and HBL. The draft manuscript was written by WJW, and was reviewed and edited by HTL, JPY, LS, PC, YML, and HBL. All authors have seen and approved the final version of the manuscript.

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Compliance with ethical standards

Disclosures Drs. Wen-Jie Wang, Hong-Tao Li, Jian-Ping Yu, Lin Su, Chang-An Guo, Peng Chen, Long Yan, Kun Li, You-Wei Ma, Ling Wang, Wei Hu, Yu-Min Li, and Hong-Bin Liu have no conflicts of interest or financial ties to disclose.

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