

Original Article



Risk Factors for the Severity of Complications in Minimally Invasive Total Gastrectomy for Gastric Cancer: a Retrospective Cohort Study

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ABSTRACT

Purpose: Minimally invasive gastrectomy is a promising surgical method with well-known benefits, including reduced postoperative complications. However, for total gastrectomy of gastric cancers, this approach does not significantly reduce the risk of complications. Therefore, we aimed to evaluate the incidence and risk factors for the severity of complications associated with minimally invasive total gastrectomy for gastric cancer.

Materials and Methods: The study included 392 consecutive patients with gastric cancer who underwent either laparoscopic or robotic total gastrectomy between 2011 and 2019. Clinicopathological and operative characteristics were assessed to determine the features related to postoperative complications after minimally invasive total gastrectomy. Binomial and multinomial logistic regression models were used to identify the risk factors for overall complications and mild and severe complications, respectively.

Results: Of 103 (26.3%) patients experiencing complications, 66 (16.8%) and 37 (9.4%) developed mild and severe complications, respectively. On multivariate multinomial regression analysis, independent predictors of severe complications included obesity (OR, 2.56; 95% CI, 1.02–6.43; P=0.046), advanced stage (OR, 2.90; 95% CI, 1.13–7.43; P=0.026), and more intraoperative bleeding (OR, 1.04; 95% CI, 1.02–1.06; P=0.001). Operation time was the only independent risk factor for mild complications (OR, 1.06; 95% CI, 1.001–1.13; P=0.047).

Conclusions: The risk factors for mild and severe complications were associated with surgery, indicating surgical difficulty. Surgeons should be aware of these potential risks that are related to the severity of complications so as to reduce surgery-related complications after minimally invasive total gastrectomy for gastric cancer.

Keywords: Gastric cancer; Gastrectomy; Laparoscopy; Postoperative complications; Risk factors

INTRODUCTION

Surgical treatment is the only curative treatment for resectable gastric cancer. Remarkable improvements in surgical techniques, devices, and perioperative management have reduced the complication rate of minimally invasive gastrectomy for gastric cancer over the past

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

decades [1,2]. Moreover, minimally invasive approaches are now increasingly considered as surgical treatment options for patients with gastric cancer because of their improved short-term postoperative results, without adverse effects on oncological outcomes, when compared with those of open surgery [3-7].

However, despite significant advances in surgical techniques, minimally invasive total gastrectomy is still associated with considerable postoperative morbidity and mortality [8,9]. Minimally invasive total gastrectomy for cancer is more complex and time-consuming than other gastrectomy procedures such as omentectomy, lymphadenectomy, and reconstruction [10]. Among them, reconstruction of minimally invasive total gastrectomy requires a more sophisticated technique than open total gastrectomy, and it may increase the risk of anastomosis-related complications [11-14]. Therefore, previous studies that investigated potential risk factors during total gastrectomy raise particular concerns regarding anastomosis-related complications [15-19].

Although several studies have reported risk factors for complications after total gastrectomy, only a few have assessed the risk factors for complications definitively for minimally invasive total gastrectomy, including both laparoscopic and robotic surgery, for gastric cancer [20-23]. Moreover, the risk factors for the severity (mild or severe) of complications, such as the multinomial logistic regression model, have not been evaluated concurrently using a unified model. Complications following minimally invasive total gastrectomy for gastric cancer remain an important clinical issue on account of their negative effects on functional and oncological outcomes. Thus, in this study, we aimed to evaluate the clinical, pathological, and operative factors associated with an increased risk for the severity of complications after minimally invasive total gastrectomy for gastric cancer by using a unified model.

MATERIALS AND METHODS

Study design and patients

We analyzed prospectively collected data of patients who underwent minimally invasive (robotic or laparoscopic) total gastrectomy for gastric cancer at the Department of Surgery, Ajou University School of Medicine, from January 2011 to December 2019. All cases of total gastrectomy were performed by three surgeons. While one surgeon had performed at least 50 minimally invasive total gastrectomies before the study period, the other two surgeons had no experience performing minimally invasive total gastrectomy. This study thus analyzed the experience of one surgeon after the learning curve and the initial experience of two surgeons for minimally invasive total gastrectomy. We included patients who underwent curative total gastrectomy and excluded those patients who underwent complete gastrectomy, palliative gastrectomy, or emergency gastrectomy. After a detailed explanation, the patients were given the choice to undergo robotic or laparoscopic gastrectomy. All patients provided written informed consent prior to surgery. The Institutional Review Board of Ajou University Hospital, Suwon, Korea, approved this study (approval number: AJIRB-MED-MDB-21-313).

Surgical procedures of minimally invasive total gastrectomy

The typical surgical procedures for minimally invasive total gastrectomy, laparoscopic and robotic, have been described previously in detail [24]. We performed lymphadenectomy according to the Korean and Japanese gastric cancer treatment guidelines [25,26]. After total gastrectomy, esophagojejunostomy using circular staplers was performed extracorporeally

or intracorporeally, whereas esophagojejunostomy using linear staplers was performed only intracorporeally. For extracorporeal esophagojejunostomy using a circular stapler, an upper midline mini-laparotomy of approximately 7 cm was performed after esophageal mobilization. For intracorporeal esophagojejunostomy using a circular stapler, a transverse mini-laparotomy was performed at the left lower port site. The circular stapler body inserted into the jejunum was placed in the peritoneal cavity. Pneumoperitoneum was maintained by covering the mini-laparotomy site with a wound protector. Esophagojejunostomy was performed using a 25- or 21-mm circular stapler, followed by jejunojunctionostomy. The surgeon selected a stapler size suitable for the esophageal lumen. In the majority of patients, a 25-mm stapler was used for esophagojejunostomy. Since 2015, we have been performing esophagojejunostomy and jejunojunctionostomy intracorporeally using linear staplers. A 45-mm linear stapler was used to create a side-to-side esophagojejunostomy between the esophagus and the prepared Roux limb [17]. Since January 2009, robotic total gastrectomy has been utilized at our institution using the da Vinci® S, Si, or Xi systems (Intuitive Surgical, Sunnyvale, CA, USA).

Complication assessment

Data related to complications were prospectively collected and discussed at a weekly conference. Postoperative complications were defined as complications that occurred in patients during the index admission or within 30 days after the initial surgery. The Clavien-Dindo classification system was used to assess postoperative morbidity and mortality [27]. Clavien-Dindo grade was further divided into two subgroups based on the severity of complications: mild (grade \leq II) and severe (grade \geq IIIa).

Outcomes

The incidence of overall, mild, and severe complications after minimally invasive total gastrectomy was assessed in all patients. Clinicopathological and operative characteristics were compared between patients who experienced mild or severe complications and those who did not. The following potential risk factors for complications were considered in the analysis: patient characteristics (age, sex, body mass index [BMI], American Society of Anesthesiologists [ASA] score, preoperative serum hemoglobin, and albumin), pathological characteristics (tumor histology, location, size, stage, and length of proximal margin), and operative characteristics (surgical approach, anastomosis method, operative time, estimated blood loss, extent of lymphadenectomy, and combined resection). We divided BMI into 2 subgroups (>27.5 and ≤ 27.5 kg/m²) according to the World Health Organization Asian-BMI classification, which defines BMI >27.5 kg/m² as obese [28].

Statistical analysis

Continuous variables were analyzed using Student's t-test and are reported as the mean and standard deviation. Student's t-test was performed to compare two continuous variables, and the analysis of variance test was used to compare more than 2 continuous variables. Categorical variables were analyzed using the χ^2 test or Fisher's exact test and are reported as numbers with percentages. For multiple post hoc comparisons based on the severity of complications, Bonferroni correction was applied to appropriately adjust the level of significance.

Binomial logistic regression analysis was used to identify the risk factors for overall complications after minimally invasive total gastrectomy. In addition, among patients who experienced complications, we evaluated the clinical, pathological, and operative factors associated with the severity of complications using multinomial logistic regression analysis

by comparing three categories of outcomes in a unified model, including no complications, mild complications, and severe complications. Multinomial logistic regression was performed using no complications (patients who did not experience any complications) as the reference. All variables (clinical, pathological, and operative) were included in the multivariate analysis, and the relative odds ratios (ORs) and their variances were calculated for retained independent factors [29,30]. The effect size of significant factors was reported as the relative OR and corresponding 95% confidence interval (CI). The relative OR was computed as the ratio of the ORs for mild versus no complications and severe versus no complications. Statistical significance was set at $P < 0.05$. Data were analyzed using IBM SPSS version 25.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Study cohort

A total of 437 patients underwent minimally invasive total gastrectomy for gastric cancer between 2011 and 2019. We excluded 45 patients who underwent completion total gastrectomy (n=33), palliative total gastrectomy (n=11), and emergency gastrectomy due to bleeding (n=1). Data from the remaining 392 patients were included in the analysis: 289 (73.7%) patients were in the “no complication group” and 103 (26.3%) patients were in the “overall complication group” (Fig. 1). The distribution of complications according to the Clavien-Dindo classification is listed in Supplementary Table 1.

Distribution of complications

As shown in Table 1, the incidence of overall complications after minimally invasive total gastrectomy for gastric cancer was 26.3% (n=103). According to the severity of complications, mild complications occurred in 66 (16.8%) patients, and severe complications were observed in 37 (9.4%) patients. Local complications (n=67, 17.1%) occurred more frequently than systemic complications (n=24, 6.1%). Ileus (n=18, 4.6%) and pulmonary complications

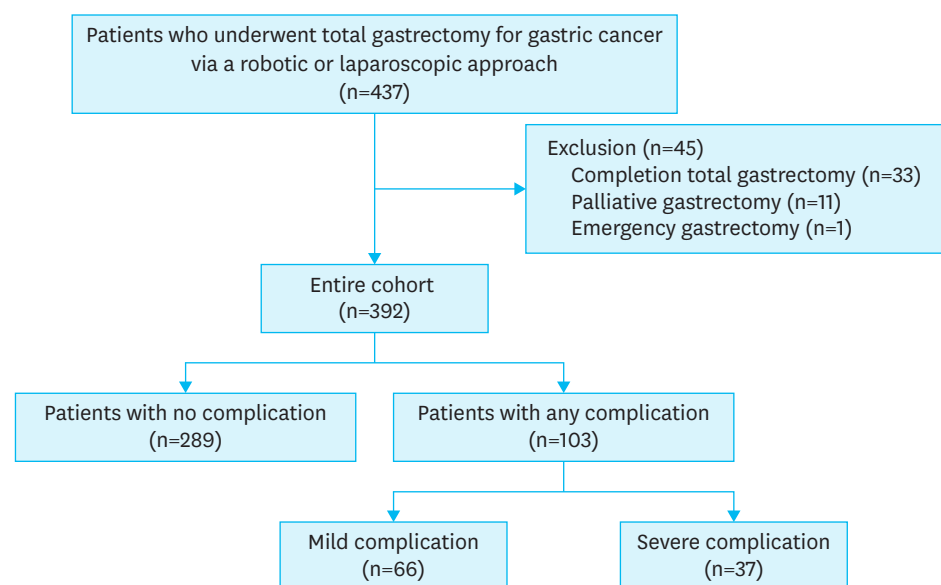


Fig. 1. Patient flow diagram.

Table 1. Distribution of complications

Complications	Overall (n=103, 26.3%)	Mild (n=66, 16.8%)	Severe (n=37, 9.4%)
Local complication	67 (17.1)	40 (10.2)	27 (6.9)
Intra-abdominal fluid collection	6 (1.5)	5 (1.3)	1 (0.3)
Intra-abdominal bleeding	6 (1.5)	3 (0.8)	3 (0.8)
Intra-luminal bleeding	7 (1.8)	2 (0.5)	5 (1.3)
Anastomotic leakage	7 (1.8)	0 (0)	7 (1.8)
Anastomotic stenosis	3 (0.8)	1 (0.3)	2 (0.5)
Ileus	18 (4.6)	12 (3.1)	6 (1.5)
Pancreatitis/Pancreatic fistula	10 (2.6)	8 (2.0)	2 (0.5)
Wound	10 (2.6)	9 (2.3)	1 (0.3)
Systemic complication	24 (6.1)	16 (4.1)	8 (2.0)
Pulmonary	15 (3.8)	9 (2.3)	6 (1.5)
Urinary	2 (0.5)	2 (0.5)	0 (0)
Hepatic	1 (0.3)	1 (0.3)	0 (0)
Cardiac	5 (1.3)	4 (1.0)	1 (0.3)
Renal	1 (0.3)	0 (0)	1 (0.3)
Other complications	12 (3.1)	10 (2.6)	2 (0.5)

Data are expressed as number (percent) unless otherwise specified.

(n=15, 3.8%) were the most frequent complications among local and systemic complications, respectively. The most common mild and severe complications were ileus (n=12, 3.1%) and anastomotic leakage (n=7, 1.8%).

Features related to overall complications

Clinical, pathological, and operative characteristics were comparable between the no complications and overall complication groups, except for operation time and estimated blood loss. Operation time was significantly longer in the overall complications group than in the no complications group (204.7±53.5 vs. 189.4±49.0 minutes; P=0.008). Estimated blood loss in the overall complication group was also significantly greater than that in the no complications group (176.1±164.3 vs. 125.9±126.5 mL; P=0.005). No mortality was observed in this study (**Table 2**). The time to soft diet (6.6±4.4 vs. 5.0±1.0 days; P<0.001) and discharge from hospital (10.8±7.0 vs. 7.1±1.3 days; P<0.001) were significantly delayed in the overall complications group compared to the no complications group (**Supplementary Fig. 1**).

Characteristics of complications according to severity

Clinical and pathological characteristics did not differ significantly among the three groups, except for BMI and ASA score. The proportion of obese patients tended to be higher in the severe complications group than in the other groups (24.3 vs. 12.8 and 9.1%, respectively; P=0.082). Patients with an ASA score of 2 or higher were marginally more common in the severe complications group than in the other groups (62.2 vs. 48.8 and 37.9%, respectively; P=0.058). Operative characteristics, operation time, and estimated blood loss were significantly different among the three groups. In multiple comparisons, operation time was longer in the mild complications group than in the no complications group (208.1±48.2 vs. 189.4±49.0 minutes; adjusted P=0.020). The estimated blood loss was greater in the severe complications group (222.7±226.0 mL) than in the no complications and mild complications groups (125.9±126.5 mL; adjusted P<0.001, and 150.0±110.1 mL; adjusted P=0.029, respectively, **Table 3**). The time to the soft diet of the severe complications group (8.6±6.5 days) was significantly delayed compared to those of the mild and no complications groups (5.5±1.6 and 5.0±1.0 days, respectively; P<0.001). Duration of hospital stay was longer in the severe and mild complications groups (15.1±9.9 and 8.5±2.7 days, respectively) than in the no complications group (7.1±1.3 days; P= 0.01 and P<0.001, respectively, **Supplementary Fig. 2**).

Risk Factors for Complications after Gastrectomy

Table 2. Features of overall complications

Factors	Entire cohort (n=392)	No complication (n=289)	Overall complication (n=103)	P-value
Clinical characteristics				
Age (yr)	60.0±12.7	59.7±12.5	60.6±13.1	0.528
BMI (kg/m ²)				0.735
<27.5	340 (86.7)	252 (87.2)	88 (85.4)	
>27.5	52 (13.3)	37 (12.8)	37 (14.6)	
Sex				0.539
Male	267 (68.1)	194 (67.1)	73 (70.9)	
Female	125 (31.9)	95 (32.9)	30 (29.1)	
ASA score				0.731
1	203 (51.8)	148 (51.2)	55 (53.4)	
≥2	189 (48.2)	141 (48.8)	48 (46.6)	
Hemoglobin (g/dL)*	13.7±1.9	13.8±1.9	13.6±1.9	0.549
Albumin (g/dL)*	4.5±0.4	4.5±0.4	4.4±0.4	0.282
Pathologic characteristics				
Tumor size (cm)	3.9±2.7	3.9±2.8	3.9±2.6	0.933
Tumor histology				>0.999
Differentiated	219 (55.9)	161 (55.7)	58 (56.3)	
Undifferentiated	173 (44.1)	128 (44.3)	45 (43.7)	
Tumor location				0.901
Upper	271 (69.1)	199 (68.9)	72 (69.9)	
Middle to lower	121 (30.9)	90 (31.1)	31 (30.1)	
Proximal margin (cm)	2.6±2.2	2.7±2.2	2.6±2.1	0.737
Pathological TNM stage†				0.833
I	245 (62.5)	183 (63.3)	62 (60.2)	
II	69 (17.6)	49 (17.0)	20 (19.4)	
III	78 (19.9)	57 (19.7)	21 (20.4)	
Operative characteristics				
Operation approach				0.551
Laparoscopy	321 (81.9)	239 (82.7)	82 (79.6)	
Robot	71 (18.1)	50 (17.3)	21 (20.4)	
Esophagojejunostomy method				0.417
Circular stapler	168 (42.9)	120 (41.5)	48 (46.6)	
Linear stapler	224 (57.1)	169 (58.5)	55 (53.4)	
Operation time (min)	193.4±50.6	189.4±49.0	204.7±53.5	0.008
Estimated blood loss (mL)	139.1±139.0	125.9±126.5	176.1±164.3	0.005
Extent of lymphadenectomy				0.422
<D2	201 (51.3)	152 (52.6)	49 (47.6)	
≥D2	191 (48.7)	137 (47.4)	51 (52.4)	
Combined resection				0.667
No	362 (92.3)	268 (92.7)	94 (91.3)	
Yes	30 (7.7)	21 (7.3)	9 (8.7)	
Mortality	0 (0.0)	0 (0.0)	0 (0.0)	NA

Data are expressed as mean ± standard deviation or as number (percent). Bold values denote statistical significance at the P<0.05 level.

BMI = body mass index; ASA = American Society of Anesthesiologists; NA = not applicable.

*Preoperative value. †The 8th edition of the American Joint Committee on Cancer TNM staging system for gastric cancer.

Risk factors for overall complications

Table 4 summarizes the outcomes of univariate and multivariate binomial logistic regression analyses for overall complications. No significant risk factors were found in the clinical and pathological characteristics. Among operative characteristics, operation time (unadjusted OR, 1.06; 95% CI, 1.01-1.11; P=0.009), and estimated blood loss (unadjusted OR, 1.02; 95% CI, 1.01-1.04; P=0.003) were risk factors for overall complications in the univariate analysis. On multivariate analysis, estimated blood loss was identified as the only independent risk factor for overall complications (adjusted OR, 1.02; 95% CI, 1.001-1.04; P=0.037).

Table 3. Features of mild and severe complications

Factors	No complication (n = 289)	Mild complication (n = 66)	Severe complication (n = 37)	P-value
Clinical characteristics				
Age (yr)	59.7±12.5	59.4±12.9	62.8±13.4	0.350
BMI (kg/m ²)				0.082
<27.5	252 (87.2)	60 (90.9)	28 (75.7)	
>27.5	37 (12.8)	6 (9.1)	9 (24.3)	
Sex				0.676
Male	194 (67.1)	48 (72.7)	25 (67.6)	
Female	95 (32.9)	18 (27.3)	12 (32.4)	
ASA score				0.058
1	148 (51.2)	41 (62.1)	14 (37.8)	
≥2	141 (48.8)	25 (37.9)	23 (62.2)	
Hemoglobin (g/dL)*	13.8±1.9	13.6±2.0	13.7±1.7	0.835*
Albumin (g/dL)*	4.5±0.4	4.4±0.5	4.4±0.4	0.520*
Pathologic characteristics				
Tumor size (cm)	3.9±2.8	3.9±2.7	3.8±2.5	0.987
Tumor histology				0.773
Differentiated	161 (55.7)	39 (59.1)	19 (51.4)	
Undifferentiated	128 (44.3)	27 (40.9)	18 (48.6)	
Tumor location				>0.999
Upper	199 (68.9)	46 (69.7)	26 (70.3)	
Middle to lower	90 (31.1)	20 (30.3)	11 (29.7)	
Proximal margin (cm)	2.7±2.2	2.4±1.8	2.9±2.5	0.553
Pathological TNM stage†				0.211
I	183 (63.3)	44 (66.7)	18 (48.6)	
II, III	106 (36.7)	22 (33.3)	19 (51.4)	0.157
Operative characteristics				
Operation approach				0.306
Laparoscopy	239 (82.7)	50 (75.8)	32 (86.5)	
Robot	50 (17.3)	16 (24.2)	5 (13.5)	
Esophagojejunostomy method				0.588
Circular stapler	120 (41.5)	32 (48.5)	16 (43.2)	
Linear stapler	169 (58.5)	34 (51.5)	21 (56.8)	
Operation time (min)	189.4±49.0	208.1±48.2	198.7±62.1	0.020 ‡
Estimated blood loss (mL)	125.9±126.5	150.0±110.1	222.7±226.0	<0.001 §
Extent of lymphadenectomy				0.595
<D2	152 (52.6)	30 (45.5)	19 (51.4)	
≥D2	137 (47.4)	36 (54.5)	18 (48.3)	
Combined resection				0.771
No	268 (92.7)	61 (92.4)	33 (89.2)	
Yes	21 (7.3)	5 (7.6)	4 (10.8)	

Data are expressed as mean ± standard deviation or as number (percent). Continuous variables were compared using the analysis of variance (ANOVA) test. Bold values denote statistical significance at the P<0.05 level.

BMI = body mass index; ASA = American Society of Anesthesiologists.

*Preoperative value. †The 8th edition of the American Joint Committee on Cancer TNM staging system for gastric cancer; ‡Adjusted P=0.020 for no complication vs. mild complication. §Adjusted P<0.001 for no complications vs. severe complications and P=0.029 for mild complications vs. severe complications.

Risk factors for the severity of complications

Among the clinical characteristics, obesity (BMI >27.5 kg/m²) marginally increased the risk of severe complications relative to no complications in the univariate multinomial logistic regression analysis (unadjusted OR, 2.19; 95% CI, 0.96–5.00; P=0.063). Among the pathological characteristics, pathological stage II or III was a risk factor for severe complications (unadjusted OR, 1.82; 95% CI, 0.92–3.63; P=0.087); however, this was not statistically significant. Estimated blood loss significantly increased the risk of severe complications relative to no complications (unadjusted OR, 1.04; 95% CI, 1.02–1.06; P=0.001). The only risk factor for mild complications relative to no complications was operative time (unadjusted OR, 1.07; 95% CI, 1.05–1.13; P=0.007). The risk factors for

Table 4. Binomial logistic regression analysis for overall complications

Factors	Unadjusted estimate		Adjusted estimate	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Clinical characteristics				
Age (yr)	1.01 (0.99–1.02)	0.527	1.01 (0.99–1.03)	0.541
BMI (kg/m ²)		0.651		0.750
<27.5	1 [Reference]		1 [Reference]	
>27.5	1.16 (0.61–2.22)		1.12 (0.56–2.22)	
Sex		0.484		0.499
Male	1 [Reference]		1 [Reference]	
Female	0.84 (0.51–1.37)		0.82 (0.45–1.47)	
ASA score		0.703		0.534
1	1 [Reference]		1 [Reference]	
≥2	0.92 (0.58–1.44)		0.85 (0.51–1.43)	
Hemoglobin (g/dL)*	0.97 (0.86–1.09)	0.548	0.95 (0.82–1.11)	0.522
Albumin (g/dL)*	0.74 (0.43–1.28)	0.282	1.001 (0.50–2.00)	0.998
Pathologic characteristics				
Tumor size (cm)	1.004 (0.92–1.09)	0.933	0.99 (0.91–1.09)	0.904
Tumor histology		0.916		0.475
Differentiated	1 [Reference]		1 [Reference]	
Undifferentiated	0.98 (0.62–1.54)		1.20 (0.72–2.00)	
Tumor location		0.844		0.750
Upper	1 [Reference]		1 [Reference]	
Middle to lower	0.95 (0.58–1.55)		0.91 (0.50–1.66)	
Proximal margin (cm)	0.98 (0.88–1.09)	0.737	0.99 (0.86–1.13)	0.834
Pathological TNM stage [†]		0.574		0.982
I	1 [Reference]		1 [Reference]	
II, III	1.14 (0.72–1.81)		1.01 (0.57–1.78)	
Operative characteristics				
Operation approach		0.485		0.547
Laparoscopy	1 [Reference]		1 [Reference]	
Robot	1.22 (0.69–2.16)		1.21 (0.65–2.25)	
Stapler for esophagojejunostomy		0.371		0.517
Circular stapler	1 [Reference]		1 [Reference]	
Linear stapler	0.81 (0.52–1.28)		0.83 (0.47–1.46)	
Operation time (min) [‡]	1.06 (1.01–1.11)	0.009	1.04 (0.99–1.09)	0.160
Estimated blood loss (mL) [§]	1.02 (1.01–1.04)	0.003	1.02 (1.001–1.04)	0.037
Extent of lymphadenectomy		0.382		0.713
<D2	1 [Reference]		1 [Reference]	
≥D2	1.22 (0.78–1.92)		1.12 (0.62–2.00)	
Combined resection		0.630		0.852
No	1 [Reference]		1 [Reference]	
Yes	1.22 (0.54–2.76)		1.09 (0.46–2.58)	

Bold values denote statistical significance at the P<0.05 level.

OR = odds ratio; CI = confidence interval; BMI = body mass index; ASA, American Society of Anesthesiologists.

*Preoperative value. [†]The 8th edition of the American Joint Committee on Cancer TNM staging system for gastric cancer. [‡]The odds ratio shown is for every 10 minutes increase in operation time. [§]The OR shown is for every 10 mL increase in estimated blood loss.

severe complications relative to mild complications were obesity (unadjusted OR, 3.21; 95% CI, 1.04–9.91; P=0.042) and an ASA score of 2 or higher (unadjusted OR, 2.69; 95% CI, 1.18–6.18; P=0.019, **Supplementary Table 2**).

Table 5 summarizes the outcomes of the multivariate multinomial logistic regression analysis according to the severity of the complications. A longer operation time increased the risk of mild complications relative to no complications (adjusted OR, 1.06; 95% CI, 1.001–1.13; P=0.047). Obesity (BMI >27.5 kg/m²), advanced stage (II or III), and increased estimated blood loss increased the risk of severe complications relative to both no complications and mild complications. The surgeon's experience as a factor was not associated with the overall

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Table 5. Multivariate multinomial logistic regression analysis according to severity of complications

Factors	Adjusted estimate					
	No vs. Mild *		No vs. Severe *		Mild vs. Severe †	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Clinical characteristics						
Age (yr)	1.01 (0.98–1.03)	0.706	1.01 (0.98–1.05)	0.511	1.01 (0.97–1.05)	0.742
BMI (kg/m ²)		0.362		0.046		0.027
≤27.5	1 [Reference]		1 [Reference]		1 [Reference]	
>27.5	0.64 (0.25–1.66)		2.56 (1.02–6.43)		3.98 (1.17–13.53)	
Sex		0.275		0.816		0.357
Male	1 [Reference]		1 [Reference]		1 [Reference]	
Female	0.67 (0.33–1.38)		1.13 (0.45–2.74)		1.66 (0.56–4.89)	
ASA score		0.136		0.325		0.071
1	1 [Reference]		1 [Reference]		1 [Reference]	
≥2	0.62 (0.33–1.16)		1.51 (0.67–3.42)		2.44 (0.93–6.41)	
Hemoglobin (g/dL) [‡]	0.93 (0.78–1.12)	0.442	1.00 (0.79–1.26)	0.969	1.07 (0.81–1.42)	0.639
Albumin (g/dL) [‡]	1.03 (0.44–2.42)	0.949	0.95 (0.34–2.61)	0.915	0.92 (0.27–3.15)	0.894
Pathologic characteristics						
Tumor size (cm)	1.01 (0.91–1.12)	0.828	0.96 (0.82–1.12)	0.573	0.95 (0.79–1.13)	0.535
Tumor histology		0.971		0.170		0.254
Differentiated	1 [Reference]		1 [Reference]		1 [Reference]	
Undifferentiated	1.01 (0.55–1.86)		1.75 (0.79–3.90)		1.73 (0.67–4.45)	
Tumor location		0.541		0.188		0.131
Upper	1 [Reference]		1 [Reference]		1 [Reference]	
Middle to lower	1.25 (0.61–2.59)		0.52 (0.20–1.37)		0.42 (0.14–1.30)	
Proximal margin (cm)	0.93 (0.78–1.10)	0.388	1.10 (0.91–1.31)	0.322	1.18 (0.93–1.50)	0.162
Pathological TNM stage [§]		0.164		0.026		0.006
I	1 [Reference]		1 [Reference]		1 [Reference]	
II, III	0.61 (0.31–1.22)		2.90 (1.13–7.43)		4.73 (1.57–14.24)	
Operative characteristics						
Operation approach		0.465		>0.999		0.678
Laparoscopy	1 [Reference]		1 [Reference]		1 [Reference]	
Robot	1.30 (0.65–2.61)		1.00 (0.33–3.04)		0.77 (0.23–2.64)	
Stapler for esophagojejunostomy		0.330		0.923		0.473
Circular stapler	1 [Reference]		1 [Reference]		1 [Reference]	
Linear stapler	0.71 (0.36–1.41)		1.05 (0.43–2.55)		1.47 (0.51–4.22)	
Operation time (min)	1.06 (1.001–1.13)	0.047	1.00 (0.93–1.08)	0.944	0.94 (0.86–1.03)	0.164
Estimated blood loss (mL)	1.004 (0.98–1.03)	0.727	1.04 (1.02–1.06)	0.001	1.04 (1.01–1.07)	0.020
Extent of lymphadenectomy		0.225		0.226		0.075
<D2	1 [Reference]		1 [Reference]		1 [Reference]	
≥D2	1.53 (0.77–3.03)		0.55 (0.21–1.45)		0.36 (0.12–1.11)	
Combined resection		0.986		0.690		0.754
No	1 [Reference]		1 [Reference]		1 [Reference]	
Yes	1.01 (0.34–2.98)		1.28 (0.38–4.39)		1.27 (0.28–5.73)	

Bold values denote statistical significance at the P<0.05 level.

OR = odds ratio; CI = confidence interval; BMI = body mass index; ASA = American Society of Anesthesiologists.

*Reference category: no complication. †Reference category: mild complication. ‡Preoperative value. §8th edition of the American Joint Committee on Cancer TNM staging system for gastric cancer. ||The odds ratio shown is for every 10 minutes increase in operation time. ¶The OR shown is for every 10 mL increase in estimated blood loss.

and severity of complications, although the surgeon's experience with minimally invasive total gastrectomy was different (**Supplementary Tables 3 and 4**).

DISCUSSION

The incidence of overall complications in the study group was 26.3%, with incidences of mild and severe complications of 16.8% and 9.4%, respectively. A longer operation time was associated with a higher risk of mild complications, and obesity (BMI >27.5 kg/m²),

advanced stage (II or III), and increased intraoperative bleeding increased the risk of severe complications accordingly. Additionally, more intraoperative bleeding was associated with a higher risk of overall complications.

The incidence of severe complications after minimally invasive total gastrectomy ranges from 1.5% to 11.6% [10,31-34]. The rate of severe complications (9.4%) in the present study is consistent with previous reports. Severe complications adversely affect both short- and long-term outcomes [35-37]. Similarly, in the present study, delayed initiation of a soft diet led to prolonged hospitalization and additional interventions for treatment in some patients.

This study is the first to evaluate the risk factors related to the severity of complications after minimally invasive total gastrectomy for gastric cancer using a unified model. Previous studies have reported patient-related factors, including age, ASA score, and comorbidities, as causes of severe complications. In the present study, obesity, higher pathological stage, and intraoperative blood loss had independent effects on the risk of severe complications; thus, severe complications were considered to be associated with surgical difficulty.

Intraoperative blood loss is a risk factor for severe complications. This is similar to open surgery, which increases the risk of short-term complications, such as anastomotic leakage. As intraoperative blood loss increases, it adversely affects long-term survival outcomes [38,39]. Lower oxygen saturation at the surgical site due to intraoperative bleeding is associated with a high incidence of surgical site infection in abdominal surgery [40]. This study revealed that intraoperative blood loss is an important risk factor for severe complications in minimally invasive total gastrectomy, similar to open surgery. However, determining the absolute cutoff value of intraoperative blood loss for severe complications is impractical. When intraoperative blood loss was divided by the quartile range, the risk of severe complications significantly increased in the fourth quartile (>200 mL) than in the first quartile (≤ 50 mL, **Supplementary Table 5**). This implies that intraoperative blood loss may reflect the quality and difficulty of the surgery.

Another risk factor for severe complications is obesity, which has become one of the most prominent public health concerns worldwide. A previous study reported that, by 2030, approximately 38% of adults will be overweight and approximately 20% will be obese worldwide [41]. Difficulty in securing the surgical field, increased intraoperative blood loss, and longer operation times in obese patients, particularly in those with excessive visceral fat, make surgery technically difficult [42]. An excessive visceral fat area increases the risk of severe complications, such as anastomotic leakage, in gastric cancer surgery [43,44]. This suggests that obesity is likely to cause increased technical challenges during gastric cancer surgery.

The advanced stage was another risk factor for severe complications. In cases of advanced stage, manipulation of the stomach with soft tissues in minimally invasive surgery is difficult, and intraoperative bleeding tends to increase. In a large cohort study in Japan, the incidence of anastomotic leakage and reoperation was found to be higher in laparoscopic total gastrectomy than in open total gastrectomy for the treatment of advanced gastric cancer, although overall complication rates were not significantly different [10]. Advanced cancer may also be regarded as a factor affecting surgical difficulty in minimally invasive total gastrectomy.

Consequently, estimated blood loss, obesity, and advanced stage were identified as risk factors for severe complications in this study, and they were all associated with surgical

difficulties [45-49]. In cases with these risk factors, the risk of severe complications is speculated to increase in minimally invasive total gastrectomy, even if the surgery is performed by an established laparoscopic surgeon.

In this study, operative time was the only risk factor for mild complications. When the operation time was divided by the quartile range, the risk of mild complications significantly increased in the fourth quartile (≥ 220 min) compared to the first quartile (< 160 minutes, **Supplementary Table 6**). The operation time of minimally invasive surgery is generally longer than that of open surgery, which can explain its inability to significantly reduce complications compared to open total gastrectomy [50,51]. The longer operation time of the minimally invasive approach could be attributed to the demanding procedures and non-standardization of procedures. In minimally invasive total gastrectomy, esophagojejunostomy or extended lymph node dissection for advanced cancer is one of the most technically challenging procedures. However, these procedures have not yet been standardized. While the use of a circular stapler has generally been the standard for open total gastrectomy for decades, the standard for esophagojejunostomy has not yet been established in minimally invasive surgery. For this reason, several methods of reconstruction using linear staplers, circular staplers, and an orally inserted anvil have been reported in the literature [15-19]. In addition, several methods for splenic hilar dissection have also been described accordingly [32,52-55]. Standardization of procedures and avoidance of unnecessary procedures may help reduce the operative time in minimally invasive total gastrectomy.

This study has several limitations. First, there was a risk of bias in patient selection due to the retrospective nature of the study. Second, the total number of patients who experienced severe complications was relatively small, although the study duration was approximately one decade. Thus, a large cohort of patients from multiple centers is warranted to verify the results of this study. Third, the generalizability of the current findings to the Western population is uncertain because of the inclusion of only an Eastern cohort in this study. Eastern populations have relatively lower BMIs and more early-stage gastric cancers than Western populations. Potential risk factors for mild and severe complications in the Western population might differ from those in the Eastern population. Therefore, validation in a Western population is warranted accordingly.

In conclusion, the risk factors for mild and severe complications after minimally invasive total gastrectomy for gastric cancer were associated with surgery, thus demonstrating the technical difficulty of the procedure. Severe complications were associated with obesity, advanced stage, and more intraoperative blood loss, and mild complications were associated with a longer operative time. Surgeons must weigh the potential risks associated with the severity of complications and continue to standardize these demanding procedures.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1

Distribution of complications according to the Clavien-Dindo classification.

[Click here to view](#)

Supplementary Table 2

Univariate multinomial logistic regression analysis according to the severity of complications.

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Supplementary Table 3

Binomial logistic regression analysis of the association of surgeon's factor with overall complications.

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Supplementary Table 4

Multivariate multinomial logistic regression analysis of the association of surgeon's factor with the severity of the complication.

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Supplementary Table 5

Effect of estimated blood loss on complications.

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Supplementary Table 6

Effect of operation time on complications.

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Supplementary Fig. 1

Comparison of the postoperative course according to the overall complications.

[Click here to view](#)

Supplementary Fig. 2

Comparison of the postoperative course according to the severity of complications.

[Click here to view](#)

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