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Frailty in Elderly Gastric Cancer Patients Undergoing Gastrectomy

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Keywords
Gastric cancer · Frailty · Gastrectomy

Abstract

Introduction: There is a dearth of literature on frailty specifically in elderly (aged ≥65 years) gastric cancer patients undergoing gastrectomy. We aim to assess the effects of frailty on postoperative outcomes. ***Methods:*** A review of a prospective database was performed from November 2011 to April 2019. Frailty was assessed by multidimensional frailty score (MFS). Outcomes assessed were early postoperative complications and mortality, and length of stay. ***Results:*** 289 patients were included. The mean age was 77.3 (range 66–94) years. 183 (63.3%) were males and 172 (59.5%) had early cancer. 275 (95.2%) underwent minimally invasive gastrectomy. 79 (27.3%) patients suffered early postoperative complications, with 47 (16.3%) suffering from Clavien-Dindo grade ≥2 complications. One-year, 90-day, 30-day, and in-hospital mortality were 6.6, 1.4, 0.7, and 0%, respectively. 111 (38.4%) of patients were classified as "frail" based on MFS > 5. "Frail" patients were associated with higher 1-year mortality (odds ratio (OR) 4.51, 95% CI 1.57–12.98, $p = 0.005$) on univariate analysis. On multivariate analysis, "frail" patients did not have significantly increased 1-year mortality. However, when definition of "frail" was changed from MFS > 5 to MFS > 6, frailty was significantly associated with increased 1-year mortality (OR 3.73, 95% CI 1.11–12.53, $p = 0.033$). ***Conclusions:*** Elderly gastric cancer patients undergoing gastrectomy with MFS > 5 do not have increased mortality risk. The influence of frailty on postoperative outcomes may vary based on the risk of the surgical procedure.

Introduction

Frailty is not a new concept. One of the earliest mentions of frailty in modern English medical literature was an opinion piece titled "fearsome frailty" in 1971 [1]. In recent years, frailty has been medically defined as a multidimensional syndrome of decreased physiologic reserve that describes an older person's vulnerability to health stressors [2]. The concept of frailty in medicine has be-

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Table 1. MFS

Item	Score		
	0	1	2
Malignant disease	No	Yes	na
Charlson Comorbidity Index	0	1–2	>2
Albumin, g/dL	>3.9	3.5–3.9	<3.5
ADLs (Modified Barthel Index)	Independent	Partially dependent	Fully dependent
IADLs (Lawton and Brody Index)	Independent	Dependent	na
Dementia (MMSE-KC)	Normal	Mild cognitive impairment	Dementia
Risk of delirium (Nu-DESC)	0–1	≥ 2	na
MNA	Normal	Risk of malnutrition	Malnutrition
Midarm circumference, cm	>27.0	24.6–27.0	<24.6

ADLs, activities of daily living; IADLs, independent ADLs; MMSE-KC, Korean version of the Mini-Mental State Examination; MNA, Mini Nutritional Assessment; na, not applicable; Nu-DESC, Nursing Delirium Screening Scale; MFS, multidimensional frailty score.

come increasingly important with global trends towards an ageing population. As surgery is a widely recognised stressor on the physiologic reserves of patients, frailty is, thus, a potentially important factor in surgical patients. Evidence to substantiate this has been increasing in recent years, with studies consistently showing that frailty is associated with adverse outcomes after surgery [3–5]. A recent study from our institution investigated frailty in elective surgical patients, with patients undergoing preoperative comprehensive geriatric assessments (CGAs) [6]. This study showed that frailty more accurately predicted all-cause mortality, discharge to nursing facility, and postoperative complications than American Society of Anaesthesiologist (ASA) classification. Despite the growing literature on frailty in surgery, there seems to be a dearth of studies specifically for patients undergoing gastrectomy for cancer, with many studies focussing on sarcopenia rather than frailty [4]. Therefore, the aim of this study is to assess the effects of frailty on postoperative outcomes specifically in elderly patients undergoing curative gastrectomy.

Materials and Methods

This is a cohort study based on a prospectively maintained database in a tertiary hospital. All patients were elderly patients (age 65 years or older) with histologically proven gastric cancer who underwent gastrectomy with curative intent from November 2011 to April 2019. Patients were only included in the study if they had a preoperative CGA performed. CGA was performed routinely for all elderly patients after 2015. The CGA performed includes 6 domains: burden of comorbidity, polypharmacy, physical function, psychological status, nutrition, and risk of postoperative delirium. Details of the CGA have been previously described [6]. The CGA was performed by a geriatric nurse. Based on the CGA, frailty was assessed using the multidimensional frailty score (MFS) (Table 1). This score has been previously described and is modelled and validated from a cohort of Korean patients undergoing general surgical procedures. It includes 9 variables: malignant disease, Charlson Comorbidity Index, albumin, Activities of Daily Living (ADL), Independent ADL (IADL), dementia (Korean version of the Mini-Mental State Examination [MMSE-KC]), risk of delirium (Nursing Delirium Screening Scale [Nu-DESC]), Mini Nutritional Assessment (MNA), and midarm circumference. The cohort was categorized into 2 groups based on the MFS. Patients with MFS > 5 were classified as "frail," and patients with a MFS of 5 or less were classified as "not frail" [6].

Patient demographics and disease-related variables were collected, along with other frailty associated variables such as walking speed (4.5 m), handgrip test (average of 2 attempts), BMI, and calf circumference. Outcomes investigated were inhospital, 30-day, 90-day, and 1-year all-cause mortality, 30-day morbidity, and postoperative length of hospital stay. Patients with no preoperative CGA or who were found to have stage-4 disease were excluded from this analysis.

Continuous variables were expressed as means (SDs) and were compared by means of unpaired *t* tests. Discrete variables were expressed as counts and percentages, and χ^2 or Fisher exact tests were used to compare proportions. The association between MFS and the outcomes was determined by logistic regression fully adjusted for the relevant prognostic variables. To predict the primary outcome, we included variables with statistical significance from the univariate analyses. Because our main variable of interest, MFS, is a composite variable combining many of the covariates we would have normally selected for inclusion in a multivariable model, none of these covariates were included to avoid collinearity issues. Differences were considered statistically significant if $p < 0.05$, and all analyses were 2-tailed. All analyses were performed with STATA/SE 15.1 software.

Table 2. Patient demographics and variables

	Control, $n = 178$	Frail, $n = 111$	p value
Gender, *n* (%)			
Male	122 (68.5)	61 (55.0)	0.020
Female	56 (31.5)	50 (45.0)	
Age	76.5 (4.1)	78.6 (5.1)	<0.001
Surgeon, *n* (%)			
1	63 (33.4)	45 (40.5)	0.065
2	52 (29.2)	41 (36.9)	
3	63 (35.4)	25 (22.5)	
EGC	124 (69.7)	48 (43.2)	<0.001
AGC	54 (30.3)	63 (56.8)	
Pathologic stage, *n* (%)			
I	130 (73.0)	55 (49.6)	<0.001
II	22 (12.4)	15 (13.5)	
III	26 (14.6)	41 (36.9)	
Type of gastrectomy, *n* (%)			
Distal	126 (70.8)	82 (73.9)	0.081
Total	25 (14.0)	22 (19.8)	
Proximal	18 (10.1)	6 (5.4)	
Pylorus preserving	9 (5.1)	1 (0.9)	
Extent of LN dissection, *n* (%)			
D1	7 (3.9)	9 (8.1)	0.076
D1+	113 (63.5)	54 (48.7)	
D2	53 (29.8)	44 (39.6)	
≥D2+	5 (2.8)	4 (3.6)	
Type of access, *n* (%)			
Minimally invasive	172 (96.6)	103 (92.8)	0.140
Open	6 (3.4)	8 (7.2)	
Walking speed over 4.5 m, m/s	2.00 (9.0)	0.86 (0.2)	0.239
Handgrip strength, kg	27.9 (8.7)	20.9 (7.5)	<0.001
ASA score, *n* (%)			
I	7 (3.9)	8 (7.2)	0.155
II	140 (78.7)	74 (66.7)	
III	30 (16.9)	28 (25.2)	
IV	1 (0.6)	1 (0.9)	

Values represent "number of" for categorical variables and mean for continuous variables. Values in parentheses represent standard deviation unless otherwise stated. EGC, early gastric cancer; AGC, advanced gastric cancer; LN, lymph node; ASA, American Society of Anaesthesiologists.

Results

During the study period, a total of 295 elderly patients underwent gastrectomy with curative intent for gastric cancer as well as preoperative CGA. After surgery, 6 patients were excluded from this study as they were found to have peritoneal metastasis during surgery and underwent palliative gastrectomy instead. The mean age was 77.3 (range 66–94) years. 183 (63.3%) were males and 172 (59.5%) had early cancer. 275 (95.2%) underwent minimally invasive gastrectomy. 261 (90.3%) of patients were operated after 2015. 79 (27.3%) patients suffered early postoperative complications, with 47 (16.3%) suffering from Clavien-Dindo grade ≥2 complications. One-year, 90-day, 30-day, and inhospital mortality were 6.6, 1.4, 0.7, and 0%, respectively. Of the remaining 289 patients, 111 (38.4%) had an MFS of more than 5 and were classified as frail, with the remaining 178 (61.6%) patients classified into the control group. Patient demographics and relevant variables were analyzed in both groups (Table 2). Frail patients significantly comprised of more females, were older, had more advanced stage of disease, had slower walking speed over 4.5 m, and weaker handgrip strength. There were no differences between frail and control group with regard to surgeon, type of gastrectomy, extent of lymph node dissection, type of surgical access, and American Society of Anaesthesiologist score.

On univariate analysis, frail patients had significantly higher 90-day mortality, 1-year mortality and early (30-day) Clavien-Dindo ≥ 2, complication rate (0 vs. 3.6%, $p = 0.011$; 3.5 vs. 14.1%, $p = 0.003$; 12.4 vs. 22.5%, $p = 0.023$, respectively). Frail patients also were found to have a higher rate of pulmonary complications (18.9 vs. 10.7%, $p = 0.048$) on univariate analysis. There were no significant differences in wound infection, postoperative haemorrhage, anastomotic leak, duodenal stump leak, intestinal obstruction, postoperative pancreatitis, and intra-abdominal abscess rates. On multivariate analysis, adjusting for variables that were significantly associated with the outcomes of concern, the odds ratios (OR) of these outcomes were not statistically significant (Table 3). On analyses of potential risk factors for 1-year mortality in all patients in this study (Table 4), pathological stage of cancer (stage I vs. stage II/III) and type of gastrectomy (distal gastrectomy vs. total/proximal/pylorus-preserving gastrectomy) were the only significant factors on multivariate logistic regression (OR 5.43, 95% CI 2.11–13.93, $p < 0.001$; OR 2.21, 95% CI 1.03–4.71, $p = 0.041$, respectively).

Subgroup analyses of patients with early gastric cancer and advanced gastric cancer did not yield any statistically significant findings on multivariate analysis. Based on the 1-year all-cause mortality rate of the patients segregated by MFS score (Fig. 1), we performed analysis on this cohort of patients using differing MFS score cut-offs to define "frail" (MFS cut-off values of 3, 4, 6, 7, 8, 9, 10, and 11 were tested). When definition of "frailty" was changed from MFS > 5 to MFS > 6 (Table 3), frailty was significantly associated with increased 1-year all-cause mortality on multivariate analysis (OR 3.73, 95% CI 1.11–12.53, $p = 0.033$).

Discussion

Between 2015 and 2050, data from the WHO report that the proportion of the world's population over 60 years old will nearly double from 12 to 22%. With the rapidly ageing population, frailty in surgery is fast becoming an exciting field of interest and research. This comes with the recognition that chronological and biological age in a patient can vary and can significantly influence surgical outcomes [7]. One of the current challenges is the diagnosis and assessment of frailty. There are a multitude of scores and criterion currently reported in the literature, with varying degrees of validation in varied populations and disease domains [3, 8]. A recent review of frailty screening tools reported the presence of at least 26 questionnaires and brief assessments and 8 frailty indicators [8]. In this study, we used MFS as it was developed and validated in Korean patients and, thus, may best suit the patient population for this study. It may be worth exploring the administration and comparison of different assessment methods on prospective patients, such as the Groningen Frailty Indicator [9], the Edmonton Frail Scale [10], or the Risk Analysis Index [11]. Though largely developed and validated in Western patient cohorts, the later tool has recently been specifically validated in a large cohort study to be of clinical use in the prediction of mortality in surgical patients [12]. Patient population differences aside, another concern with most frailty scores used in the perioperative setting, are that they are developed largely from cohorts of patients undergoing a wide variety of surgical procedures [6, 11]. The stress response from surgery largely depends on the specific procedure [13]. Thus, it would be reasonable to assume that patients undergoing different surgical procedures may have differing threshold definitions of "frailty" within each scoring system. This is highlighted in our study, which suggests that the MFS cut-off definition for increased postoperative mortality risk should be higher (increased from MFS > 5 to MFS > 6) in gastrectomy patients. It is important to note that this sub-analysis is exploratory and hypothesis generating, and the answers to these questions can only be answered by well-designed head-to-head comparisons of existing scoring systems in large cohort studies.

There are several explanations for the findings of this study when the MFS definition threshold was set at >5. Firstly, our institution routinely utilises an enhanced recovery protocol for gastrectomy patients [14]. This protocol serves to limit surgical stress and aid recovery, thus, mitigating some of the negative effects of frailty. Second-

Table 3. Univariate and multivariate outcome analysis between control and Frail patients using MFS ≥ 5 and MFS ≥ 6 as the definitions of "Frail"

	Univariate analysis			Multivariate analysis		Univariate analysis			Multivariate analysis	
	control, *n* = 178	frail MFS ≥ 5, *n* = 111	*p* value	OR (95% CI)	*p* value	control, *n* = 229	frail MFS ≥ 6, *n* = 60	*p* value	OR (95% CI)	*p* value
All-cause mortality										
Inhospital	0 (0%)	0 (0%)	–	–	–	0 (0%)	0 (0%)	–	–	–
30 Day	0 (0%)	2 (1.8%)	0.072	–	–	0 (0%)	2 (3.3%)	0.006	–	–
90 Day	0 (0%)	4 (3.6%)	0.011	–	–	1 (0.4%)	3 (5.0%)	0.007	4.95 (0.46–52.87)	0.186
1 Year	5 (3.5%)	14 (14.1%)	0.003	2.14 (0.61–7.54)	0.236	7 (3.8%)	12 (21.8%)	<0.001	3.73 (1.11–12.53)	0.033
Early postoperative complications										
All	46 (25.8%)	33 (29.7%)	0.471	–	–	64 (28.0%)	15 (25.0%)	0.648	–	–
Clavien-Dindo ≥2	22 (12.4%)	25 (22.5%)	0.023	1.87 (0.96–3.66)	0.067	35 (15.3%)	12 (20.0%)	0.378	–	–
Clavien-Dindo ≥3	9 (5.1%)	11 (9.9%)	0.114	–	–	13 (5.7%)	7 (11.7%)	0.104	–	–
Nonsurgical complications	26 (14.6%)	25 (22.5%)	0.086	–	–	39 (17.0%)	12 (20.0%)	0.591	–	–
Wound infection	3 (1.7%)	0 (0%)	0.169	–	–	3 (1.3%)	0 (0%)	0.373	–	–
Postoperative haemorrhage	3 (1.7%)	0 (0%)	0.169	–	–	3 (1.3%)	0 (0%)	0.373	–	–
Anastomosis leak	3 (1.7%)	3 (2.7%)	0.555	–	–	5 (2.2%)	1 (1.67%)	0.803	–	–
Duodenal stump leak	0 (0%)	2 (1.8%)	0.072	–	–	0 (0%)	2 (3.3%)	0.006	–	–
Intestinal obstruction	3 (1.7%)	4 (3.6%)	0.302	–	–	5 (2.2%)	2 (3.3%)	0.606	–	–
Postoperative pancreatitis	1 (0.6%)	0 (0%)	0.429	–	–	1 (0.4%)	0 (0%)	0.608	–	–
Intra-abdominal abscess	4 (2.3%)	1 (0.9%)	0.393	–	–	5 (2.2%)	0 (0%)	0.248	–	–
Pulmonary complications	19 (10.7%)	21 (18.9%)	0.048	1.60 (0.66–3.85)	0.298	31 (13.5%)	9 (15.0%)	0.770	–	–
Postoperative length of stay, days	6.3 (3.7)	7.3 (5.6)	0.064	–	–	6.6 (0.3)	7.2 (6.7)	0.306	–	–

OR, odds ratio; MFS, multidimensional frailty score.

Table 4. Univariate and multivariate outcome analysis for risk factors associated with 1-year all-cause mortality

Variables	Univariate analysis	*p* value	Multivariate analysis	*p* value
	Deaths at 1 year (%)/ mean (SD)		OR (95% CI)	
Gender, *n* (%)				
Male	13 (8.97)	0.444	–	–
Female	6 (6.25)			
Age	77.35 (0.30)	0.002	1.11 (0.99–1.24)	0.084
Surgeon, *n* (%)				
1	9 (9.78)	0.363	–	–
2	4 (4.60)			
3	6 (9.68)			
Pathologic stage				
I	1 (0.65)	<0.001	Reference	<0.001
II/III	18 (20.69)		5.43 (2.11–13.93)	
Type of gastrectomy				
Distal	7 (4.07)	0.001	Reference	0.041
Total/proximal/pylorus preserving	12 (17.39)		2.21 (1.03–4.71)	
Extent of LN dissection				
D1+	4 (2.80)	<0.001	Reference	0.342
D1/D2/≥D2+	15 (15.31)		1.32 (0.75–2.33)	
Type of access				
Minimally invasive	16 (7.05)	0.053	–	–
Open	3 (21.43)			
Walking speed over 4.5 m, m/s	1.73 (0.57)	0.718	–	–
Handgrip strength, kg	24.47 (0.62)	0.388	–	–
ASA score				
I/II	14 (7.33)	0.533	–	–
III/IV	5 (10.00)			

OR, odds ratio; ASA, American Society of Anaesthesiologist; LN, lymph node.

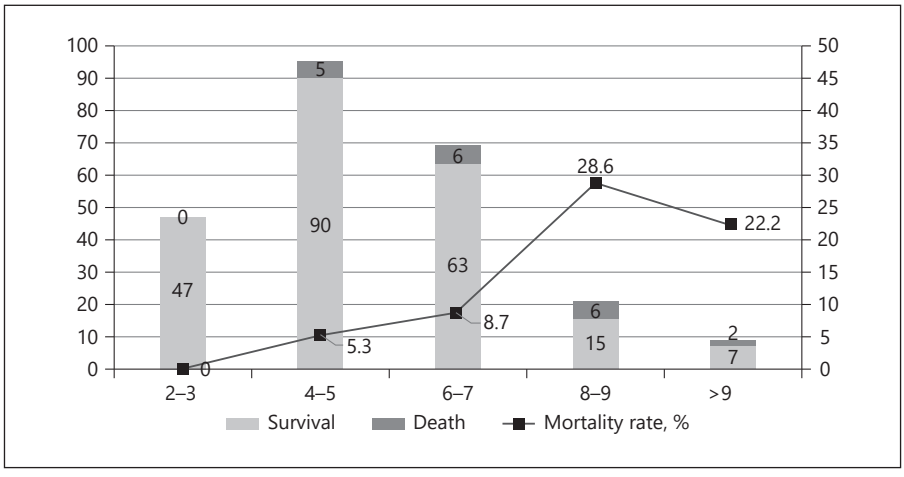

Fig. 1. Number of patients and 1-year all-cause mortality rate by MFS. MFS, multidimensional frailty score.

ly, gastrectomy is a highly standardized procedure at our tertiary institution, which is a high-volume centre for gastrectomy for cancer, with all cases performed by 3 senior surgeons [15]. These factors may contribute to gastrectomy being a relatively "low-risk" procedure at our institution, the assumption being that frailty may have greater impact on "high-risk" procedures as compared to "low-risk" procedures. This may also be a factor influencing the

differing threshold for MFS for gastrectomy as compared to surgery in general.

The stage of disease seems to be the most important factor influencing 1-year all-cause mortality in this study. The significant differences in the frail group of patients, who had a larger proportion of advanced-stage disease, seem to imply that frailty is strongly associated with disease stage for gastric cancer. This may be associated with malnutrition, which is more commonly seen in advanced cancers of the upper gastrointestinal tract as compared to other gastrointestinal or intra-abdominal cancers [16]. In addition, it is interesting to note that 3 of the 9 items in the MFS are related to malnutrition (albumin, MNA, and midarm circumference).

A limitation of this study is the relatively small sample size, which, coupled with the relatively low event rate (mortality), may result in an increased likelihood of type II error. We also did not investigate the long-term outcomes of these patients, as the hypothesis in this study is that frail patients undergoing gastrectomy are less likely to tolerate surgical trauma, and that long-term survival is more likely linked to patient comorbidities, performance status, and cancer biology. We also did not assess for quality of life or discharge status (whether the patient is discharged to a nursing institute, to the home, or requires home care) in this study – important components of cancer survivorship [17]. Furthermore, as patients above 65-year old were only routinely sent for CGA after 2015, selection bias may be present. Another limitation of this study is that it may not be directly applicable to Western populations, where there are notable differences in gastric cancer and gastrectomy outcomes. Gastric cancer in "Western" populations tends to be located more proximally (with a larger proportion of total gastrectomies being performed) and present at a later stage, with resultant differences in morbidity and mortality outcomes [9, 15, 18]. It is interesting to note that there was a significant relationship between gastric cancer and frailty in a study with an overall 30-day mortality of 8.8%, where "frail" patients had a 30-day mortality rate of 23.3 versus 5.2% [9]. However, this relationship is a lot more modest in another Western study with a much lower mortality rate [18]. This lends credence to the hypothesis that frailty would have a larger clinical implication in "high-risk" procedures as compared to "low-risk" procedures.

This remains the largest reported cohort of elderly patients specifically undergoing gastrectomy with preoperative frailty data in the literature. As the screening, evaluation and intervention (prehabilitation) for "frail" patients is a resource-intensive endeavour, and it is important to establish a clear association for frailty in specific surgical populations, such as gastrectomy for gastric cancer in elderly patients. Otherwise, frailty assessments in these patients would merely be much ado about nothing.

Conclusion

Elderly gastric cancer patients undergoing gastrectomy with MFS > 5 do not have increased mortality risk. The influence of frailty on postoperative outcomes may vary based on the risk of the surgical procedure.

Statement of Ethics

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. Ethical approval was obtained from the local Institutional Review Board (B-1909/564-106). Informed consent was not necessary as this was a retrospective review of anonymized data.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

G. Kim, Min, Y.S. Park, Ahn, D.J. Park, and H. Kim contributed to the study conception and design. G. Kim, Min, Won, Lee, Youn, and Tan contributed to the acquisition of data. Analysis and interpretation of data were performed by G. Kim, Y.S. Park, Ahn, D.J. Park, and H. Kim, drafting of the manuscript by G. Kim, and critical revision of the manuscript was performed by Min, Won, Lee, Youn, Tan, Y.S. Park, Ahn, D.J. Park, and H. Kim.

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