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Short- and Long-term Outcome After Gastric Cancer Resection in Patients Aged 80 Years and Older

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Abstract. *Background/Aim: We aimed to assess the risk factors for postoperative complications and long-term outcome of patients aged ≥80 years after curative resection for gastric cancer (GC). Patients and Methods: Patients aged ≥80 years who underwent curative gastrectomy for stage I-III GC between 2013 and 2020 were included. Clinical factors were retrospectively analyzed. Results: Of all 109 patients, 29 (26.6%) had 33 postoperative complications (Clavien–Dindo grade ≥2). The rate of postoperative complications was higher in those with greater blood loss (≥170 ml, p<0.001). In multivariate analysis, greater blood loss was confirmed as an independent predictor of postoperative complications (p<0.001). The 30-day, 180-day, 1-year, and 3-year cumulative overall survival rates were 100%, 97.0%, 91.6%, and 74.7%, respectively. Multivariate analysis showed postoperative complications (p=0.014) and low prognostic nutritional index (PNI, p=0.044) were independent prognostic factors for poor overall survival. Conclusion: Performing operations with less bleeding is important to reduce postoperative complications. According to the analysis of long-term survival, patients who experience postoperative complications and patients with a low preoperative PNI require special attention in the follow-up period. Nutritional support should be considered in patients with malnutrition.*

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Key Words: Gastric cancer, elderly, postoperative complication.

Gastric cancer (GC) is the fifth most common malignant neoplasm with the third leading incidence of cancer-related death globally (1). *Helicobacter pylori* infection is highly prevalent in the elderly population, decreasing with lower age to less than 10% in the younger population born around the 1990s (2). In Japan, the number of incident GC cases has been increasing due to the aging of the population (2).

Although surgical resection is the main therapeutic approach for GC, it has the potential to result in significant worsening of an elderly patient's quality of life and postoperative complications can lead to poor outcomes (3, 4). In general, the incidence of postoperative complications increases in elderly patients owing to higher rates of comorbid disease, functional impairments, and reduced physiological function (5). Patients aged ≥80 years are reported to experience severe complications more frequently than others (6, 7). Postoperative complications are related to poor long-term outcomes after radical gastrectomy for GC (8), with a reduction in the tolerance of adjuvant chemotherapy (9).

Several prognostic factors that affect long-term survival after curative resection for GC in elderly GC patients have been reported including male sex (10), sarcopenia (11), preoperative restrictive pulmonary dysfunction (12), and postoperative complications (13) for several definitions of 'elderly'.

Although there are studies analyzing long-term survival after gastrectomy limited to patients aged ≥80 years, those mainly compared the outcomes of elderly patients with those of younger patients. The risk factors for poor survival outcomes have not been fully established. The aim of this study was to review clinical data and evaluate various clinical factors in terms of their relationship with short- and long-term outcomes in patients aged ≥80 years who underwent curative resection for GC.

Patients and Methods

In this study, we defined very elderly patients as patients aged ≥80 years. A retrospective review of the medical records of consecutive

patients who underwent curative gastrectomy for GC from January 2013 to December 2020 at Sasebo City General Hospital was performed. Patients who had undergone emergency surgery and patients who had stage IV disease, including metastatic lesions and positive peritoneal washing cytology, were excluded. Only adenocarcinomas were included. Finally, 109 patients were included in the present analysis. This retrospective study was approved by the Institutional Review Board of Sasebo City General Hospital, and the need for informed consent was waived. The ethics approval number was 2020-A042.

We reviewed and recorded the following data: age, sex, body mass index (BMI), the American Society of Anesthesiologists Physical Status, Onodera's prognostic nutritional index (PNI) (14), type of surgery, operative time, bleeding, degree of lymph node dissection, pathological T-stage, pathological N-stage, histological type, GC stage based on the seventh edition of the American Joint Committee on Cancer TNM Classification System (15), postoperative complications, length of stay after operation, adjuvant chemotherapy, postoperative recurrence, overall survival (OS) and cause of death.

Curative resection was defined as macroscopically complete resection without invasion of the surgical margins on histological examination. The tumor stage was classified in accordance with TNM classification. Postoperative complications were defined as complications occurring within 30 days of the primary surgery. Patients with Clavien–Dindo grade ≥2 complications were included in the group with complications. Postoperative mortality was defined as death within 30 days after surgery or any later death considered directly due to postoperative complications.

Statistical analysis was performed using Bell Curve for Excel software, version 2.02 (Social Survey Research Information Co., Ltd., Tokyo, Japan). Continuous data were compared using Student's *t*-test, and categorical data were compared using Fisher's exact test or the chi-squared test, as appropriate. The cutoff values for the operation time, bleeding, and PNI were determined experimentally using receiver-operating characteristic curve analysis of complications. The point that was closest to the upper left-hand corner of the graph was chosen as the cutoff that simultaneously maximized both sensitivity and specificity. The data are presented as median values with ranges.

The risk factors that determined complications were investigated using univariate and multivariate analysis. All variables related to the risk of complications with a *p*-value of less than 0.05 on univariate analysis were included in the multivariate analysis. Multivariate logistic regression models were then constructed to examine the effects of significant perioperative variables on the odds of each complication. All *p*-values of less than 0.05 were considered significant.

OS was calculated in accordance with the Kaplan–Meier method and defined as the duration from operation to death or the last follow-up. Multivariate analysis using a Cox hazards model was used to identify the independent risk factors for OS. All variables related to the risk of OS with a value of $p<0.05$ on univariate analysis were included in the multivariate analysis. All associations with $p<0.05$ were considered significant.

Results

Table I shows the baseline demographic and clinical characteristics of the 109 patients. The study population comprised 69 male (62.4%) and 41 female (37.6%) patients, with a median age of 83 (range=80-94) years. The median BMI was 21.6 (range=14.7-30.6) kg/m^2. Among these patients, 12 (11.0%) had a poor performance status (≥3). Most patients were diagnosed with differentiated adenocarcinoma (n=70, 64.2%). Open surgery was performed in 54 patients (49.5%) and laparoscopic surgery was performed in 55 patients (50.5%). Distal gastrectomy was performed in 70 patients (64.2%), comprising 30 treated with the Billroth I procedure and 40 with the Roux-en-Y procedure. Total gastrectomy was performed in 37 patients (33.9%) and proximal gastrectomy with double tract reconstruction was performed in two patients (1.8%). D2 lymph node dissection was performed in 38 patients (34.9%). Histopathologically, most patients were diagnosed with stage I or II disease (n=84, 76.4%). The median operative time was 285 (range=153-878) min, and the median intraoperative bleeding was 85 (0-1,469) ml. Twenty-nine patients (26.6%) had 33 postoperative complications of Clavien–Dindo grade ≥2. Although there were no cases of early postoperative mortality within 30 days, one patient (0.9%) died in the hospital following anastomotic leakage of intra-mediastinal anastomosis after total gastrectomy. Ten patients (9.2%) had grade 3 or worse postoperative complications including anastomotic leakage (n=3, 2.8%), pancreatic fistula (n=2, 1.8%), biliary tract infection (n=2, 1.8%), remnant gastric perforation (n=1, 0.9%), duodenal stump leakage (n=1, 0.9%), and deep vein thrombosis (n=1, 0.9%). The remaining 23 patients had grade 2 complications including delirium (n=4, 3.7%), anastomotic leakage (n=4, 3.7%), wound infection (n=3, 2.8%), intra-abdominal abscess (n=3, 2.8%), pneumonia (n=2, 1.8%), chylous ascites (n=2, 1.8%), prolonged ileus (n=2, 1.8%), duodenal stump leakage (n=1, 0.9%), anastomotic bleeding (n=1, 0.9%), and arrhythmia (n=1, 0.9%).

Table II shows the clinical differences between patients with and without postoperative complications. The rate of postoperative complications was higher in the group with greater blood loss (≥170 ml, $p<0.001$) and tended to be higher in patients who underwent open surgery ($p=0.053$). Except for these variables, there was no difference between the two groups.

Table III shows the results of univariate and multivariate analyses of risk factors for postoperative complications. Greater intraoperative blood loss ($p<0.001$) and an open surgical approach ($p=0.032$) were significantly associated with complications on univariate analysis. Multivariate analysis showed that only greater blood loss was an independent predictor of postoperative complications [odds ratio (OR)=5.347, 95% confidence interval (CI)=2.110-13.551; $p<0.001$].

Among the 109 patients, the median follow-up period was 23.9 (range=0.4-81.9) months. The 30-day, 180-day, 1-year, and 3-year cumulative OS rates were 100%, 97.0%, 91.6%, and 74.7%, respectively (Figure 1). Thirty-four patients died during the follow-up period, and the number and causes of death at various time intervals after the operation are shown in Table IV.

Table I. *Clinical characteristics of the patients (n=109).*

Characteristic		Value
Age, years	Median (range)	83 (80-94)
Gender , n (%)	Male	68 (62.4%)
	Female	41 (37.6%)
BMI, kg/m^2	Median (range)	21.6 (14.7-30.6)
ASA-PS, n (%)	1	10 (9.2%)
	2	87 (80.0%)
	3	12 (11.0%)
	4	0 (0.0%)
Histological type, n (%)	Differentiated	70 (64.2%)
	Undifferentiated	39 (35.8%)
Surgical approach, n (%)	Open	54 (49.5%)
	Laparoscopic	55 (50.5%)
Extent of resection, n (%)	DG	70 (64.2%)
	DG B-I	30 (27.5%)
	DG RY	40 (36.7%)
	PG	2 (1.8%)
	TG	37 (33.9%)
Lymph node dissection, n (%)	D1/D1+	71 (65.1%)
	D2	38 (34.9%)
pTNM Stage, n (%)	I	53 (48.6%)
	II	31 (28.4%)
	III	25 (22.9%)
Co-morbidity, n (%)	Respiratory disease	15 (13.8%)
	Diabetes	24 (22.0%)
	Hypertension	80 (73.4%)
	Cardiovascular disease	35 (32.1%)
	Dementia	11 (10.1%)
	Liver disease	6 (5.5%)
	Renal disease	19 (17.4%)
	Anticoagulation treatment	23 (21.1%)
Operative time, min	Median (range)	285 (153-878)
Blood loss, ml	Median (range)	85 (0-1469)
Number of retrieved LNs	Median (range)	24 (0-86)
Post-operative hospital days	Median (range)	17 (9-91)
Post-operative complication, n (%)*	Yes	29 (26.6%)
	No	80 (73.4%)
Specific complication (n=33), n (%)	Anastomotic leakage	7 (6.4%)
	Delirium	4 (3.7%)
	Wound infection	3 (2.8%)
	Intra-abdominal abscess	3 (2.8%)
	Pneumonia	2 (1.8%)
	Chylous ascite	2 (1.8%)
	Prolonged ileus	2 (1.8%)
	Pancreatic fistula	2 (1.8%)
	Biliary tract infection	2 (1.8%)
	Duodenal stump leakage	2 (1.8%)
	Remnant gastric perforation	1 (0.9%)
	Arrhythmia	1 (0.9%)
	Anastomotic bleeding	1 (0.9%)
	DVT	1 (0.9%)
Adjuvant chemotherapy	Yes	13 (11.9%)

ASA-PS: American Society of Anesthesiologists Physical Status; BMI: body mass index; DVT: deep venous thrombosis; LNs: lymph nodes. *Clavien–Dindo grade ≥2.

Nine patients (n=9, 26.5%) died from recurrence of GC and other cases died from other diseases or unknown reason. OS was significantly poor in the group with postoperative complications of Clavien–Dindo grade ≥2 (Figure 2A, p=0.005), low PNI (<44.2) (Figure 2B, p=0.049) and low BMI (<25 kg/m^2) (Figure 2C; p=0.019). Table V shows the results

Table II. *Comparison of the clinical characteristics between patients with and without postoperative complications of Clavien–Dindo grade ≥2.*

Characteristic	Subgroup	Postoperative complications		*p*-Value
		With (n=29)	Without (n=80)	
Gender	Male	17 (25.0%)	51 (75.0%)	0.263
	Female	12 (29.3%)	29 (70.7%)	
BMI	≥25 kg/m^2	8 (44.4%)	10 (55.6%)	0.080
	<25 kg/m^2	21 (23.1%)	70 (76.9%)	
ASA-PS	I, II	27 (27.8%)	70 (72.2%)	0.510
	III, IV	2 (16.7%)	10 (83.3%)	
Serum albumin level	≥3.5 g/dl	23 (27.4%)	61 (72.6%)	0.803
	<3.5 g/dl	6 (24.0%)	19 (76.0%)	
PNI	≥44.2	21 (29.2%)	51 (70.8%)	0.495
	<44.2	8 (21.6%)	29 (78.4%)	
Diabetes mellitus	Yes	7 (29.2%)	17 (70.8%)	0.796
	No	22 (25.9%)	63 (74.1%)	
Hypertension	Yes	22 (27.5%)	58 (72.5%)	0.810
	No	7 (24.1%)	22 (75.9%)	
Cardiovascular disease	Yes	12 (34.3%)	23 (65.7%)	0.249
	No	17 (23.0%)	57 (77.0%)	
Renal disease	Yes	4 (21.1%)	15 (78.9%)	0.776
	No	25 (27.8%)	65 (72.2%)	
Respiratory disease	Yes	3 (20.0%)	12 (80.0%)	0.755
	No	26 (27.7%)	68 (72.3%)	
Hepatic disease	Yes	1 (16.7%)	5 (83.3%)	0.136
	No	28 (27.2%)	75 (72.8%)	
Dementia	Yes	3 (27.3%)	8 (72.7%)	>0.999
	No	26 (26.5%)	72 (73.5%)	
Anticoagulation therapy	Yes	7 (30.4%)	16 (69.6%)	0.608
	No	22 (25.6%)	64 (74.4%)	
Surgical approach	Open	19 (35.2%)	35 (64.8%)	0.053
	Laparoscopic	10 (18.2%)	45 (81.8%)	
Total gastrectomy	Yes	13 (35.1%)	24 (64.9%)	0.173
	No	16 (22.2%)	56 (77.8%)	
D2 Lymph node dissection	Yes	10 (26.3%)	28 (73.7%)	>0.999
	No	19 (26.8%)	52 (73.2%)	
Blood loss	≥170 ml	19 (48.7%)	20 (51.3%)	<0.001
	<170 ml	10 (14.3%)	60 (85.7%)	
Blood transfusion	Yes	5 (23.8%)	16 (76.2%)	>0.999
	No	24 (27.3%)	64 (72.7%)	
Pathological stage	I	11 (21.2%)	41 (78.8%)	0.279
	II, III	18 (31.6%)	39 (68.4%)	
Histological type	Differentiated	21 (30.0%)	49 (70.0%)	0.367
	Undifferentiated	8 (20.5%)	31 (79.5%)	

ASA-PS: American Society of Anesthesiologists Physical Status; BMI: body mass index; PNI: prognostic nutritional index.

of univariate and multivariate analyses of risk factors for a poor OS. Multivariate analysis showed that postoperative complications (OR=2.380, 95% CI=1.190-4.761; p=0.014) and low PNI (<44.2) (OR=2.056, 95% CI=1.019-4.148; p=0.044) were independent prognostic factors for poor OS.

Discussion

In Japan, the number of deaths due to GC in elderly patients has been increasing despite the decrease in overall GC-related death following the introduction of eradication therapy for *H. pylori*-related gastritis (16). Most incident cases and deaths are in patients aged ≥60 years and are prominent among those aged ≥70 years. The number of GC-related deaths in patients in their 80s was two times higher than that in patients in their 70s and four times higher than that in patients in their 60s (16). To identify the prognostic factors after gastrectomy for very elderly patients, we performed this study on this cohort.

Although gastrectomy is a curative treatment for GC, both postoperative complications and mortality are reported to be

Table III. *Clinical factors predicting postoperative complications of Clavien–Dindo grade ≥2 after curative gastrectomy for gastric cancer in patients aged ≥80 years.*

		Univariate analysis	Multivariate analysis		
Factor	Subgroup	*p*-Value	HR	95% CI	*p*-Value
Gender	Male	0.196			
BMI	≥25 kg/m^2	0.067			
ASA-PS	≥3	0.416			
Serum albumin level	≥3.5 g/dl	0.866			
PNI	≥44.2	0.400			
Diabetes mellitus	Yes *vs*. no	0.748			
Hypertension	Yes *vs*. no	0.726			
Cardiovascular disease	Yes *vs*. no	0.215			
Renal disease	Yes *vs*. no	0.548			
Respiratory disease	Yes *vs*. no	0.535			
Hepatic disease	Yes *vs*. no	0.577			
Dementia	Yes *vs*. no	0.958			
Anticoagulation therapy	Yes *vs*. no	0.640			
Surgical approach	Open *vs*. laparoscopic	0.048	2.135	0.831-5.485	0.115
Gastrectomy	Total *vs*. other	0.152			
Lymph node dissection	D2 *vs*. other	0.960			
Operative time	≥292 min	0.805			
Blood loss	≥170 ml	<0.001	5.347	2.110-13.551	<0.001
Blood transfusion	Yes *vs*. no	0.747			
Pathological stage	II-III vs I	0.221			
Histological type	Differentiated *vs*. undifferentiated	0.285			

ASA-PS: American Society of Anesthesiologists Physical Status; BMI: body mass index; CI: confidence interval; HR: hazard ratio.

high in aged patients with GC (17). Several studies reported the risk factors for postoperative complications and long-term poor survival after gastrectomy for GC in elderly patients (7, 12, 13, 18-22). However, most of these compared the outcomes of very elderly patients with those of younger patients. The risk factors for poor OS after gastrectomy in very elderly patients have not been fully established. Meta-analysis confirmed that very elderly patients had preoperative comorbidities and experienced postoperative complications more frequently than younger patients (7). In that analysis, the rates of respiratory complications, cardiac events, abscess, and anastomotic leakage were higher among very elderly patients after gastrectomy compared to patients younger than 80 years (7).

Several risk factors for postoperative complications after gastrectomy in elderly patients were reported as follows: Low serum albumin level (18), low preoperative albumin-to-fibrinogen ratio as a nutrition-inflammation score (19), male sex (18, 23), and total gastrectomy (18). Our cohort revealed that greater intraoperative blood loss is a risk factor for postoperative complications. Although there was no significant difference between surgical approaches, laparoscopic surgery tended to reduce the risk of postoperative complications. Several other studies have reported that laparoscopic surgery for very elderly patients is considered to be safe with comparable (20, 24) or lower (23) complication rates.

Regarding long-term survival, the reported 3-year OS ranged from 47.9% to 74.2% (20, 21, 25, 26) after curative gastrectomy for GC in very elderly patients. Our cohort showed comparable outcomes. Postoperative complications have a negative influence on long-term survival, with a reduction in tolerance of adjuvant chemotherapy (9, 10), and can have an effect on the progression of the malignancy because of host immunosuppression and inflammatory change (27). Adjuvant chemotherapy followed by gastrectomy with D2 lymph node dissection for patients with stage II and III disease is recommended by the Japanese guidelines for the treatment of GC, based on the ACTS-GC trial, which included patients aged 80 years or younger (28, 29). Our cohort included 13 patients (22.8%) who received adjuvant chemotherapy among the 57 patients with stage II or III disease. Although there was no statistical difference, the rate of patients who had adjuvant chemotherapy and experienced postoperative complications tended to be lower (15.4% vs. 36.4%, p=0.19). From this result, postoperative complications might have a negative influence on the long-term outcome in very elderly patients.

Our result also showed that low PNI was associated with poor long-term survival. The PNI is based on a combination

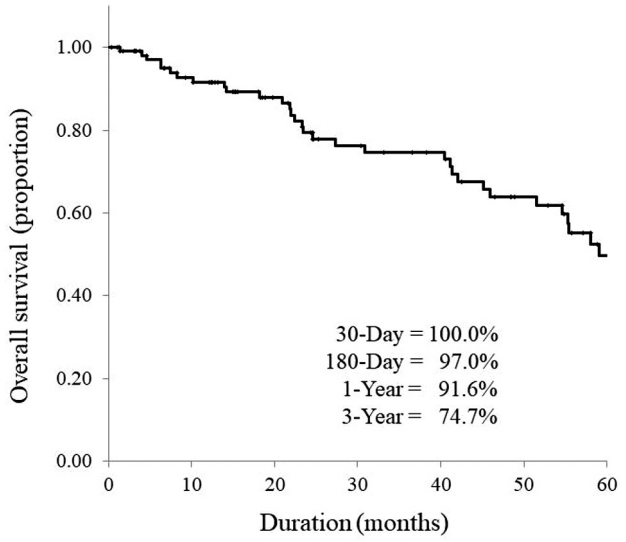

Figure 1. *Overall survival estimates (n=109).*

Table IV. *Number and cause of death at various intervals after surgery (n=34).*

Time after operation		Frequency
≤30 Days	Total	0 (0.0%)
>30-180 Days	Total	3 (8.8%)
	Anastomotic leakage	1
	Pneumonia	1
	Unknown	1
>180≤1year	Total	5 (14.7%)
	Terminal malignancy	2
	Gastrointestinal perforations	1
	Other malignant disease	1
	Unknown	1
>1-3 Years	Total	12 (35.3%)
	Terminal malignancy	6
	Pneumonia	1
	Other malignant disease	1
	Unknown	4
>3 Years	Total	14 (41.2%)
	Other malignant disease	2
	Terminal malignancy	1
	Stroke	1
	Unknown	10

of the serum albumin level and lymphocyte count. Several other studies reported low PNI as a predictor of poor OS after gastrectomy for GC in elderly patients (20, 30, 31). Low PNI values can be associated with indigestion and inadequate caloric intake, leading to physical inactivity and immune dysfunction in patients with GC. It can also contribute to earlier tumor recurrence and shorter survival time (30).

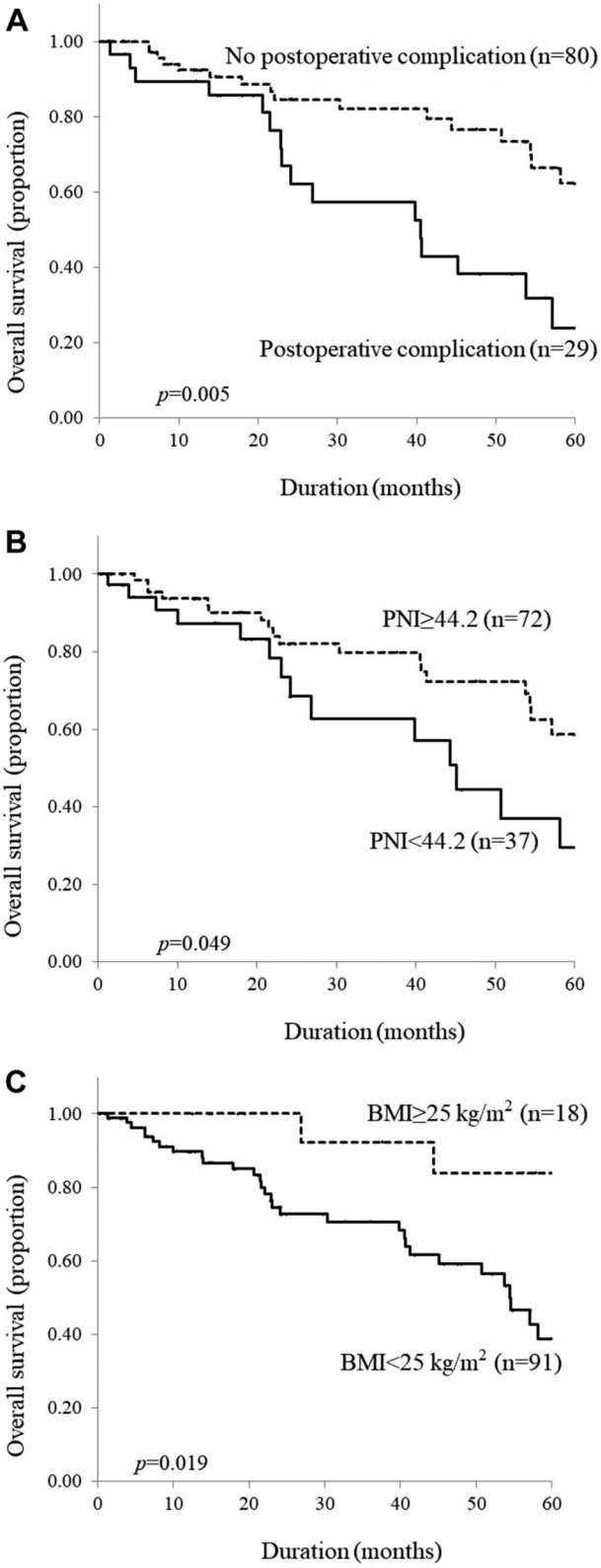

Figure 2. *Overall survival (OS) estimates based on the (A) presence or absence of postoperative complications, (B) PNI ≥44.2 vs. PNI <44.2, and (C) BMI ≥25 kg/m^2 vs. BMI <25 kg/m^2.*

Table V. *Clinical factors predicting overall survival after curative gastrectomy for gastric cancer in patients aged ≥80 years.*

		Univariate analysis	Multivariate analysis		
		p-Value	HR	95% CI	*p*-Value
Gender	Male	0.551			
BMI	≥25 kg/m^2	0.019	3.001	0.902-9.980	0.073
ASA-PS	≥3	0.939			
PNI	≥44.2	0.049	2.056	1.019-4.148	0.044
Diabetes mellitus	Yes *vs*. no	0.554			
Hypertension	Yes *vs*. no	0.780			
Cardiovascular disease	Yes *vs*. no	0.326			
Renal disease	Yes *vs*. no	0.800			
Respiratory disease	Yes *vs*. no	0.692			
Hepatic disease	Yes *vs*. no	0.402			
Dementia	Yes *vs*. no	0.151			
Anticoagulation therapy	Yes *vs*. no	0.824			
Surgical approach	Open *vs*. laparoscopic	0.518			
Gastrectomy	Total *vs*. other	0.712			
Lymph node dissection	D2	0.679			
Operative time	≥292 min	0.222			
Blood loss	≥170 ml	0.502			
Blood transfusion	Yes *vs*. no	0.361			
Postoperative complications*	Yes *vs*. no	0.005	2.380	1.190-4.761	0.014
Pathological stage	II-III *vs*. I	0.075			
Histological type	Differentiated *vs*. undifferentiated	0.171			
Adjuvant chemotherapy	Yes *vs*. no	0.659			

ASA-PS: American Society of Anesthesiologists Physical Status; BMI: body mass index; CI: confidence interval; HR: hazard ratio. *Clavien–Dindo grade ≥2.

There have been several studies on the relationship between BMI and postoperative outcomes in GC. Patients with higher BMI (>25 kg/m^2) had better postoperative 5-year survival rates, especially for early-stage GC, in a previous report (32). In another study, BMI >30 kg/m^2 was a predictor for better prognosis in patients with cancer (33). In contrast, low BMI (<18.5 kg/m^2) had a negative influence on long-term survival after gastrectomy for GC (34). In their cohort, high BMI was also associated with good long-term outcomes in the univariate analysis. According to our results, a high BMI can be a predictor of better survival after gastrectomy in very elderly patients.

The present study has several limitations. Firstly, the study design was retrospective and the treatment decision depended on the patients, their families, and the surgeons. Secondly, a comparison with patients who were treated without a surgical procedure was not performed.

Our cohort only included consecutive patients aged 80 years or older who had elective curative resection for GC. Data on short-term and long-term outcomes and analysis of the risk factors for poor OS after resection for GC in elderly patients are limited.

In conclusion, a greater intraoperative blood loss was an independent risk factor for postoperative complications. Postoperative complications and PNI <44.2 were independent prognostic factors for poor OS after curative resection for GC in patients aged ≥80 years. Performing operations with smaller amounts of bleeding is important to reduce postoperative complications. According to the analysis of long-term survival, patients who experience postoperative complications and patients with a low preoperative PNI require special attention in the follow-up period. Nutritional support should be considered in patients with malnutrition.

Conflicts of Interest

None of the Authors has financial interests related to this study to disclose.

Authors' Contributions

Shintaro Hashimoto and Masato Araki were responsible for the study concept. Shintaro Hashimoto, Masato Araki, Yorihisa Sumida, Kouki Wakata, Kiyoaki Hamada, Tota Kugiyama, Ayako Shibuya and Masato Nishimuta collaborated in the patients' medical care. Yorihisa Sumida and Akihiro Nakamura reviewed the article. All Authors approved the final article.

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