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Impact of Frailty on Postoperative Outcomes for Laparoscopic Gastrectomy in Patients Older than 80 Years

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ABSTRACT

Background. This study aimed to clarify the relationship between frailty and postoperative outcomes of laparoscopic gastrectomy for old–old patients with resectable gastric cancer.

Methods. The study retrospectively analyzed 96 consecutive patients (age $\geq$ 80 years) who had undergone R0 resection by laparoscopic gastrectomy for gastric cancer between 2006 and 2012. The patients were retrospectively scored using the clinical frailty scale (CFS) and categorized based on their scores (1–2, 3–4, and 5–7). Postoperative complications, 5-year survival rate, risk factors for morbidity, and prognosis were analyzed.

Results. The morbidity rate for Clavien–Dindo grades 2 or higher and 3a or higher were respectively 27.1% and 12.5%. Operative complications, especially systemic complications, were positively associated with an increase in CFS scores (p = 0.026). The overall 5-year survival rate was 59.8%, and the 5-year survival rates for those with a CFS score of 1–2, 3–4, and 5–7 were respectively 70.9%, 59.8%, and 35.1%. Specifically, the prognosis for the patients with a CFS score of 5–7 with stage 2 or 3 disease was significantly worse than for those with a lower CFS score (p = 0.009). The multivariate analysis showed that a total gastrectomy or blood loss of 200 g or more was a significant risk factor for morbidity (both p = 0.004), and that the independent risk factors for overall survival were a CFS score of 5–7 (p = 0.006), a body mass index lower than 18.5 kg/m^2 (p = 0.039), and morbidity (grade $\geq$ 3a; p = 0.002).

Conclusions. Frailty has a great impact on operative morbidity and prognosis in the elderly, and the CFS score could be a promising prognostic predictor, especially for frail patients with advanced gastric cancer.

Gastric cancer is the third most common cause of deaths in Japan.[1] Population aging means that the old–old population (age $\geq$ 80 years) with gastric cancer has been increasing. This has corresponded with advances in minimally invasive surgery, faster recovery times and improved outcomes after surgery.[2] Several studies have shown favorable short-term outcomes of laparoscopic gastrectomy (LG) for elderly patients with early gastric cancer, but the long- and short-term outcomes for the old–old patients with advanced gastric cancer remain unclear.[3–11]

Advanced age is one of the most common factors contributing to postoperative complications, sometimes leading to extended convalescence and hospital stays that can adversely affect a person's quality of life.[12,13] However, in practice, some elderly patients recover better, and others fare worse than expected.[13] Frailty, defined as impaired physical response to stressors, portends increased vulnerability to adverse outcomes after stressful medical or surgical conditions.[14] Recently, frailty has attracted attention because of the increasing elderly population. A frail patient's loss of energy reserves, physical ability, cognition, and health leads to vulnerability.[15] Thus, postoperative outcomes for elderly patients with gastric cancer might be affected by their frailty. Among the currently available measurements of frailty, the clinical frailty

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scale (CFS) is reported to be a simple, semi-quantitative tool that provides clinically valuable evaluation of frailty.[15,16]

This study was designed to determine the relationship between frailties evaluated using CFS and postoperative outcomes of LG for old–old patients with resectable gastric cancer.

PATIENTS AND METHODS

Patients

We performed a retrospective review of our prospectively maintained database and identified consecutive patients with a diagnosis of gastric cancer between 2006 and 2012. In the Department of Surgery, Fujita Health University Hospital, 111 consecutive elderly patients age 80 years or older underwent gastrectomy (1 open, 8 robotic, 102 laparoscopic surgeries). Among the 102 patients who underwent LG, R0 resection was achieved for 96 patients, who were enrolled in the study for data analysis.

Routine preoperative evaluation to determine operability included a complete blood count, serum chemistry, arterial blood gas analysis, electrocardiography, spirometry, creatinine clearance (Ccr), activated partial thromboplastin time, and prothrombin time. The patients who met the following criteria were considered eligible for radical gastrectomy under general anesthesia: Eastern Cooperative Oncology Group (ECOG) performance status[17] ≤ 2, white blood cell count $\geq 3000/mm^3$, hemoglobin concentration ≥ 10 g/dL, platelet count $\geq 100{,}000/mm^3$, total bilirubin ≤ 1.2 mg/dL, aspartate aminotransferase ≤ 80 IU/L, alanine aminotransferase ≤ 80 IU/L, serum creatinine ≤ 1.2 mg/dL, blood urea nitrogen ≤ 25 mg/dL, Ccr ≥ 60 mL/min, arterial oxygen pressure (PaO_2) ≥ 70 torr, forced expiratory volume in 1 s > 1.5 L, percentage of vital capacity $> 40\%$, and fasting blood sugar count < 140 mg/dL.

The patients were involved in all decisions and provided informed consent to participate in the study. This study was approved by the institutional review board of our hospital.

Classification of CFS Score

According to the CFS criteria, 96 eligible patients were evaluated and scored using clinical data obtained from medical records.[15] For simplicity, the CFS scores (1: very fit, 2: well, 3: well with treated comorbid disease, 4: apparently vulnerable, 5: mildly frail, 6: moderately frail, and 7: severely frail) were categorized into the following three simple classes of increasing frailty based on the following scores: 1–2 (without significant frailty, fit), 3–4 (not active but independent, vulnerable), and 5–7 (severe limitations in activities, frail).[16]

Procedures

The extent of lymph node dissection was determined based on the consensus of experienced surgeons at the weekly preoperative case conferences, considering the *Japanese Gastric Cancer Treatment Guidelines 2014* (version 4) as well as the aforementioned stage eligibility criteria for radical gastrectomy, comorbidities, and nonobjective parameters such as appearance, motivation, and family support. Basically, standard gastrectomy with D2 lymph node dissection was indicated for potentially curable T2–T4 tumors and cT1N+ tumors ($n = 12$), whereas modified gastrectomy with reduced lymph node dissection (D1+ or D1) was indicated for cT1N0 tumors ($n = 49$).[18] However, modified gastrectomy also was used on some elderly patients with advanced gastric cancer ($n = 35$).

In this study, D1 lymphadenectomy included No. 8a for distal gastrectomy and No. 8a and 9 for total gastrectomy. Conversely, D2 lymphadenectomy included spleen-preserving lymphadenectomy with or without No. 10 sampling in total gastrectomy. The surgical approach (laparoscopic or open surgery in 2006–2008; laparoscopic, robotic, or open surgery in 2009–2012) was chosen by patient preference. All surgery was performed or guided by I.U., S.K., or S.S., each of whom had performed at least 100 totally laparoscopic D2 gastrectomy procedures.

Outcomes of Interest

Each patient was categorized into one of three groups (fit, vulnerable, or frail) based on the retrospectively assessed CFS scores. The clinicopathologic features and the short- and long-term outcomes for each group were examined, and the factors contributing to postoperative complications and prognosis were evaluated. The postoperative complications were graded by the Clavien–Dindo (CD) classification.[19,20] Any complication classified as grade 2 or higher was considered clinically significant. The postoperative complications were classified as systemic complications (e.g., pseudomembranous colitis, pneumonia, respiratory failure, cardiac failure, arrhythmia, delirium) or local complications (anastomotic leakage, stasis, wound infection, pancreatic fistula, abdominal abscess, intraabdominal bleeding, anastomotic stenosis, entero-cutaneous fistula). Operative mortality was defined as CD grade 5 within 30 days after gastrectomy.

Nutritional status was evaluated using Onodera's Prognostic Nutrition Index (PNI) ([10 $\times$ albumin

g/dL] + [0.005 × total lymphocyte count/mm^3])[21–23] and the patients' hemoglobin and albumin levels. Comorbidities were classified according to the Charlson Comorbidity Index (CCI).[24] Cancer staging was determined based on the *Japanese Classification of Gastric Carcinoma,* 14th edition.[25]

To determine the long-term outcomes, we evaluated the patients on the basis of overall survival (OS) and disease-specific survival (DSS) not affected by other causes of death. The OS time was determined as the time from the diagnosis of gastric cancer to death for any reason or to the interruption of the follow-up evaluation. The DSS time was determined as the time from the diagnosis of gastric cancer to death from the primary disease, including operative mortality but excluding other causes of death, or to the interruption of the follow-up evaluation.

Statistical Analysis

Statistical analysis was performed using IBM SPSS version 22.0 J for Windows (IBM Corp., Armonk, NY, USA). The Chi square test, Fischer's exact test, the Kruskal–Wallis test, and logistic regression analysis were used for statistical analysis as appropriate. Long-term outcomes were analyzed using the Kaplan–Meier method with the log-rank test and the Cox proportional hazard model. Data are expressed as the median (range) unless otherwise stated. Multivariate analysis was performed with the variables that had a p value lower than 0.10 in univariate analysis. Otherwise, a p value lower than 0.05 (two-tailed) was considered statistically significant.

RESULTS

Patient Characteristics and Operative Outcomes

The characteristics and operative outcomes of all 96 eligible patients ages 80–92 years stratified according to CFS scores (1–2, 3–4, and 5–7) are summarized in Table 1. Significant differences among the three groups were observed in terms of Performance status ($p < 0.001$), American Society of Anesthesiology (ASA) score ($p < 0.001$), comorbidity ($p < 0.001$), CCI ($p < 0.001$), preoperative hemoglobin ($p = 0.022$), preoperative albumin ($p < 0.001$), PNI ($p < 0.001$), preoperative blood transfusion ($p = 0.008$), tumor depth ($p = 0.012$), and pStage ($p = 0.011$). In other words, as the CFS increased, the number of patients with lower activities, poorer nutrition status, and higher tumor stages also increased. No significant differences in operative time, blood loss, or postoperative hospital stays were observed. Regarding quality-of-life parameters 12 months after surgery, the CFS score ($p < 0.001$), performance status ($p = 0.042$), and albumin levels ($p = 0.031$) differed significantly among the three groups.

Postoperative Complications

Descriptive results for the complication rates are summarized in Table 2. The postoperative complications were CD 2 or higher for 26 patients (27.1%) and CD 3a or higher for 12 patients (12.5%). Pancreatic fistula was seen in three patients (3.1%), all of whom were CD 3a or higher. Three deaths occurred in this study (3.1%). The causes were anastomotic leakage from an esophagojejunostomy, severe pancreatic fistula caused by tumor dissection from the pancreatic head, and pulmonary edema followed by respiratory failure. The mortality rate was considerably high (11.8%) in the CFS 5–7 group.

We categorized the postoperative complications into systemic and local complications, as shown in Table 2. The systemic complication rate (CD $\geq$ 2) was found to increase as the CFS score increased ($p = 0.026$). Pneumonia and respiratory failure were the most frequent systemic complications, followed by cardiac failure and arrhythmia. Anastomotic leakage was the most frequent local complication, followed by stasis and surgical-site infection.

Long-Term Outcomes

The long-term outcomes are summarized in the lower section of Table 2. Tumors recurred in 15 patients (15.6%), with peritoneal and lymph node metastasis as the most common. Only 4 of 15 patients who had tumor recurrence underwent adjuvant chemotherapy after surgery. Moreover, chemotherapy was not used for seven patients after tumor recurrence was determined.

Overall, 32 patients (33.3%) died during the observation period, including 16 patients (16.7%) who died of other diseases, 13 patients (13.5%) who died of primary disease, and 3 patients (3.1%) who died of postoperative complications. The unrelated causes of death were pneumonia (5 patients), other malignancy (3 patients), cardiovascular disease (2 patients), sepsis (1 patient), peritonitis (1 patient), and unknown cause (4 patients).

The 3-year OS and DSS rates were respectively 73.7% and 84.3%, and the 5-year rates were 59.8% and 78.8% (Fig. 1a). The 5-year OS (and DSS) rates stratified as pStages 1, 2, and 3 were respectively 65.5% (98.3%), 35.6% (54.8%), and 49.3% (59.2%) (Fig. 1b). The 3- and 5-year OS and DSS rates are summarized in the lower part of Table 3 for all the patients according to CFS scores 1–2, 3–4, and 5–7. The 5-year OS (and DSS) rates were 70.9% (86.0%) for CFS scores 1–2, 59.8% (80.2%) for CFS scores 3–4, and 35.1% (54.1%) for CFS scores 5–7. The 3- and 5-year OS and DSS rates decreased as the CFS score increased. The Kaplan–Meier survival curves of

TABLE 1 Clinicopathologic features and operative outcomes in 96 old–old patients by clinical frailty scale (CFS) score

		All (n = 96)	CFS score			p Value
			1–2 (n = 27)	3–4 (n = 52)	5–7 (n = 17)	
Clinicopathologic features						
Age (years)	Median (range)	82 (80–92)	81 (80–86)	82 (80–91)	83 (80–92)	0.098
Sex	Male/female	70/26	19/8	41/11	10/7	0.245
BMI	Median (range)	21.3				
(15.2–27.7)	21.8 (15.4–25.3)	20.9				
(15.7–26.3)	21.9 (15.2–27.7)	0.596				
Performance status (ECOG)	0/1/2/3/4	24/58/8/5/1	15/12/0/0/0	9/36/5/2/0	0/10/3/3/1	< 0.001
ASA	2/3	58/38	26/1	28/24	4/13	< 0.001
Comorbidity	Present/absent	88/8	19/8	52/0	17/0	< 0.001
CCI	0/1–2/3–4/5–	32/53/10/1	19/8/0/0	13/34/5/0	0/11/5/1	< 0.001
Preoperative hemoglobin (g/dL)	Median (range)	11.8 (7.4–16.1)	12.4 (9.2–15.5)	11.9 (7.4–16.1)	11.0 (8.5–13.5)	0.022
Preoperative albumin (g/dL)	Median (range)	3.9 (2.4–5.0)	4.1 (3.5–5.0)	3.7 (2.8–4.5)	3.5 (2.4–4.4)	< 0.001
PNI	Median (range)	45.5				
(26.6–57.8)	50.3 (38.1–57.8)	44.5				
(35.5–54.3)	43.3 (26.6–52.3)	< 0.001				
Preoperative blood transfusion	Present/absent	11/85	0/27	6/46	5/12	0.008
Dementia	Present/absent	8/88	0/27	5/47	3/14	0.065
Tumor depth	cT1/cT2≤	51/45	20/7	26/26	5/12	0.012
pStage	1/3/4	58/18/20	21/5/1	31/7/14	6/6/5	0.011
Preoperative chemotherapy	Present/absent	6/90	2/25	3/49	1/16	1.000
Postoperative chemotherapy	Present/absent	9/87	2/25	6/46	1/16	0.805
Short-term outcomes						
Type of resection	DG/TG/CG/PG	65/17/7/7	20/3/2/2	33/12/3/4	12/2/2/1	0.828
Extent of lymphadenectomy	Standard (D2)/modified (≤ D1+)	12/84(51/33)	5/22(10/12)	4/48(35/13)	3/14(6/8)	0.308
Compliance of lymphadenectomy with the guidelines	Yes/no	50/46	18/9	25/27	7/10	0.180
Operative time (min)	Median (range)	279 (152–600)	291 (152–479)	266 (180–600)	298 (164–475)	0.875
Blood loss (g)	Median (range)	31 (0–770)	33.0 (0–288)	26.5 (0–770)	70.0 (0–689)	0.376
Postoperative hospital stay (days)	Median (range)	16 (8–128)	14 (8–47)	17 (8–128)	17 (11–62)	0.567
QoL-related parameters						
CFS at PO 12 months	1–2/3–4/5–7/not assessed	21/41/13/21	21/1/2/3	0/38/4/10	0/2/7/8	0.001
Performance status at PO 12 months	0/1/2/3/4/not assessed	5/48/15/5/2/21	5/16/2/1/0/3	0/27/10/3/2/10	0/5/3/1/0/8	0.042
Deterioration of performance status	Yes/no/not assessed	27/48/21	9/15/3	16/26/10	2/7/8	0.740
Postoperative/preoperative BW ratio	Median (range)	0.90				
(0.72–1.10)	0.91 (0.74–1.10)	0.89				
(0.72–1.02)	0.92 (0.76–0.99)	0.196				
BMI at PO 12 months	Median (range)	18.9 (13–23)	19.2 (15–23)	18.5 (13–23)	19.2 (14–23)	0.236
Albumin at PO 12 months	Median (range)	3.9 (1.4–4.8)	4.2 (1.4–4.8)	3.9 (2.6–4.8)	3.6 (3.1–4.5)	0.031
Postoperative/preoperative albumin ratio	Median (range)	1.00				
(0.32–1.67)	1.01 (0.32–1.20)	1.00				
(0.67–1.32)	1.06 (0.84–1.67)	0.492				

BMI Body Mass Index, *ECOG* Eastern Cooperative Oncology Group, *ASA* American Society of Anesthesiologists, *CCI* Charlson Comorbidity Index, *PNI* Prognostic Nutrition Index, *DG* distal gastrectomy, *TG* total gastrectomy, *CG* completion gastrectomy, *PG* proximal gastrectomy, *QoL* quality of life, *PO* postoperative

TABLE 2 Postoperative complications and long-term outcomes for 96 old–old patients by clinical frailty scale (CFS) score

	All (n = 96) n (%)	CFS Score			p Value
		1–2 (n = 27) n (%)	3–4 (n = 52) n (%)	5–7 (n = 17) n (%)	
Postoperative complications					
Morbidity (CD ≥ 2)	26 (27.1)	4 (14.8)	14 (26.9)	8 (47.1)	0.071
Systemic complications	10 (10.4)	0	6 (11.5)	4 (23.5)	0.026
Pneumonia	4 (4.2)	0	2 (3.8)	2 (11.8)	
Respiratory failure	4 (4.2)	0	2 (3.8)	2 (11.8)	
Cardiac failure	3 (3.1)	0	2 (3.8)	1 (5.9)	
Arrhythmia	3 (3.1)	0	1 (1.9)	2 (11.8)	
Delirium	2 (2.1)	0	1 (1.9)	1 (5.9)	
Pseudomembranous colitis	1 (1.0)	0	0	1 (5.9)	
Local complications	19 (19.8)	4 (14.8)	9 (17.3)	6 (35.3)	0.237
Anastomotic leakage	5 (5.2)	1 (3.7)	3 (5.8)	1 (5.9)	
Stasis	4 (4.2)	1 (3.7)	2 (3.8)	1 (5.9)	
Wound infection	4 (4.2)	1 (3.7)	2 (3.8)	1 (5.9)	
Pancreatic fistula	3 (3.1)	1 (3.7)	1 (1.9)	1 (5.9)	
Abdominal abscess	3 (3.1)	1 (3.7)	0	2 (11.8)	
Intraabdominal bleeding	1 (1.0)	0	0	1 (5.9)	
Anastomotic stenosis	1 (1.0)	0	1 (1.9)	0	
Enterocutaneous fistula	1 (1.0)	0	0	1 (5.9)	
All complications (CD ≥ 3a)	12.0 (12.5)	2 (7.4)	7 (13.5)	3 (17.6)	0.591
Systemic complication (CD ≥ 3a)	4 (4.2)	0	2 (3.8)	2 (11.8)	0.152
Local complication (CD ≥ 3a)	10 (10.4)	2 (7.4)	5 (9.6)	3 (17.6)	0.536
Mortality	3 (3.1)	0	1 (2.0)	2 (11.8)	0.142
Long-term outcomes					
Tumor recurrence	15 (15.6)	3 (11.1)	8 (15.4)	4 (23.5)	0.557
Recurrence site (P/LN/H/bone/Pul/local)	6/6/5/1/1/1	1/1/0/1/0/0	2/4/4/0/1/0	3/1/1/0/0/1	–
pStage (2/3)	7/8	2/1	3/5	2/2	0.804
Adjuvant chemotherapy (yes/no)	4/11	1/2	2/6	1/3	1.000
Chemotherapy for recurrent disease (yes/no)	8/7	0/3	6/2	2/2	0.125
Survival event	32 (33.3)	7 (25.9)	17 (32.7)	8 (47.1)	0.393
Operative-related death	3 (3.1)	0	1 (1.9)	2 (11.8)	0.142
Tumor-related death	13 (13.5)	3 (11.1)	7 (13.5)	3 (17.6)	0.847
Other cause of death	16 (16.7)	4 (14.8)	9 (17.3)	3 (17.6)	1.000
Survival rates (%)					
All stages					
OS (3-year/5-year)	73.7/59.8	87.6/70.9	76.0/59.8	35.1/35.1	0.001/0.008
DSS (3-year/5-year)	84.3/78.8	91.1/86.0	87.4/80.2	54.1/54.1	0.014/0.034
pStage 1					
OS (3-year/5-year)	83.1/73.3	95.0/79.2	75.7/68.8	75.0/–	0.251/0.579
pStages 2 and 3					
OS (3-year/5-year)	59.9/40.5	66.7/44.4	75.2/47.7	17.1/17.1	0.008/0.032

CD, Clavien–Dindo grade; P, Peritoneal; LN, lymph node; H, Liver; Pul, Pulmonary; OS, overall survival; DSS, disease-specific survival

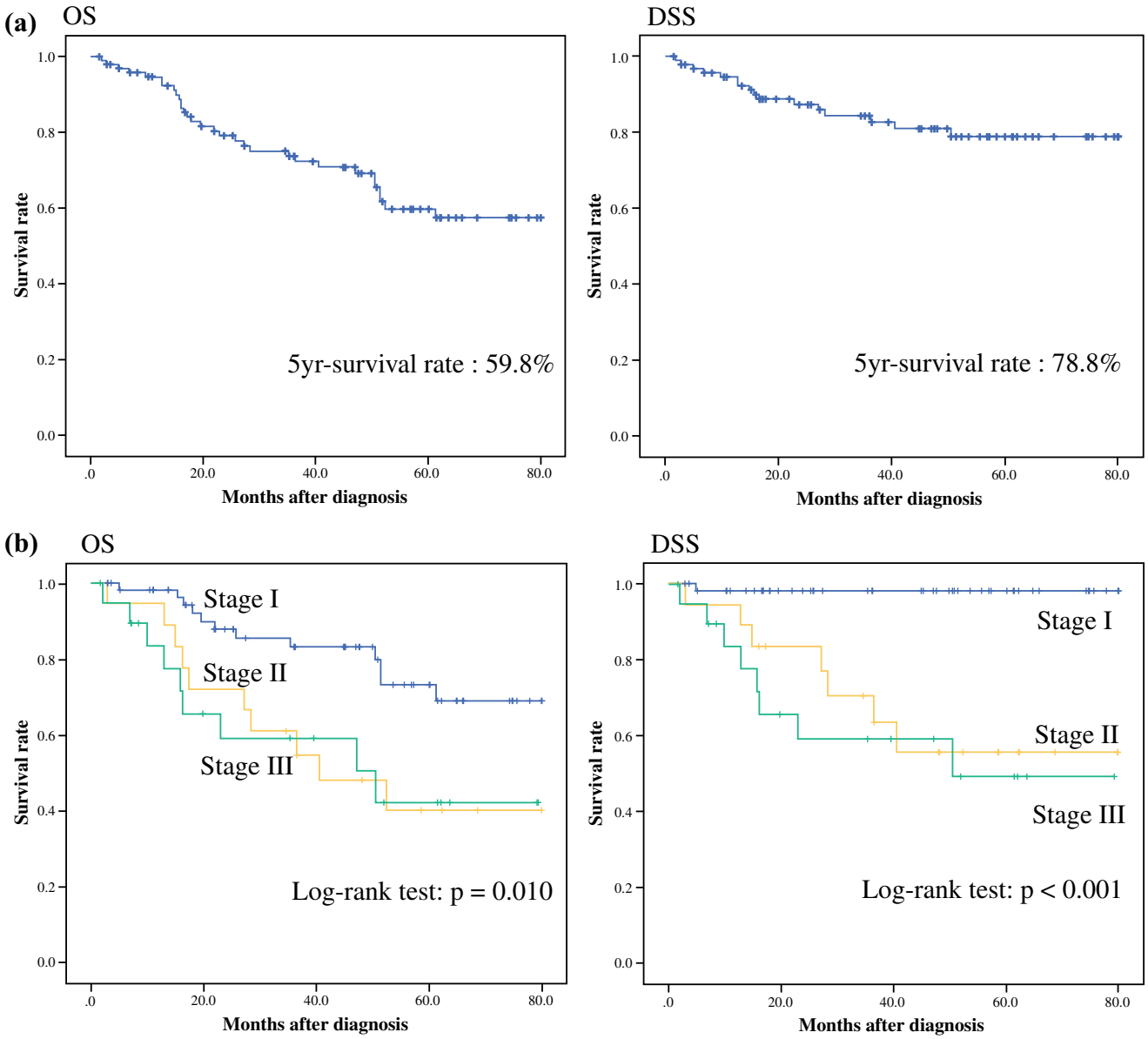

FIG. 1 Kaplan–Meier survival curves. Overall survival (OS) and disease-specific survival (DSS) curves are shown for the 96 old–old patients. The OS and DSS curves are shown for elderly patients stratified by gastric cancer disease stage. Stage 1 (stages 1A and 1B), stage 2 (stages 2A and 2B), stage 3 (stages 3A, 3B, and 3C)

OS and DSS were well stratified by CFS score (respectively $p = 0.008$ and $p = 0.034$ log-rank) (Fig. 2a). The OS in pStage 1 and pStages 2 and 3 disease stratified by CFS scores 1–4 and 5–7 also was assessed (Fig. 2b). The OS for the patients with CFS scores of 5–7 was significantly worse in pStages 2 and 3 ($p = 0.009$) than in pStage 1.

Risk of Complications by Uni- and Multivariate Analyses

The risk factors for complications were analyzed by uni- and multivariate analyses. As shown in Table 3, total gastrectomy/completion gastrectomy (TG/CG) and blood loss were independent risk factors for morbidity. The odds ratio produced by TG/CG and blood loss were respectively 4.654 (95% confidence interval [CI], 1.632–13.275) and 13.570 (95% CI 2.335–80.955). A modified lymphadenectomy was not a risk factor for morbidity.

Analysis of Risk Factors for Prognosis

Finally, we analyzed the risk factors for prognosis based on the OS and DSS rates (Table 3). The univariate analysis showed that a CFS score of 5–7, a hemoglobin (Hb) level

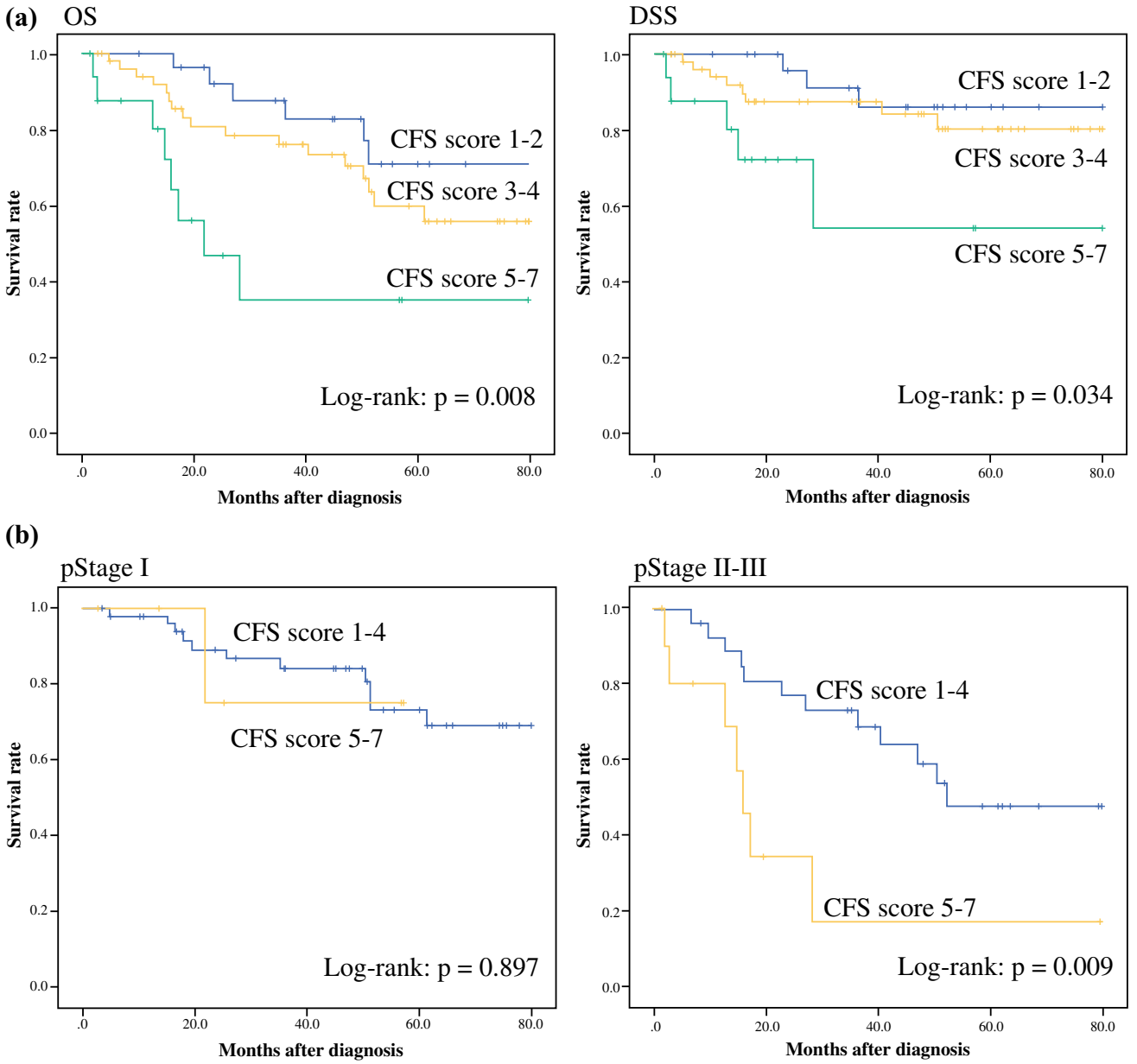

FIG. 2 Kaplan–Meier survival curves stratified by clinical frailty scale (CFS) score. Overall survival (OS) and disease-specific survival (DSS) curves are shown for elderly patients stratified using the three CFS scores as follows: 1–2 (without significant frailty), 3–4 (not active but independent), and 5–7 (severe limitations in activities). The OS curves are shown for elderly patients stratified using two CFS scores as follows: scores 1–4 and scores 5–7 for pStage 1 and pStages 2–3

lower than 10 g/dL, a CD grade of 3a or higher, and a pStage of 2 or higher were significantly associated with OS. The multivariate analysis showed that a CFS score of 5–7 ($p = 0.006$), a body mass index (BMI) lower than 18.5 kg/m^2 ($p = 0.039$), and a CD grade of 3a or higher ($p = 0.002$) were independent prognostic factors for OS. The univariate analysis then indicated that a CFS score of 5–7, a hemoglobin level lower than 10 g/dL, a CD grade of 2 or higher, a CD grade of 3a or higher, and a pStage of 2 or higher were significantly associated with DSS. The multivariate analysis indicated that a CFS of 5–7 ($p = 0.024$), a CD score of 3a or higher ($p = 0.002$), and a pStage of 2 or higher ($p = 0.005$) remained independent prognostic factors for DSS.

DISCUSSION

To the best of our knowledge, this is the first report using the CFS score to suggest that postoperative complications and prognoses are strongly affected by frailty in old–old patients with gastric cancer who undergo LG. The study had three major findings.

TABLE 3 The risk factors for operative complications, overall survival, and disease-specific survival

Variable	Univariate analysis			Multivariate analysis		
	p Value	OR	95% CI	*p* Value	OR	95% CI
All complications (CD ≥ 2)						
CFS score (5–7 vs. 1–2 or 3–4)	0.047	3.012	1.015–8.940	0.107	2.724	0.807–9.198
Age (≥ 83 vs. < 83 years)	0.378	0.662	0.264–1.658			
Sex (male vs. female)	0.295	1.880	0.598–5.414			
BMI (≥ 23.1 vs. < 23.1 kg/m^2)	0.521	1.386	0.512–3.752			
Performance status (≥ 2 vs. 0 or 1)	0.435	1.614	0.486–5.360			
ASA (≥ 3 vs. 2)	0.423	1.451	0.583–3.607			
CCI (≥ 3 vs. 0 or 1–2)	0.988	1.011	0.247–4.143			
PNI (≤ 40 vs. > 40)	0.733	0.961	0.765–1.207			
Preoperative hemoglobin (< 10 vs. ≥ 10 g/dL)	0.608	0.700	0.179–2.738			
Type of resection (TG or CG vs. DG or PG)	0.020	3.215	1.202–8.601	0.004	4.654	1.632–13.275
Modified lymphadenectomy (≤ D1+ vs. D2)	0.393	2.000	0.408–9.810			
Lymphadenectomy (less than the guideline vs. based on the guideline)	0.107	2.133	0.849–5.359			
Operative time (≥ 420 vs. < 420 min)	0.105	2.700	0.813–8.972			
Blood loss (≥ 200 vs. < 200 g)	0.017	8.095	1.462–44.815	0.004	13.750	2.335–80.955
pStage (≥ 2 vs. 1)	0.206	1.800	0.724–4.476			
Overall survival						
CFS (5–7 vs. 1–2 or 3–4)	0.006	3.141	1.390–7.097	0.006	3.428	1.429–8.224
Age (≥ 83 vs. < 83 years)	0.525	0.792	0.387–1.623			
Sex (male vs. female)	0.785	1.114	0.514–2.414			
BMI (< 18.5 vs. ≥ 18.5 kg/m^2)	0.074	2.279	0.924–5.619	0.039	2.718	1.052–7.024
Performance status (≥ 2 vs. 0 or 1)	0.431	1.526	0.533–4.371			
ASA (≥ 3 vs. 2)	0.848	1.073	0.522–2.203			
CCI (≥ 3 vs. 0 or 1–2)	0.890	0.920	0.280–3.021			
PNI (≤ 40 vs. > 40)	0.450	1.008	0.988–1.028			
Preoperative hemoglobin (< 10 vs. ≥ 10 g/dL)	0.034	2.377	1.066–5.302	0.189	1.758	0.758–4.074
Type of resection (TG or CG vs. DG or PG)	0.480	1.323	0.609–2.877			
Modified lymphadenectomy (≤ D1+ vs. D2)	0.714	0.836	0.322–2.174			
Lymphadenectomy (less than the guideline vs. based on the guideline)	0.217	1.561	0.770–3.162			
Morbidity (CD ≥ 2 vs. none)	0.341	1.440	0.680–3.051			
Morbidity (CD ≥ 3a vs. none or 2)	0.002	3.701	1.587–8.635	0.002	4.538	1.777–11.593
pStage (≥ 2 vs. 1)	0.004	2.811	1.380–5.729	0.058	2.052	0.975–4.320
Disease-specific survival						
CFS score (5–7 vs. 1–2 or 3–4)	0.018	3.641	1.224–10.660	0.024	4.002	1.201–13.338
Age (≥ 83 vs. < 83 years)	0.155	0.440	0.142–1.364			
Sex (male vs. female)	0.842	0.898	0.312–2.585			
BMI (< 18.5 vs. ≥ 18.5 kg/m^2)	0.603	0.583	0.076–4.452			
Performance status (≥ 2 vs. 0 or 1)	0.222	2.196	0.622–7.759			
ASA (≥ 3 vs. 2)	0.299	1.681	0.630–4.482			
CCI (≥ 3 vs. 0 or 1–2)	0.622	0.601	0.079–4.548			
PNI (≤ 40 vs. > 40)	0.868	0.941	0.458–1.932			
Preoperative hemoglobin (< 10 vs. ≥ 10 g/dL)	0.009	3.888	1.411–10.713	0.157	2.173	0.741–6.367
Type of resection (TG or CG vs. DG or PG)	0.905	1.072	0.345–3.327			
Modified lymphadenectomy (≤ D1+ vs. D2)	0.161	0.445	0.143–1.380			
Lymphadenectomy (less than the guideline vs. based on the guideline)	0.103	2.409	0.837–6.936			
Morbidity (CD ≥ 2 vs. none)	0.030	2.956	1.108–7.885			
Morbidity (CD ≥ 3a vs. none or 2)	<0.001	6.791	2.449–18.832	0.002	6.063	1.969–18.671

TABLE 3 continued

Variable	Univariate analysis			Multivariate analysis		
	p Value	OR	95% CI	*p* Value	OR	95% CI
pStage (≥ 2 vs. 1)	0.002	26.142	3.451–198.039	0.005	18.477	2.405–141.972

OR odds ratio, *CI* confidence interval, *CD* Clavien–Dindo grade, *CFS* clinical frailty scale, *BMI* Body Mass Index, *ASA* American Society of Anesthesiologists, *CCI* Charlson Comorbidity Index, *PNI* Prognostic Nutritional Index, *TG* total gastrectomy, *CG* completion gastrectomy, *DG* distal gastrectomy, *PG* proximal gastrectomy

First, we identified frailty defined by a CFS score of 5–7, a leptosome defined by a BMI lower than 18.5 kg/m^2, and postoperative complications defined by a CD grade of 3a or higher as independent risk factors for OS. A CFS score of 5–7, a CD grade of 3a or higher, and a pathologic stage were independent risk factors for DSS. These data suggest that among old–old patients, long-term outcomes are affected by oncologic factors as well as physical and surgical factors, consistent with the results of previous reports.[26–28] Given that our patients had many comorbidities, the 5-year OS (59.8%) was much lower than the 5-year DSS (78.8%). This is in agreement with the 5-year OS (51.4%) published in the 2009 annual report of the Japanese Gastric Cancer Association nationwide registry.[29] In our study, modified lymphadenectomy was not an independent prognostic factor for either OS or DSS, which suggested that the oncologic benefit of standard lymphadenectomy might be negated by frailty and postoperative complications in this population. On the other hand, OS in pStages 2 and 3 disease significantly deteriorated for patients with a CFS score of 5–7, suggesting that frailty might have a greater impact on the prognosis of patients with advanced gastric cancer than on the prognosis of patients with early gastric cancer. This might be associated with the data indicating that frailty is associated with poor nutrition (lower albumin, lower PNI, and lower hemoglobin levels), a higher grade of performance status, and poor tolerability of chemotherapy. Further studies are warranted to confirm this association.

Second, frailty was associated with systemic complications. As the CFS score increased, the systemic complication rate increased in this study. This may be true at least partly because the patients with an increased CFS score in our study had severe comorbidities and a worse nutritional status. The morbidity (27.1%) and mortality (3.1%) rates in our series were comparable with those in reports of open gastrectomy (respective ranges of 23.3%–50.5% and 0%–3.8%).[30–34] Although local complications, including pancreatic fistulas (6.5%) and abdominal abscesses (4.8%), were frequently observed in an earlier study by our team, their incidences were lower in this study (both 3.1%).[35] We had expected that modified lymphadenectomy would contribute to fewer postoperative complications, especially local complications, but the procedure was not associated with the incidence of morbidity in this study.[36] In addition, frail patients had not improved their performance status and had poor nutrition 12 months after gastrectomy, even though they had undergone a modified lymphadenectomy.

Third, the CFS score is a simple and easy tool for assessing the patient's preoperative activity of daily living and independence during daily physical and cognitive activity.[37] Although the CFS score does not include an objective measurement of mobility, sarcopenia, or nutritional status, it is strongly associated with poor nutrition. Therefore, patients categorized as having a CFS score of 5–7, especially those with advanced cancer, had higher morbidity and mortality rates, leading to a poorer prognosis.

Surgeons may need to give greater consideration to whether these patients should undergo surgical treatment. Further studies are warranted to determine whether preoperative management to improve the CFS score, including nutritional status before gastrectomy, for this patient population might help to reduce the risk of systemic complications and improve their prognoses.

This study, conducted at a single institution in a retrospective manner, had some limitations. First, the sample was small, and interruption of observation may have affected the reported OS rates. A prospective, large-scale, multicenter study is required to confirm whether the current outcomes are reproducible. Second, the CFS score was determined retrospectively by examining the medical records, which resulted in a severe study limitation in terms of scoring accuracy. Third, a modified lymphadenectomy had been performed for most patients, and a few patients with advanced cancer had undergone adjuvant chemotherapy and/or chemotherapy for the recurrent disease. This might have accounted for the results showing that DSS for pStage 2 patients was mediocre. To determine

whether a modified gastrectomy, but not a standard gastrectomy, would be sufficient for frail patients with advanced gastric cancer, clear indications for a modified gastrectomy should be determined in a future study using the CFS score.

Fourth, only a LG was used in this study, and it is unclear whether the outcomes could be extrapolated to open gastrectomy. Moreover, nonsurgical treatment cases were not included in our database because they had been treated in a different department, and the short- and long-term outcomes for frail patients with gastric cancer who did not undergo surgery were unclear.

In conclusion, frailty could have a great impact on the operative morbidity and prognosis in an old–old cohort, and the CFS score could be a promising prognostic predictor, particularly for frail patients with advanced gastric cancer.

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