Original Article

Prognostic risk factors for postoperative long-term outcomes in elderly stage IA gastric cancer patients

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Background: The number of gastric cancer (GC) patients with other diseases is increasing due to the aging of the population. In particular, in stage IA GC patients who have multiple diseases, surgical indications should be considered after identifying prognostic factors. We therefore investigated prognostic factors for stage IA GC in the elderly.

Methods: Patient characteristics were collected and analyzed retrospectively for elderly patients with stage IA GC who underwent curative surgical treatment at Okayama University Hospital between 2010 and 2015, and an elderly group (EG; 75–79 years old) and very elderly group (VEG; ≥80 years old) were compared.

Results: Fifty-three patient in the EG and 31 patients in the VEG were compared. No factors associated with clinicopathological characteristics or surgical or postoperative short-term outcomes differed significantly between groups. Although no factors in the EG appeared significantly associated with poor overall survival (OS), severe comorbidity [Charlson Comorbidity Index (CCI) ≥2; P=0.019], open gastrectomy (P=0.012), high volume of blood loss (≥300 mL; P=0.013) and long postoperative hospital stay (≥14 days; P=0.041) were significantly associated with poor OS. Furthermore, only CCI ≥2 [hazard ratio (HR) =9.2; 95% confidence interval (CI): 1.2–68.9; P=0.032] was an independent prognostic factor associated with poor OS. Five-year OS was 88.9% for CCI 0/1 patients and 62.3% for CCI ≥2 patients, representing very impressive results.

Conclusions: CCI ≥2 is an important prognostic factor in clinical decisions in stage IA GC patients ≥2, so careful determination of surgical indications is desirable.

Keywords: Gastric cancer (GC); elderly; stage IA; comorbidity; Charlson comorbidity index (CCI)

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Introduction

The elderly proportion in the general population has been increasing in Japan. According to a government report (1), 28.4% of the population was ≥65 years of age and 14.7% was ≥75 years of age in 2019. Mean lifespan at that point was 81.4 years for men and 87.5 years for women, and mean life expectancies were 9.2 and 12.0 years for 80-year-old men and women, respectively, and 6.5 and 8.6 years for 85-year-old men and women, respectively (2).

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Although this population includes not only the not-healthy elderly but also many healthy elderly, this indicates that surgery for cancer in the elderly is acceptable in cases where the expected survival following cancer surgery is ≥5 years. Of course, correct evaluation of health status is necessary, but evaluation system according for age and comorbidities are needed, such as the Charlson comorbidity index (CCI) (3) and age-adjusted CCI (added as a score for age) (4). However, the evaluation of these systems can be very difficult using these systems alone, because uniform evaluation based on age are not feasible, and we consider that making evaluations on an individualized basis is desirable. Furthermore, treatments for malignant neoplasm, vascular heart disease, brain disease and pneumonia are suggested to improve lifespan in the affected (2).

The number of elderly gastric cancer (GC) patients undergoing surgery has also been increasing for these reasons. On the other hand, the number of cancer-related deaths was lower in GC patients ≥75 years of age compared to those <75 years of age (5). The number of cancer related-deaths tended to be lower in elderly patients than in younger patients for stage IA GC (6), while for stage I GC, elderly patients showed significantly poorer overall survival (OS) compared to non-elderly patients (7). However, factors affecting life expectancy for stage IA GC patients remain unclear, because patients at this age may have a wide variety of comorbidities. Many previous reports on prognosis have compared elderly patients with non-elderly patients. However, no reports limited to analysis of stage IA appear to have examined risk factors for prognosis among the elderly, although some reports have included all stages of GC. This study aimed to evaluate the associations of comorbidities with outcomes in stage IA GC patients ≥75 years of age, to clarify the differences between 75–79 and ≥80 years old, and to elucidate prognostic factors relevant for surgical indications. We present the following article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-527/rc).

Methods

Patients and data collection

In this study, GC of stage IA was defined in accordance with the Japanese Classification of Gastric Carcinoma (English edition, ver. 3) (8). For the present study, we defined "elderly" as individuals ≥75 years of age due to the previous study (9), and evaluated and analyzed elderly stage IA GC patients who underwent curative surgical treatment in the Department of Gastroenterological Surgery at Okayama University Hospital between January 2010 and December 2015. Medical records of all patients were obtained from the hospital database. Preoperative factors [age, sex, body mass index (BMI), prognostic nutritional index (PNI), American Society of Anesthesiologists-physical status (ASA-PS), CCI, and blood test results], surgical factors (approach, procedure, operation time, and blood loss), postoperative factors [Clavien-Dindo (CD) classification, length of hospital stay, histopathological data, and follow-up period] were examined retrospectively. We defined "good BMI" for prognosis of the elderly as a BMI ≥22.5 kg/m^2 but <27 kg/m^2 based on previous studies (10-16). Scores on cancer-related items of the CCI were excluded for GC patients targeted in this evaluation as all patients had cancer, and added scores depending on age were excluded. ASA-PS, CCI and CD classification were categorized as class 2 or ≥3 (no patients were categorized as class 1), ≤1 or ≥2, and ≤I or ≥II, respectively. The reason for this classification of CCI was that many clinical trials have actually allowed registration with CCI ≤1. Procedures were categorized as distal gastrectomy (DG), proximal gastrectomy (PG) or total gastrectomy (TG). Histological types were categorized as differentiated (well-differentiated, moderately differentiated, or papillary) or undifferentiated (poorly differentiated, signet-ring cell carcinoma, or mucinous). Lymphatic invasion and venous invasion were both categorized as negative or positive. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional review board (IRB) of Okayama University Hospital (approval No. 2201-008). Informed consent was taken from the patients or their families according to the IRB.

Postoperative follow-up

Many patients were followed-up every 3–6 months with physical examinations and laboratory blood tests. Patients underwent computed tomography every 6 months and esophagogastroduodenoscopy every 1 year.

Statistical analysis

All statistical analyses were performed using JMP version 14.2 software (SAS Institute, Cary, NC, USA). Pearson's chi-squared test or Fisher's exact test was used for categorical variables, and the Mann-Whitney U test was

Table 1 Clinicopathological characteristics of the EG and VEG

Variable	EG (n=53)	VEG (n=31)	P value
Age, years			<0.001
Median (IQR)	77 (76–78)	82 (80–84)	
Sex, n (%)			0.28
Male	40 (75.5)	20 (64.5)	
Female	13 (24.5)	11 (35.5)	
BMI, kg/m^2			0.077
Median (IQR)	23.0 (19.6–25.4)	21.2 (19.9–23.4)	
PNI			0.36
Median (IQR)	49.3 (47.1–53.8)	50.1 (46.6–54.7)	
ASA-PS, n (%)			0.46
≤2	39 (73.6)	25 (80.6)	
≥3	14 (26.4)	6 (19.4)	
CCI			0.47
Median (IQR)	1 (0–2)	1 (0–2)	
Approach, n (%)			0.60
Open	12 (22.6)	9 (29.0)	
Laparoscopy	41 (77.4)	22 (71.0)	
Procedure, n (%)			0.44
DG	35 (66.0)	18 (58.1)	
PG	11 (20.8)	6 (19.3)	
TG	5 (9.4)	7 (22.6)	
Local	2 (3.8)	0 (0.0)	
LN dissection, n (%)			0.053
D0	0 (0.0)	1 (3.2)	
D1	3 (5.7)	7 (22.6)	
D1+	43 (81.1)	21 (67.7)	
D2	7 (13.2)	2 (6.5)	
pT stage, n (%)			0.46
M	18 (34.0)	13 (41.9)	
SM	35 (66.0)	18 (58.1)	
Histological type, n (%)			0.33
Differentiated	41 (77.4)	27 (87.1)	
Undifferentiated	9 (17.0)	4 (12.9)	
Unknown	3 (5.6)	0 (0.0)	
Lymphatic invasion, n (%)			0.89
Ly0	18 (34.0)	11 (35.5)	
Ly1	35 (66.0)	20 (64.5)	
Vascular invasion, n (%)			0.70
V0	14 (26.4)	7 (22.6)	
V1	39 (73.6)	24 (77.4)	

EG, elderly group; VEG, very elderly group; IQR, interquartile range; BMI, body mass index; PNI, prognostic nutritional index; ASA-PS, American Society of Anesthesiologists-physical status; CCI, Charlson comorbidity index; DG, distal gastrectomy; PG, proximal gastrectomy; TG, total gastrectomy; LN, lymph node; M, mucosa; SM, submucosa.

used for continuous variables. The Kaplan-Meier method was used to estimate OS in each group, and survival rates were compared using the Wilcoxon test. Probability values of $P<0.05$ were considered significant.

Results

Patient clinicopathological characteristics, and surgical and postoperative short and long-term outcomes

First, we categorized an elderly group (EG) and a very elderly group (VEG). The EG included 51 patients ranging in age from 75 to 79 years old and the VEG included 31 patients ≥80 years old. No significant differences were seen between EG and VEG in OS (Figure S1), and 5-year OS in each group was approximately 80%. No clinicopathological characteristics differed significantly between the EG and VEG (*Table 1*).

Surgical factors (operation time and blood loss) were broadly the same in EG and VEG, and postoperative complications also did not differ significantly although the frequency of CD grade ≥III tended to be slightly higher in the EG (*Table 2*). In terms of long-term outcomes, no patients showed any recurrences during postoperative follow-up or at the time of death. Although cause of death also varied, among factor in the CCI, only metastatic solid tumor was associated with cause of death and many comorbidities included in the CCI were not direct causes of death (*Table 3*).

Table 2 Surgical and postoperative short-term outcomes in the EG and VEG

Variable	EG (n=53)	VEG (n=31)	P value
Operation time, min			0.18
Median (IQR)	271 (226–325)	254 (226–325)	
Blood loss, mL			0.51
Median (IQR)	120 (20–170)	93 (0–189)	
CD grade, n (%)			0.75
None or I	38 (71.7)	25 (80.6)	
II	9 (17.0)	5 (16.2)	
≥III	6 (11.3)	1 (3.2)	
Postoperative stay, days			0.93
Median (IQR)	12 (11–14)	12 (11–13)	

EG, elderly group; VEG, very elderly group; IQR, interquartile range; CD, Clavien-Dindo.

Table 3 Long-term outcomes in the EG and VEG

Variable	EG (n=53)	VEG (n=31)	P value
Recurrence, n (%)	0 (0.0)	0 (0.0)	1
Alive, n (%)	40 (75.5)	21 (67.7)	0.4433
Cause of death, n (%)			
GC	0 (0.0)	0 (0.0)	
Other malignancy	4 (7.5)	2 (6.5)	
Respiratory disease	2 (3.8)	1 (3.2)	
Cardiac disease	1 (1.9)	0 (0.0)	
Urinary tract infection	0 (0.0)	2 (6.5)	
Stroke	0 (0.0)	1 (3.2)	
Blood disease	1 (1.9)	0 (0.0)	
Accident	2 (3.8)	0 (0.0)	
Unknown	3 (5.7)	4 (12.9)	

EG, elderly group; VEG, very elderly group; GC, gastric cancer.

Risk factors for OS

We performed uni- and multivariate analyses to clarify risk factors for poor OS in both the EG and VEG (*Table 4*). In the EG, no factors were identified as significant risk factors for poor OS, even in univariate analyses. On the other hand, in the VEG, univariate analysis identified severe comorbidity (CCI ≥2; P=0.019), open gastrectomy (P=0.012), high blood loss (≥300 mL; P=0.013) and long postoperative hospital stay (≥14 days; P=0.041) as significant risk factors for poor OS. Interestingly, the status of patient background excluding CCI, tumor-associated clinicopathological features, and postoperative complications were not risk factors associated with poor OS. In addition, multivariate analysis including only the 4 aforementioned risk factors (severe comorbidity, open gastrectomy, high blood loss, and long postoperative hospital stay) revealed severe comorbidity [hazard ratio (HR) =9.2; 95% confidence interval (CI): 1.2–68.9; P=0.032] as the only independent risk factor associated with poor OS. The 5-year OS in the mild comorbidity (CCI ≤1) group was 88.9%, compared to 62.3% in the severe comorbidity group (CCI ≥2) (*Figure 1*). Patients who died within 3 years comprised 2 patients with metastatic tumors and another 2 patients with history of other localized tumors died within 5 years.

Risk factors from the CCI in patients ≥80 years old

Next, we analyzed what diseases in CCI were involved in OS. In the severe comorbidity group (CCI ≥2), although there were some diseases that no patients suffered, patients who had been receiving treatment or follow-up for other malignant metastatic tumors showed significantly poorer prognosis (*Table 5*). Two patients had been receiving treatment or follow-up treatment for other malignant metastatic tumors. One was a patient with recurrent gastrointestinal stromal tumor, and another one had recurrent hepatocellular carcinoma. Each case had shown stable disease (SD) or partial response (PR) at the time of gastrectomy, but disease condition changed to progressive disease (PD) leading to death.

In all patients ≥80 years old, we analyzed factors of CCI associated with prognosis (Table S1). Congestive heart failure (CHF) (P=0.0046), hemiplegia (P=0.035) and solid tumor with metastasis (P<0.001) were significantly associated with OS, while cerebrovascular accident or transient ischemic attack, chronic obstructive pulmonary disease, peptic ulcer disease, mild liver disease, uncomplicated diabetes mellitus, solid tumor with localized and moderate to severe liver disease were not. No other diseases were applicable in the present study.

Discussion

Worldwide, life expectancy at birth reached 72.6 years in

Table 4 Risk factor for poor OS in the EG and VEG

Variable	EG				VEG			
	Univariate analysis	Multivariate analysis			Univariate analysis	Multivariate analysis		
	P value	P value	HR	95% CI	P value	P value	HR	95% CI
Sex (male)	0.49	–	–	–	0.17	–	–	–
BMI (<22.5, ≥27 kg/m^2)	0.86	–	–	–	0.82	–	–	–
PNI (<45)	0.16	–	–	–	0.11	–	–	–
ASA-PS (≥3)	0.76	–	–	–	0.97	–	–	–
CCI (≥2)	0.15	–	–	–	0.019	0.032	9.2	1.2–68.9
Approach (open)	0.64	–	–	–	0.012	0.49	–	–
Procedure (TG)	0.84	–	–	–	0.072	–	–	–
LN dissection (D0/D1)	0.19	–	–	–	0.34	–	–	–
Pt stage (SM)	0.65	–	–	–	0.69	–	–	–
Histological type (undifferentiated)	0.62	–	–	–	0.53	–	–	–
Lymphatic invasion (Ly1)	0.71	–	–	–	0.062	–	–	–
Vascular invasion (V1)	0.47	–	–	–	0.23	–	–	–
Operation time (≥240 min)	0.63	–	–	–	0.31	–	–	–
Blood loss (≥300 mL)	0.22	–	–	–	0.013	0.084	–	–
CD grade (≥2)	0.90	–	–	–	0.20	–	–	–
Postoperative stay (≥14 days)	0.83	–	–	–	0.041	0.69	–	–

OS, overall survival; EG, elderly group; VEG, very elderly group; HR, hazard ratio; CI, confidence interval; BMI, body mass index; PNI, prognostic nutritional index; ASA-PS, American Society of Anesthesiologists-physical status; CCI, Charlson comorbidity index; TG, total gastrectomy; LN, lymph node; SM, submucosa; CD, Clavien-Dindo.

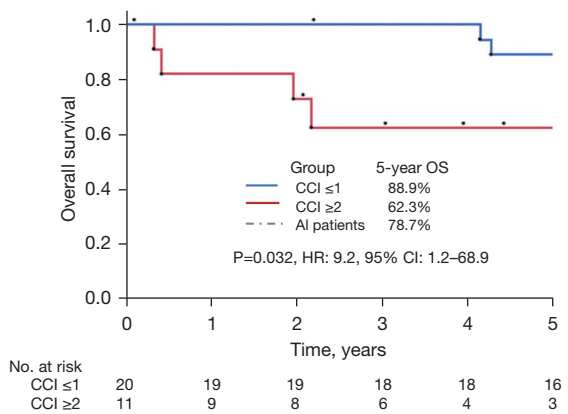

Figure 1 Kaplan-Meier curve of the VEG with stage IA GC; CCI ≥2 and ≤1, and all patients. OS, overall survival; CCI, Charlson comorbidity index; HR, hazard ratio; CI, confidence interval; VEG, very elderly group; GC, gastric cancer.

2019, up from 64.2 years in 1990 (17), and the proportion of elderly individuals in the general population has also been increasing in Japan. Many healthy elderly individuals are present in society, but so are unhealthy elderly individuals with various diseases. In terms of the cause of death at each age in Japan, malignant neoplasm was the cause of death for 25.0% in men at 75 years of age, compared to 15.6% at 90 years of age. In contrast, vascular heart disease, pneumonia, kidney disease and senile decay were causes in 14.5%, 10.1%, 2.4% and 8.3% in 75-year-old men, but 16.2%, 12.6%, 2.6% and 15.6% for 90-year-old men, respectively (2). Although the outcomes of GC depend on age and disease stage (18), stage I GC generally shows good outcomes, and often may not be the cause of death.

In Japan, the appropriate therapeutic strategy for patients with GC is outlined in the Japanese Gastric Cancer

Table 5 Involvement the factor of CCI in the cause of death (limited in CCI ≥2 and ≥80 years of age)

Variable	No. of patients	P value
Myocardia infarction	0	–
CHF	1	0.1803
Peripheral vascular disease	0	–
CVA or TIA	0	–
Dementia	0	–
COPD	0	–
Connective tissue disease	0	–
Peptic ulcer disease	0	–
Liver disease (mild)	3	0.1921
Diabetes mellitus (uncomplicated)	3	0.955
Hemiplegia	1	0.3764
Moderate to severe CKD	0	–
Diabetes mellitus (end-organ damage)	0	–
Solid tumor (localized)	6	0.1441
Leukemia	0	–
Lymphoma	0	–
Liver disease (moderate to severe)	3	0.982
Solid tumor (metastasis)	2	0.0309
AIDS	0	–

CCI, Charlson comorbidity index; CHF, congestive heart failure; CVA, cerebrovascular accident; TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; AIDS, acquired immune deficiency syndrome.

Guidelines (8,19,20). Clear descriptions are provided regarding treatment strategy by stage, but not regarding differences by age and comorbidity. Elderly individuals be in poor physical condition such as assessed by physical status (PS) and activities of daily living, and in the presence of any comorbidity, surgical treatment may lead to dismal results. Actually, various evaluation systems use age and comorbidities, including the CCI (3) and age-adjusted CCI (adding a score for age) (4). However, we considered that assessments should be made on individual basis because the heterogeneity of health is bigger in the elderly. In particular, stage IA GC patients are generally considered able to survive several years and maintain their physical condition without treatment (21), and we considered that the most critical goal is for elderly individuals to not only avoid being bedridden but also to be able to support themselves.

The present study evaluated risk factors for survival in elderly patients with surgical treatment for stage IA GC, who are generally considered likely to survive for several years without treatment. One of the present findings was that no factors were identified as significant risk factors for poor OS in individuals at 75–79 years old. This result indicates that the prognosis of elderly individuals between 75 and 79 years old was unaffected by various factors, which seems very impressive. On the other hand, individuals ≥80 years old were affected by various factors, and CCI ≥2, open gastrectomy, high volume of blood loss (≥300 mL), and long postoperative hospital stay are significantly associated with poor prognosis in univariate analyses. Generally, although CCI has classifications of 0, 1–2, 3–4, and ≥5, and grades of low, medium, high, and very high, respectively, our study separated patients into 0–1 or ≥2 as this was an evaluation of elderly individuals. CCI ≥2 was a significant risk factor for death after gastrectomy for elderly stage IA patients. Quan *et al.* (22) suggested updating and validating the CCI, because the relationship of the CCI to mortality is likely to have changed since its development in 1984. Hashimoto *et al.* (7) also suggested multiple comorbidities as a risk factor for death from other diseases in elderly patients, and Nunobe *et al.* (23) claimed that elderly patients with stage I GC frequently died due to other diseases. However, those studies did not concretely specify what diseases and conditions were relevant, differing from the present study. On the other hand, we showed that many elderly patients with CCI 0/1 died from other diseases more than 5 years after surgery. In fact, Sakurai *et al.* (6) also reported that, in elderly stage I GC patients (including stage IA and IB), no deaths were due to relapse and all were caused by other diseases or malignancies. Another report (5) revealed that many elderly individuals died despite a low rate of recurrence. This means that elderly individuals frequently die from other diseases, supporting our finding that CCI ≥2 is a poor prognostic factor, and many elderly individuals die from diseases other than cancer. Based on this result, we suggest that the evaluation for stage IA GC patients ≥80 years old patients use the modified classification separated into CCI 0, 1 or ≥2. CHF, hemiplegia and solid tumor with metastasis affected OS in the present study, and aggressive treatment of these diseases has been suggested to improve OS (2). Importantly, we should consider prioritizing treatment for patients with multiple diseases including early GC and comorbidities and clarify appropriate surgical indications.

The CCI includes 17 comorbidities, with weightings

assigned for each (3). The validity and efficacy of this index for predicting mortality in cancer has already been shown (24). In the present study, metastatic solid tumor in patients with CCI ≥2 was significantly associated with poor survival, representing an important factor. In a previous study (22) that validated the CCI items and reassigned weights, metastatic solid tumor had a high HR and was assigned the highest score. In our study, patients whose metastatic tumor condition had remained as SD or PR, unfortunately progressed to PD after surgery. Although several reasons might explain the change in status to PD, we concluded that gastrectomy for patients with metastatic tumor was unsuitable, especially in cases of early GC, which is generally considered to allow survival over several years.

The present study may have some important implications for clinical practice, but also showed several limitations. First, this study was not a randomized controlled trial, and instead retrospectively investigated a small cohort from a single institution. Second, since patients were older, some were not able to be contacted during follow-up. The shortest observation periods involved only a 1-month postoperative visit, with one such patient in each group. Third, some diseases included in the CCI, such as myocardia infraction, peripheral vascular disease, dementia, connective tissue disease, moderate to severe chronic kidney disease, diabetes mellitus; end-organ damage, leukemia, lymphoma and acquired immune deficiency syndrome (AIDS) (Table S1) were not applicable in this study. Despite these limitations, the results were considered acceptable for elderly GC patients.

Conclusions

This retrospective study identified prognostic factors for survival after surgery in elderly stage IA GC patients. For cancer patients, particularly the elderly, treatment strategies need to consider the balance between oncological survival and quality of life. We hope that our results will aid in the development of better treatment strategies for elderly GC patients.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-527/rc

Data Sharing Statement: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-527/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-527/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolves. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the IRB of Okayama University Hospital (approval No. 2201-008). Informed consent was taken from the patients or their families according to the IRB.

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Supplementary

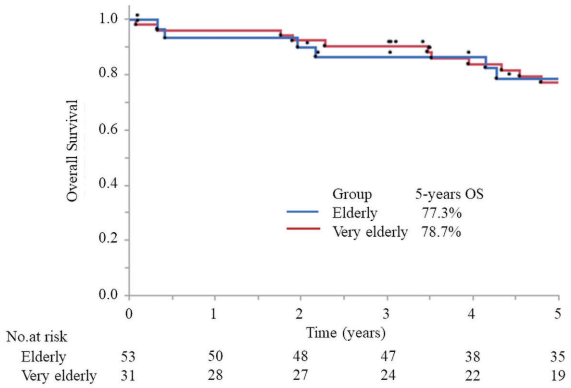

Figure S1 Kaplan-Meier curve of the EG and VEG with stage IA GC. OS, overall survival; EG, elderly group; VEG, very elderly group; GC, gastric cancer.

Table S1 Involvement the factor of CCI in the cause of death (all patients of ≥80 years of age)

Variable	No. of patients	P value
Myocardia infarction	0	–
CHF	1	0.0046
Peripheral vascular disease	0	–
CVA or TIA	1	0.70
Dementia	0	–
COPD	3	0.66
Connective tissue disease	0	–
Peptic ulcer disease	1	0.21
Liver disease (mild)	5	0.86
Diabetes mellitus (uncomplicated)	4	0.26
Hemiplegia	1	0.035
Moderate to severe CKD	0	–
Diabetes mellitus (end-organ damage)	0	–
Solid tumor (localized)	6	0.88
Leukemia	0	–
Lymphoma	0	–
Liver disease (moderate to severe)	3	0.34
Solid tumor (metastasis)	2	<0.001
AIDS	0	–

CCI, Charlson comorbidity index; CHF, congestive heart failure; CVA, cerebrovascular accident; TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; AIDS, acquired immune deficiency syndrome.

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