ORIGINAL

Prognostic impact of frailty after gastrectomy in elderly gastric cancer patients

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Abstract : Background : Frailty plays a crucial role in cancer patients who have received surgery in this recent aging society. We aimed to investigate frailty as a prognostic factor in elderly gastric cancer (GC) patients who underwent curative gastrectomy. Methods : We analyzed 86 elderly (over 75 years old) GC patients who underwent curative gastrectomy. Patients were assigned to two groups ; frailty group ($n = 29$) and no-frailty group ($n = 57$). Clinicopathological values were compared between the two groups. Results : The OS rate of the frailty group was significantly poorer than that of the no-frailty group (5-yr OS rate ; frailty group 52.49% vs. no-frailty group 74.87%, $p < 0.05$). Multivariate analysis of the OS showed that frailty tended to be significant prognostic factor ($p = 0.09$). The DFS rate of the frailty group was significantly poorer than that of the no-frailty group (5-yr DFS rate ; frailty group 42.30% vs. no-frailty group 71.55%, $p < 0.05$). Multivariate analysis of the DFS showed that frailty tended to be significant prognostic factor ($p = 0.14$). Conclusion : We identified the clinical impact of frailty prognostic factor for elderly GC patients who underwent gastrectomy. J. Med. Invest. 70 : 423-429, August, 2023

Keywords **:** *Gastric cancer, Frailty, Elderly patients*

INTRODUCTION

With the recent increasing aging of society in many countries, the average life expectancy of the elderly has been rising. Major social, medical, and economic consequences result from an aging population (1). With elevated numbers of the elderly cancer patients, the frequency of surgical cases for malignant disease has been increasing (2).

Gastric cancer (GC) is one of the most common malignancies, particularly in East Asia. It results in 44,000 mortalities annually in Japan (3). Although the total number of GC deaths has been decreasing in Japan, those among the elderly has increased (3). Surgical intervention for GC is the only curative treatment and is well standardized. GC surgery can lead to body weight loss, appetite loss, malnutrition anemia, and osteoporosis after surgery despite the curative effect of such a resection (4, 5).

Frailty is a multidimensional and heterogeneous syndrome associated with instability (6-10). It has been gaining attention in surgery with respect to the recently increasingly aged society. We previously reported the significance of frailty in elderly hepatocellular carcinoma patients after hepatectomy and in pancreatic ductal adenocarcinoma patients following pancreatectomy (9, 10). By contrast, little is known about the clinical impact of frailty in GC (11-13).

In the present study, we investigated the clinical impact of frailty in elderly GC patients.

Received for publication December 27, 2022 ; accepted June 21, 2023.

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METHODS

Patients

A total of 86 elderly GC patients who underwent standard curative gastrectomy with regional lymphadenectomy at the Tokushima University Hospital from 2011 to 2015 were enrolled in this study. Patient selection was based on the following inclusion criteria : (1) over 75 years old, (2) without any neoadjuvant chemotherapy, and (3) with pathologically confirmed gastric adenocarcinoma. Patients who received neoadjuvant chemotherapy, palliative surgery, or combined resection (hepatectomy, colectomy) or had a non-adenocarcinoma condition were excluded. All patients signed a written informed consent form for the surgery after detailed explanation of the procedure and the surgical risk. Patient background and disease baseline characteristics were obtained from medical records. The classification of lymph node station was according to the Japanese Classification of Gastric Carcinoma (The 15th edition) (14). The surgical indications followed the Japanese Gastric Cancer Treatment Guidelines 2018 (ver. 5) (15). The median follow-up period was 4.7 years (0.1–9.7 years). Frailty was defined as a clinical frailty scale score of ≥ 4 (9). The immune-nutritional prognostic factors were also assessed using the total lymphocyte count (TLC), lymphocyte c-reactive protein (CRP) ratio (LCR) (16), neutrophil lymphocyte ratio (NLR) (17), modified Glasgow prognostic score (mGPS) (18), and prognostic nutritional index (PNI) (19). The definition of sarcopenia and osteopenia was described previously (20). The frailty assessment was described previously (8, 9). This study was authorized in advance by The Ethics Committee of Tokushima University Hospital (TOCMS : 3215-1). Limited lymph node dissection was defined as lymph node dissected that did not reach recommended lymph node dissection from the Japanese gastric cancer guideline (21).

Definition of comorbidity

Comorbidities in each patient were defined as follows ; renal failure : dialysis or serum creatinine level ≥ 2 mg/dl, liver cirrhosis : preoperative indocyanine green R15 $\geq 15\%$, cardiac

disease : previous history of myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, or heart failure, pulmonary disease : % vital capacity or forced expiratory volume 1.0 ≤ 50%, diabetes mellitus : insulin use, leanness : body mass index (BMI) ≤ 18.5%.

Statistical analysis

Values are shown as the mean ± standard deviation. All statistical analyses were performed using statistical software (JMP 8.0.1. ; SAS Institute, Cary, NC, USA). Chi square test or Mann–Whitney U test were used to compare clinicopathological factors. Overall survival (OS) and disease-free survival (DFS) curves were generated using the Kaplan–Meier method using the log-rank test. Cox proportional hazard regression model was used in multivariate analysis. The variables with a p value < 0.2 on univariate analyses included in the multivariate Cox model. For all statistical analyses, p value < 0.05 was considered to indicate statistical significance.

RESULTS

According to the clinical frailty score, patients were divided to two groups ; frailty group (n = 29) and no-frailty group (n = 57). The distribution of clinical frailty scale scores was shown in Fig. 1. The patients' characteristics in the frailty and no-frailty groups are summarized in Table 1. There were no significant differences in age, sex, BMI, white blood cell count, TLC, serum albumin level, CRP level, tumor markers and comorbidity between the two groups. In terms of the immuno-nutrition status, the respective prognostic scores, including the NLR, PNI, LCR, mGPS, sarcopenia and osteopenia displayed no significant differences between the two groups. Regarding the perioperative factors, there were no significant differences in tumor or surgical factors, including surgical procedure, blood loss, lymph node dissection, and limited lymph node dissection. Respective complications (Clavien–Dindo classification II ≤), including pancreatic fistula, anastomotic leakage, stasis, and pneumonia, showed no significant differences between the two groups (Table 2).

Regarding long-term outcomes, the OS rate of the frailty group was significantly poorer than that of the no-frailty group (5-yr OS rate ; frailty group 52.49% vs. no-frailty group 74.87%, p < 0.05) (Fig. 2a). Univariate analysis of the OS showed that frailty was a significant prognostic factor (p < 0.05) (Table 3). Multivariate analysis revealed that frailty was tended to be an independent prognostic factor (p = 0.09) (Table 3). Furthermore, the DFS rate of the frailty group was significantly poorer than that of the no-frailty group (5-yr DFS rate ; frailty group 42.30% vs. no-frailty group 71.55%, p < 0.05) (Fig. 2b). Univariate analysis of the DFS showed that frailty and CA19-9 were significant prognostic factors (p < 0.05) (Table 4). Multivariate analysis revealed that frailty was tended to be an independent prognostic factor (p = 0.14) (Table 4).

DISCUSSION

In the current study, we identified frailty as a significant prognostic factor in elderly GC patients and a relationship between frailty and clinicopathological factors, including comorbidity and the immune-nutritional status.

Elderly patients have multiple physiological and social problems. Major abdominal surgery for malignancy is generally considered to be associated with a high risk for peri-operative complications in elderly patients. These complications are associated with cardiac, pulmonary, liver, renal, neurological, or metabolic comorbidities. A retrospective cohort study demonstrated that the surgical outcome of GC surgery was comparable between young and elderly patients (22). By contrast, another study suggested that elderly GC patients experienced a higher incidence of postoperative morbidity than non-elderly patients (23). Furthermore, the survival benefit in elderly GC patients were poor because of the high incidence of non-cancer related mortality (23). For some elderly GC patients, it may be appropriate to reconsider the treatment strategy regarding the balance between the invasiveness of the surgery and the patient's prognosis (24).

Frailty is a useful evaluative tool for an individual's functional physiologic reserve and ability rather than chronological age. The frailty prevalence in elderly patients ranged over 4.6–27.3% based on previous reports (25-27). It can predict the patient's response after surgery. In GC, frailty was associated with both the short- and long-term outcomes (11-13). Tanaka *et al*. reported that frailty increased systemic postoperative complications, and frailty and leanness were significant prognostic factors (13).

Several prognostic scores, including the NLR, LCR, PNI, and mGPS, which are the surrogate markers of systemic or local inflammation in the tumor microenvironment, immune-nutritional status, and host-tumor interaction, were recognized as vital biomarkers for several malignancy types (16-19). These scoring systems are readily measurable from routine blood examination and reflects host-immunity, nutritional status and

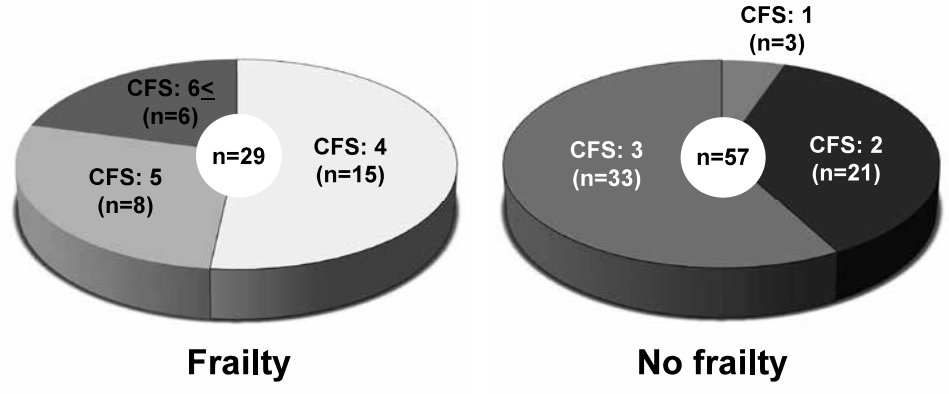

Fig 1. The distribution of clinical frailty scale scores

Table 1. Patients' characteristics in the no-frailty and frailty groups

Variables	No frailty (n = 57)	Frailty (n = 29)	p value
Patients' factors			
Age	80.33 ± 4.16	81.79 ± 4.47	0.10
Male/Female	38/19	21/8	0.58
BMI (kg/m^2)	22.52 ± 3.49	22.28 ± 3.84	0.44
WBC (/μl)	5724 ± 1509	5817 ± 1585	0.77
TLC (/μl)	1408 ± 549	1379 ± 718	0.53
PLT (*10^4/μl)	23.49 ± 10.15	26.18 ± 10.71	0.15
ALB (g/dl)	3.60 ± 0.70	3.50 ± 0.63	0.41
CRP (mg/dl)	0.67 ±1.35	0.25 ± 0.23	0.74
CEA (<5/≥5 ng/ml)	52/5	24/5	0.26
CA19-9 (<37/≥37 IU/ml)	53/4	24/5	0.15
Comorbidity			
Renal failure (No/Yes)	55/2	26/3	0.22
Liver cirrhosis (No/Yes)	53/4	27/2	0.98
Cardiac disease (No/Yes)	54/3	27/2	0.76
Pulmonary disease (No/Yes)	54/3	26/3	0.39
Diabetes mellitus (No/Yes)	55/2	28/1	0.99
Leanness (No/Yes)	54/3	26/3	0.39
Tumor factors			
Differentiation (dif./undif.)	39/18	19/10	0.77
Tumor diameter (mm)	43.79 ± 26.99	43.09 ± 29.30	0.85
fT 1/2/3/4	18/15/16/2	11/6/8/4	0.42
fN (−/+)	29/28	15/14	0.94
Surgical factors			
DG/TG	36/21	16/13	0.48
LN dissection (D0/D1/D1+/D2)	1/5/25/26	0/5/9/15	0.40
Operation time (min)	303.79 ± 68.61	297.69 ± 73.75	0.59
Bleeding (ml)	121.14 ± 107.06	147.48 ± 134.19	0.64
Limited LN dissection (Yes/No)	10/47	6/23	0.22
Immuno-nutrition status			
NLR	4.65 ± 2.27	16.35 ± 63.19	0.41
PNI	42.89 ± 8.57	41.93 ± 8.04	0.49
LCR	16038 ± 12733	12666 ± 12733	0.46
mGPS (0/1, 2)	37/20	17/12	0.57
Sarcopenia (No/Yes)	50/7	24/5	0.54
Osteopenia (No/Yes)	28/29	17/12	0.40

BMI body mass index, *WBC* white blood cell, *TLC* total lymphocyte count, *PLT* platelet, *ALB* white albumin, *CRP* C reactive protein, *CEA*, carcinoembryonic antigen, *CA19-9* carbohydrate antigen 19-9, *DG* distal gastrectomy, *TG* total gastrectomy, *LN* lymph node, *NLR*, neutrophil lymphocyte ratio, *PNI* prognostic nutritional index, *LCR* lymphocyte-to CRP ratio, *mGPS* modified Glasgow Prognostic Score. Values are shown as the mean ± standard deviation.

Table 2. Postoperative morbidity in the no-frailty and frailty groups

Variables	No frailty (n = 57)	Frailty (n = 29)	p value
Pancreatic fistula	4 (7.0%)	0 (0%)	
Anastomotic leakage	1 (1.8%)	2 (6.9%)	
Stasis	1 (1.8%)	2 (6.9%)	
Pneumonia	1 (1.8%)	2 (6.9%)	
Total	7 (12.3%)	6 (20.7%)	0.31

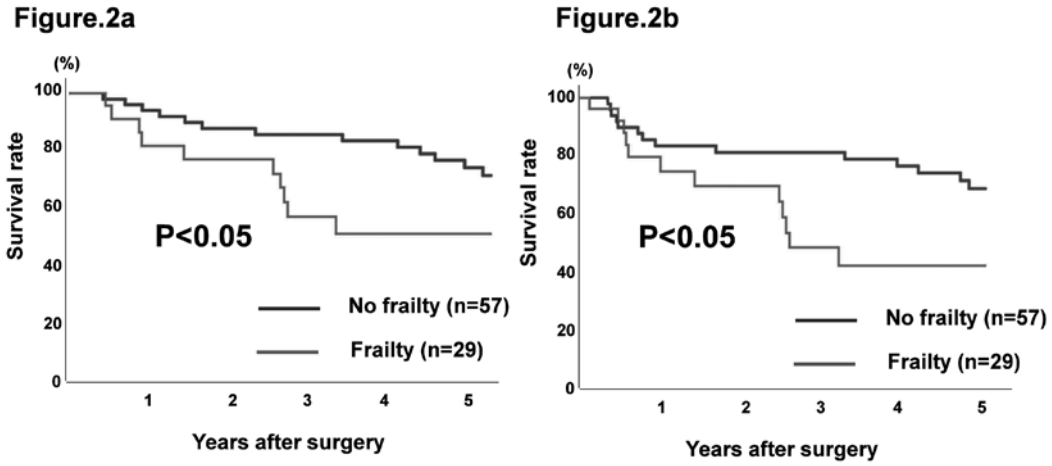

Fig 2. Comparison of overall survival (OS) (a) and disease-free survival (DFS) (b) rates of elderly gastric cancer patients after gastrectomy between the frailty and no-frailty groups. The OS and DFS were estimated using the Kaplan-Meier method

Table 3. Univariate and multivariate Cox proportional hazard regression analyses of overall survival

Variables	Univariate analysis		Multivariate analysis		
	5-year OS (%)	*p* value	HR	95% CI	*p* value
Patients and tumor factors					
Age (<85/≥85)	72.39/56.25	0.13	2.20	0.95 -5.11	0.07
Sex (M/F)	65.85/71.77	0.68			
Differentiation (dif./undif.)	65.58/72.75	0.31			
pT factor (T1,2/3.4)	68.89/73.97	0.58			
pN (−/+)	72.54/63.35	0.20	1.25	0.71-2.21	0.42
CEA (<5/≥5 ng/ml)	67.82/46.67	0.20	2.13	0.77-5.29	0.16
CA19-9 (<37/≥37 IU/ml)	69.55/50.79	0.31			
DG/TG	74.26/58.44	0.12	1.23	0.67-2.30	0.50
LN dissection (D0, D1, D1+/D2)	70.35/64.76	0.70			
Limited LN dissection (Yes/No)	71.94/58.64	0.55			
Comorbidity					
Renal failure (No/Yes)	68.16/100	0.26			
Liver cirrhosis (No/Yes)	68.42/62.50	0.76			
Cardiac disease (No/Yes)	68.76/60.00	0.83			
Pulmonary disease (No/Yes)	68.34/50.00	0.84			
Diabetes mellitus (No/Yes)	67.47/75.00	0.49			
Leanness (No/Yes)	70.11/55.56	0.49			
Immuno-nutritional factor					
Frailty (No/Yes)	74.87/52.49	<0.05	1.81	0.92-3.53	0.09
NLR (<4/≥4)	66.06/78.67	0.23			
PNI (<40/≥40)	60.35/71.61	0.91			
LCR (<6000/≥6000)	79.34/59.14	0.11	1.06	0.61-1.84	0.83
mGPS (0/1, 2)	73.55/59.35	0.40			
Sarcopenia (No/Yes)	69.68/68.57	0.68			
Osteopenia (No/Yes)	63.26/72.63	0.27			

CI confidence interval, *CEA* carcinoembryonic antigen, *CA19-9* carbohydrate antigen 19-9, *DG* distal gastrectomy, *HR* hazard ratio, *OS* overall survival, *TG* total gastrectomy, *LN* lymph node, *NLR*, neutrophil lymphocyte ratio, *PNI* prognostic nutritional index, *LCR* lymphocyte-to CRP ratio, *mGPS* modified Glasgow Prognostic Score.

Table 4. Univariate and multivariate Cox proportional hazard regression analyses of disease-free survival

Variables	Univariate analysis		Multivariate analysis		
	5-year DFS (%)	*p* value	HR	95% CI	*p* value
Patients and tumor factors					
Age (<85/≥85)	66.01/50.51	0.26			
Sex (M/F)	63.72/65.27	0.99			
Differentiation (dif./undif.)	63.53/65.38	0.30			
pT factor (T1,2/3.4)	65.55/57.93	0.84			
pN (−/+)	71.44/56.98	0.12	1.40	0.61-3.23	0.43
CEA (<5/≥5 ng/ml)	64.07/32.81	0.85			
CA19-9 (<37/≥37 IU/ml)	68.63/0	<0.001	5.38	18.00	<0.05
DG/TG	69.63/57.78	0.19	1.54	0.68-3.53	0.30
LN dissection (D0, D1, D1+/D2)	71.22/56.33	0.24			
Limited LN dissection (Yes/No)	53.20/66.19	0.93			
Comorbidity					
Renal failure (No/Yes)	62.59/100	0.23			
Liver cirrhosis (No/Yes)	64.50/62.50	0.81			
Cardiac disease (No/Yes)	69.28/53.33	0.67			
Pulmonary disease (No/Yes)	64.61/0	0.97			
Diabetes mellitus (No/Yes)	61.10/66.67	0.44			
Leanness (No/Yes)	66.38/50.79	0.49			
Immuno-nutritional factor					
Frailty (No/Yes)	71.55/42.30	<0.05	1.89	0.81-4.42	0.14
NLR (<4/≥4)	62.79/70.62	0.43			
PNI (<40/≥40)	57.84/63.49	0.87			
LCR (<6000/≥6000)	74.87/58.29	0.20	1.83	0.79-4.24	0.15
mGPS (0/1, 2)	66.32/57.31	0.57			
Sarcopenia (No/Yes)	63.31/68.57	0.91			
Osteopenia (No/Yes)	58.09/70.95	0.29			

CI confidence interval, *CEA* carcinoembryonic antigen, *CA19-9* carbohydrate antigen 19-9, *DFS*: disease free survival, *DG* distal gastrectomy, *HR* hazard ratio, *TG* total gastrectomy, *LN* lymph node, *NLR*, neutrophil lymphocyte ratio, *PNI* prognostic nutritional index, *LCR* lymphocyte-to CRP ratio, *mGPS* modified Glasgow Prognostic Score.

the inflammatory condition.

To prevent postoperative morbidity, prolong the patients' survival, and avoid the detrimental physical and psychological impacts of frailty, perioperative rehabilitation is adapted for the frail patients (28, 29). Rehabilitation for frail patients may be an appropriate process through which the operative risk can be decreased (28, 29). In our department, perioperative nutrition and exercise intervention was adapted for elderly and frail patients and improved the surgical outcomes (30).

The current study has several potential limitations. This was a retrospective cohort study at a single center, the number of cases was relatively limited, and there may have been potential selection bias. A further prospective study with larger sample size is warranted to confirm the present results.

In conclusion, we identified the clinical impact of frailty a prognostic factor for elderly GC patients who underwent curative gastrectomy. These findings highlight optimizing treatment strategies and improving patient selection and management for elderly GC patients.

ETHICS APPROVAL

The protocol for this research project was approved by the Ethics Committee of Tokushima University, Approval No. 3215-1. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions.

DISCLOSURE

ETHICS APPROVAL AND CONSENT TO PARTICIPATE / CONSENT FOR PUBLICATION

The protocol for this research project was approved by the Ethics Committee of Tokushima University, Approval No. 3215-1. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration

of 1964 and later versions and all patients signed a written informed consent form for the surgery after a detailed explanation of the procedure and the surgical risk.

FUNDING

No funding.

AUTHORS' CONTRIBUTIONS

M Nishi, and M Shimada designed the study. M Nishi, K Yoshikawa, C Takasu, T Tokunaga and T Nakao performed the data analyses. M Nishi, Y Wada drafted the manuscript. M Nishi, Y Wada , H Kashihara, T Yoshimoto prepared the table and Figure. All authors read and approved the final manuscript.

CONFLICT OF INTEREST

Masaaki Nishi, Yuma Wada, Kozo Yoshikawa, Chie Takasu, Takuya Tokunaga, Toshihiro Nakao, Hideya Kashihara, Shinichiro Yamada, Toshiaki Yoshimoto, and Mitsuo Shimada, have no conflicts of interest or financial ties to disclose.

ACKNOWLEDGMENT

We thank Robert Blakytny, DPhil, from Edanz (https://jp.edanz.com/ac) for editing a draft of this manuscript.

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