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Analysis of factors affecting progression-free survival of first-line chemotherapy in older patients with advanced gastrointestinal cancer

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ABSTRACT

Objectives: Few studies have investigated factors influencing the efficacy of chemotherapy in older patients with cancer. This study aimed to evaluate the usefulness of G8, geriatric assessment (GA), and factors measured in general clinical practice for evaluating progression-free survival (PFS) of first-line palliative chemotherapy in older patients with advanced gastrointestinal cancer.
Materials and methods: This was a prospective observational study of older patients (age ≥ 70 years) with advanced gastrointestinal cancer. The modified cut-off value of G8 was determined by referring to two or more abnormal GA conditions. The usefulness of baseline GA and G8 (conventional and modified cut-off value) was assessed according to the efficacy (PFS and disease control rate) of the administered first-line palliative chemotherapy.
Results: Overall, 93 patients were evaluated between March 2017 and February 2019. A modified G8 cut-off value of ≤12 had a sensitivity and specificity of 68.9% and 46.9%, respectively. PFS was significantly prolonged in the patients with G8 > 12, serum albumin ≥3.5 g/dl, and in whom grade ≥ 3 adverse events occurred. There was no significant difference in the PFS between monotherapy and combination therapy. GA was not useful for predicting PFS prolongation or the occurrence of serious adverse events in first-line treatment.
Conclusion: Among older patients with advanced gastrointestinal cancer who receive first-line chemotherapy, a modified G8 cut-off value of 12 points, occurrence of grade 3 or higher adverse events, albumin levels, rather than age or performance status were predictors of PFS prolongation.

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1. Introduction

The population of older patients with cancer has markedly increased in developed countries due to the aging of the population, including in Japan. However, older patients are underrepresented in cancer clinical trials [1,2]. Although older patients are enrolled, their number is inadequate to generalize the results in the overall older population. Moreover, aging is associated with various physiological changes that cannot be evaluated only by chronological age, with the older population being heterogeneous. Thus, the treatment of older patients with cancer requires a more individualized approach.

Geriatric assessment (GA) is useful for clarifying the problems specific to older patients and those that are often missed in routine clinical practice. Interventions for GA-identified vulnerabilities prolong prognosis and enable living at home [3]. Hurria et al. reported that the Cancer and Aging Research Group model, which includes GA variables and predicts adverse events, is more useful than the Karnofsky Performance Status score for predicting severe chemotherapy-associated adverse events in older patients with cancer [4,5,6]. However, GA is time-consuming and is thus underutilized in clinical practice [7,8]. Therefore, a screening tool (ST) that can be administered more quickly and easily than GA has been developed [9–12]. The G8 Questionnaire (G8) is one of the most widely administered STs. It enables a holistic assessment by including several factors, such as body mass index (BMI), loss of

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appetite, and weight loss. A G8 score ≤ 14 indicates vulnerabilities; however, the G8 score may vary greatly depending on the country, race, and cancer site [13,14,15]. In a Japanese study in which majority of the patients had gastrointestinal cancer, dividing the G8 score into three groups (< 11, 11–14, > 14) was useful for predicting prognosis [16]. G8 is generally used to screen patients who do not need to undergo GA. However, G8 is not routinely used in clinical practice for older patients with cancer; this is probably because few subjects can be distinguished using the conventional cut-off value for G8.

Many GA studies for older patients with cancer undergoing chemotherapy have been conducted in various cancer types and treatment settings, and thus heterogeneous populations were analyzed. Accordingly, the results have shown that the usefulness of GA differs with the cancer type [17,18,19]. Statistical data in 2017 showed that 75% of cancer deaths in Japan are in patients aged ≥70 years, and half of these deaths are due to gastrointestinal cancer [20]. The goal of chemotherapy for advanced gastrointestinal cancer is symptomatic relief and survival, while avoiding fatal adverse events, and thus highly effective regimens are needed. However, although the opportunities for chemotherapy for older patients with gastrointestinal cancer are increasing [21,22], the prognosis of advanced gastrointestinal cancer remains poor even with intensive chemotherapy [23–27]. As such, it is important to determine the efficacy of chemotherapy before its initiation in older patients.

This study was conducted to identify the factors contributing to the prolongation of progression-free survival (PFS) in older patients with advanced gastrointestinal cancer admitted to a general hospital.

2. Materials and Methods

2.1. Study Design and Patients

This prospective observational study was approved by the ethics committee of Kagoshima City Hospital and was conducted according to the 1964 Helsinki Declaration and its later amendments. Written informed consent to participate in the study was obtained after the chemotherapy regimen was determined by the attending physician. G8 was performed by the attending physician. GA was mainly performed by a clinical research associate before the start of treatment, and the results of GA were not known to the attending physician. The subjects were older patients (i.e., aged ≥70 years) with advanced gastrointestinal cancer admitted to our hospital. They were recruited between March 2017 and February 2019 according to the following eligibility criteria: (1) Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0 to 2 and (2) eligibility for first-line palliative chemotherapy.

2.2. Treatment and Assessment

The treatment regimen was selected by the attending physician according to the established standard treatment guidelines for each cancer type. The regimen of bevacizumab plus fluoropyrimidine therapy for colorectal cancer was defined as monotherapy. G8 was used as the ST. Specifically, G8 [28] was used to evaluate overall vulnerabilities. GA included the following seven geriatric conditions: (1) activities of daily living (ADLs) as assessed with the Barthel Index (cut-off score ⟨100) [29]; (2) instrumental ADLs as assessed with the guidelines by Lawton and Brody (cut-off score < 5 items for men and <8 items for women) [30]; (3) polypharmacy, which was defined as abnormal if ≥5 medications were taken per day; (4) mood as assessed with the Geriatric Depression Scale-15 (cut-off score for depression, > 5) [31]; (5) cognition as assessed with the Mini-Mental State Examination (MMSE) (cut-off score for cognitive impairment, < 24) [32]; (6) comorbidity as assessed with the updated version of the Charlson Comorbidity Index (CCI, cut-off score for comorbidities, ≥ 1) [33]; and (7) nutritional status as assessed with the BMI (cut-off score for undernutrition, < 20 kg/m^2). Considering the large influence of nutritional status in gastrointestinal cancer, the baseline albumin level (cut-off for undernutrition: < 3.5 g/dl) and percentage of unintentional weight loss in the last 3 months (cut-off score for undernutrition: > 3 kg) were included as references for the nutritional status evaluation.

Frailty was defined as two or more abnormalities in the seven geriatric conditions [11], and this definition was used to determine the optimal cut-off value of G8 in our study. The attending physicians administered the G8 questionnaire to all the patients before treatment initiation. Treatment-related toxicity was graded according to the Common Toxicity Criteria Adverse Event version 4 [34]. Treatment response among patients with measurable lesions was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [35]. Meanwhile, treatment response was evaluated by clinical judgment in those without measurable lesions. All evaluations were conducted when the best effect was observed at all measured time points during the observation period.

2.3. Statistical Analysis

The chi-square test was used to assess differences between categories. Fisher's exact test was used in the analysis in which the expected value of the sample was less than 10. Univariate binary logistic regression analysis was performed to investigate the association between baseline characteristics and disease control rate of first-line chemotherapy, grade ≥ 3 adverse events, or grade ≥ 3 adverse events requiring unplanned hospitalization. Covariates with a p-value <0.05 in the univariable analysis were included in the multivariable analysis. The significant predictive factors of PFS from first-line chemotherapy were identified by generating Kaplan–Meier survival plots. PFS was calculated from the date of registration of our study to the date of disease progression. The Cox proportional hazards model was used to estimate the effect of baseline factors on PFS. Based on two or more geriatric conditions in GA as the reference test, the area under the receiver operating characteristic (AUROC) curve was used to determine the optimal cut-off score of G8 using the Youden index. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS®) version 24.0 (IBM, Armonk, NY, USA). A p-value <0.05 was considered statistically significant.

3. Results

3.1. Patient Characteristics

Initially, 94 patients consented to participation, but one patient withdrew consent, and thus 93 patients were included in the analysis. The patients' baseline characteristics are listed in Table 1. The median length of follow-up for the censored cases was 7.8 months (3 or more: 27.2 months) as of June 30, 2019. The median age was 76 years, and 36 patients were female (38.7%). In total, 65 and 28 patients had an ECOG PS score of 0 and 1–2, respectively. Most of the patients had distant metastases (n = 40, 43%) or postoperative recurrence (n = 24, 26%). There were three patients with recurrence after definitive chemoradiotherapy for esophageal cancer. Twelve patients with localized tumors had esophageal cancer, many of whom were diagnosed with locally advanced esophageal cancer or could not tolerate a thoracotomy. One patient with adenocarcinoma of the gastroesophageal junction was suspected to have a tumor plug in the portal vein and was judged to be incurable. Thirteen patients with biliary or pancreatic cancer were diagnosed as unresectable due to the disease being locally advanced.

3.2. Screening Tool and Geriatric Assessment at Baseline

The results from the ST are shown in Table 2-1. The median G8 score was 11 points, and 76 patients (81.7%) were considered frail, based on the G8 conventional cut-off value of ≤14. The results from the GA are shown in Table 2-2. The most common geriatric condition was

Table 1
Baseline characteristics of patients.

Characteristic		n	%
Gender	Male	57	61.3%
	Female	36	38.7%
Age	Median	76 years	
	Range	70–88 years	
	70–74 years	37	39.8%
	75–79 years	24	25.8%
	80–84 years	22	23.7%
	85- years	10	10.8%
ECOG PS	0	65	69.9%
	1	20	21.5%
	2	8	8.6%
Current living situation	Lives alone	22	23.7%
	Lives with spouse, partner, or child	68	73.1%
	Residential care	3	3.2%
Tumor site	Esophagus	18	19.4%
	Stomach	11	11.8%
	Colorectal	22	23.7%
	Biliary tree	20	21.5%
	Pancreas	21	22.6%
	Peritoneum	1	1.1%
Stage	Localized	26	28.0%
	Metastatic	40	43.0%
	Recurrence*	27	29.0%
Chemotherapy	Mono	42	45.2%
	Doublet	51	54.8%

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status.
Footnote:
Recurrence 3 patients after concurrent chemoradiotherapy for localized esophageal cancer.
24 patients after radical surgery.

Table 2-1
Baseline assessment of screening tool (G8).

G8	score	
median	11	
mean	11.6	
range	7–17	
Normal (>14)	$n = 17$	18.3%
Abnormal (≤14)	$n = 76$	81.7%

G8: G8 Questionnaire.

Table 2-2
Baseline geriatric assessment.

Instrument		n	%
Barthel Index	100 points	60	64.5
	< 100 points	33	35.5
IADL	normal ≥5 items for men and ≥ 8 items for women	65	70
	abnormal <5 items for men and < 8 items for women	28	30.1
Polypharmacy	0–4 types of medication	47	50.5
	≥ 5 types of medication	46	49.5
GDS-15	< 5 points	69	74.2
	≥ 5 points	24	25.8
MMSE	≥ 24 points	85	91.4
	< 24 points	8	8.6
Updated CCI	0	65	69.9
	≥ 1	28	30.1
Nutrition			
BMI	≥ 20 kg/m^2	58	62.4
	< 20 kg/m^2	35	37.6
Serum albumin	≥ 3.5 g/dl	65	69.9
	< 3.5 g/dl	28	30.1
Weight loss during the last 3 months	≤ 3 kg	48	51.6
	> 3 kg	45	48.4
Number of geriatric conditions	0	10	10.8
	1	17	18.3
	2	22	23.7
	3	19	20.4
	4 or greater	27	29.1

Abbreviations: IADL: instrumental activities of daily living, GDS-15: geriatric depression scale 15, MMSE: mini mental state examination, Updated CCI: updated version of Charlson comorbidity index, BMI: Body mass index.

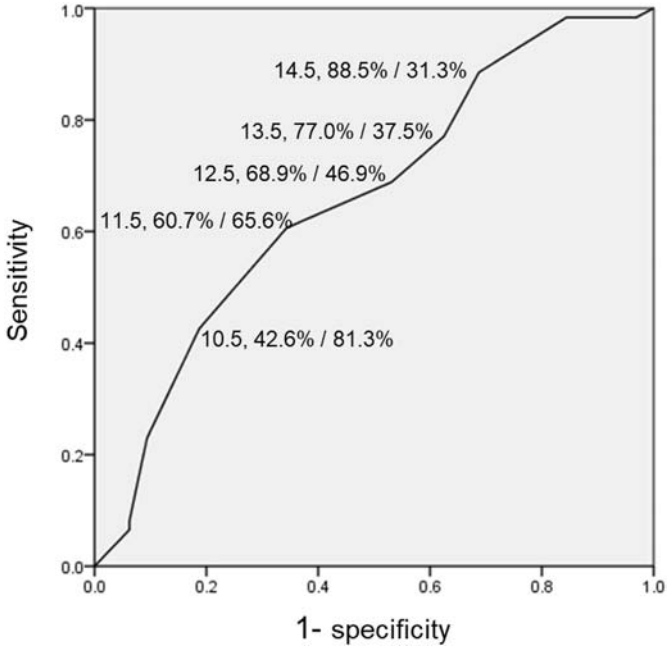

Fig. 1. ROC curve for G8 with two or more geriatric conditions of GA as reference test.
Footnote: For each point on the curve, the G8 score, sensitivity, specificity is indicated.
Abbreviations: ROC: Receiver operating characteristics, G8: G8 questionnaire, GA: geriatric assessment.

polypharmacy ($n = 46$, 49.5%). Cognitive impairment ($n = 9$, 9.7%) was less prevalent. Ten patients had no geriatric condition.

3.3. Diagnostic Accuracy of G8

When two or more abnormalities were defined as vulnerable in the seven-item elderly function evaluation, the G8 cut-off value of ≤14 had a sensitivity of 88.5%; specificity, 31.3%; negative predictive value, 58.8%; and positive predictive value, 71.1%. Using two or more geriatric conditions as the reference test, the area under the curve was 0.66, and the optimal cut-off value of G8 was 11.5, as identified using the Youden index (Fig. 1). When the cut-off value was set to ≤12, the sensitivity was 70.0%; specificity, 46.9%; negative predictive value, 44.1%; and positive predictive value, 71.2%.

3.4. Progression-Free Survival

The median PFS was 5.7 months (95% CI: 4.6–6.8) in the overall cohort. The results of the multivariable Cox regression analysis for PFS for the GA and other factors at baseline are shown in Table 3. The median PFS was 5.2 months (95% confidence interval [CI]: 3.7–6.7) in the group with two or more geriatric conditions, whereas it was 7.0 months (95% CI: 4.4–9.6) in the group with less than two geriatric conditions (hazard ratio [HR]: 1.435; 95% CI: 0.880–2.340; $p = 0.147$). The median PFS was 5.2 months (95% CI: 4.1–5.5) in the group with G8 ≤ 14, whereas it was 7.0 months (95% CI: 5.8–13.2) in the group with G8 > 14 (HR: 1.404; 95% CI: 0.776–2.541; $p = 0.261$). The median PFS was 4.8 months (95% CI: 4.1–5.5) in the group with G8 ≤ 12, whereas it was 9.5 months (95% CI: 5.8–13.2) in the group with G8 > 12 (HR: 2.023, 95% CI: 1.218–3.359; $p = 0.006$) (Fig. 2).

Table 3
Multivariable Cox regression analysis for progression free survival for geriatric assessment and other factors at baseline.

			Univariate analysis				Multivariate analysis			
	Variable	n=	HR	95% CI		*p*-value	HR	95% CI		p-value
Age	< 80 years	61	1							
	≥ 80 years	32	1.069	0.653	1.750	0.791				
Site of cancer	non CRC	71	1							
	CRC	22	0.995	0.580	1.707	0.986				
ECOG PS	0	65	1							
	1–2	28	1.367	0.824	2.267	0.226				
Stage	Localized	26	1							
	Rec / Mets	67	1.728	0.993	3.006	0.053				
G8	> 14 points	17	1							
	≤ 14 points	76	1.404	0.776	2.541	0.261				
	> 12 points	34	1							
	≤ 12 points	59	2.023	1.218	3.359	0.006	1.836	1.048	3.217	0.034
Barthel Index	100 points	60	1							
	< 100 points	33	0.939	0.576	1.53	0.801				
IADL	Normal	65	1							
	Abnormal	28	1.53	0.935	2.504	0.091				
Polypharmacy	0–4 types	47	1							
	5 ≥ types	46	1.593	0.992	2.556	0.054				
GDS-15	< 5 points	65	1							
	≥ 5 points	28	1.462	0.872	2.452	0.15				
MMSE	> 24 points	85	1							
	≤ 24 points	8	0.873	0.376	2.03	0.753				
Updated CCI	0	65	1							
	≥ 1	28	1.361	0.825	2.244	0.228				
BMI	≥ 20	58	1							
	< 20	35	1.242	0.766	2.013	0.38				
Serum albumin at baseline	≥ 3.5 g/dl	65	1							
	< 3.5 g/dl	28	2.152	1.295	3.574	0.003	1.805	1.041	3.131	0.036
Weight loss	≤ 3 kg	48	1							
	> 3 kg	45	1.489	0.929	2.387	0.098				
Geriatric condition	< 2 conditions	34	1							
	≥ 2 conditions	59	1.435	0.880	2.340	0.147				
Chemotherapy	doublet	50	1							
	mono	43	1.404	0.875	2.254	0.16				
Dose reduction	no	58	1							
	yes	35	1.554	0.973	2.483	0.065				
Grade ≥ 3 adverse events	no	22	1							
	yes	71	0.532	0.312	0.906	0.02	0.448	0.259	0.776	0.04
Grade ≥ 3 adverse events requiring hospitalization	no	59	1							
	yes	34	1.381	0.854	2.232	0.188				

Abbreviations: G8: G8 Questionnaire, IADL: instrumental activities of daily living, GDS-15: geriatric depression scale 15, MMSE: mini mental state examination, Updated CCI: updated version of Charlson comorbidity index, BMI: Body mass index, non CRC: not colorectal cancer, CRC: colorectal cancer, Rec: Recurrence, Mets: Metastatic.

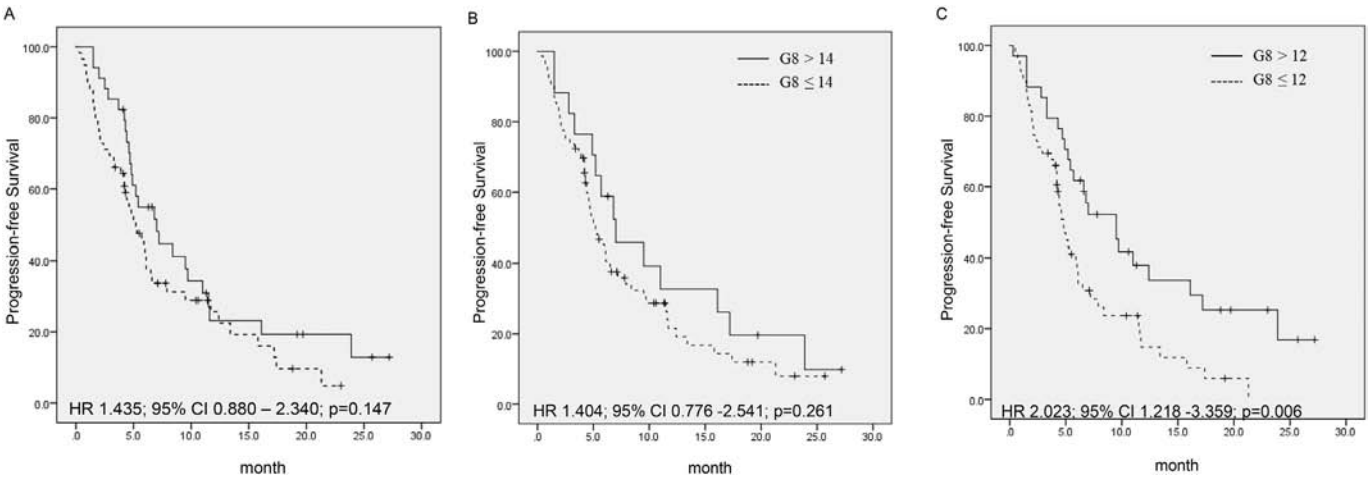

Fig. 2. Kaplan-Meyer survival plots for progression-free survival. A. Patients with less than two geriatric conditions versus patients with two or more geriatric conditions. B. Patients with G8 > 14 versus patients with G8 ≤ 14. C. Patients with G8 > 12 versus patients with G8 ≤ 12.

The patients who experienced grade ≥ 3 adverse events during first-line chemotherapy had longer PFS than those who did not experience these events (HR: 0.532, 95% CI: 0.31–0.91; $p = 0.020$). There was no significant correlation between adverse events requiring hospitalization and PFS (HR: 1.381; 95% CI: 0.854–2.232; $p = 0.188$).

Age (< 80 years vs. ≥ 80 years [HR: 1.069, 95% CI: 0.653–1.750; $p = 0.791$]), sex (male vs. female [HR: 1.009, 95% CI: 0.794–1.282; $p = 0.941$]), ECOG PS score (0 vs. 1–2 [HR: 1.367; 95% CI: 0.824–2.267; $p = 0.226$]), cognitive impairment (MMSE score [HR: 0.987; 95% CI: 0.450–2.168; $p = 0.974$), therapy (doublet vs. mono [HR: 1.404; 95% CI: 0.875–2.254; $p = 0.162$]), conventional cut-off G8 (> 14 vs. ≤ 14 [HR: 1.404; 95% CI: 0.776–2.541; p = 0.261]), abnormal geriatric conditions (< 2 vs. ≥ 2 [HR: 1.435; 95% CI: 0.880–2.340; $p = 0.147$]), and site of cancer (non CRC vs. CRC [HR: 0.995; 95% CI: 0.580–1.707; $p = 0.986$]) were also not significantly associated with PFS. Patients with higher serum albumin levels (≥ 3.5 g/dl at baseline) had longer PFS than those with lower serum albumin levels (< 3.5 g/dl at baseline) (HR: 2.152, 95% CI: 1.295–3.754; $p = 0.003$).

3.5. Toxicity

Overall, 71 patients (76.3%) experienced grade ≥ 3 adverse events. One patient died of Takotsubo cardiomyopathy [36], and a possible treatment-related death could not be ruled out. Grade ≥ 3 hematologic and non-hematologic toxicities occurred in 33 (35.5%) and 57 (61.3%) patients, respectively (Table 4-1). The association of individual geriatric conditions, ST, and other baseline factors with grade ≥ 3 adverse events is shown in Table 4-2. GA and G8 (cut-off values: 14 or 12) were not significantly associated with grade ≥ 3 adverse events. Patients with an ECOG PS score ≥ 1 experienced significantly more grade ≥ 3 adverse events than patients with PS 0 (OR: 5.78, 95% CI: 1.249–26.73, $p = 0.01$). Patients with high CCI experienced significantly less grade ≥ 3 adverse events than patients with a normal updated CCI (odds ratio (OR): 0.315, 95% confidence interval (CI): 0.116–0.854, $p = 0.02$).

Meanwhile, there was no significant difference in the incidence of grade ≥ 3 adverse events by age (< 80 years vs. ≥ 80 years), sex (male vs. female), dose reduction at first administration (yes vs. no), and chemotherapy regimen (doublet vs. mono). Patients with abnormal ADLs (Barthel index) tended to experience grade ≥ 3 toxicities (OR: 3.11, 95% CI: 0.95–10.15, $p = 0.052$). The incidence of grade ≥ 3 adverse events tended to be lower in the group with cognitive impairment (MMSE ≤24 points) than in the group without cognitive impairment (MMSE >24 points) (OR: 0.269, 95% CI: 0.061–1.181, $p = 0.067$). This could be because only eight patients had cognitive impairment, and all but one had a caregiver to manage the occurrence of adverse events.

3.6. Overall Response Rate and Disease Control Rate

The overall response rate (ORR) and disease control rate (DCR) in patients with and without measurable lesions are shown in Tables 5-1 and 5-2. In patients with measurable disease, the DCR was significantly different by ECOG PS (0 VS. 1 or 2), G8 (cut-off values: 12), instrumental ADLs (normal vs. abnormal), CCI (low vs. medium), serum albumin at baseline (≥ 3.5 g/dl vs. < 3.5 g/dl), geriatric condition (< 2 conditions vs. ≥ 2 conditions), and grade ≥ 3 adverse events (no vs. yes). In the multivariate analysis by significant factors, only grade ≥ 3 adverse events (no vs. yes) were significantly different (OR: 16.70, 95% CI: 3.007–92.64; $p = 0.001$).

Table 4-1
Summary of grade ≥ 3 adverse events.

		$n = 93$	
Grade 3–4 toxicity	Overall toxicity	71	76.3%
	Hematological toxicity	33	35.5%
	Non-hematological toxicity	58	62.4%
	Requiring hospitalization	34	36.6%

4. Discussion

Several studies have reported that GA is useful for assessing older patients who are eligible for chemotherapy. However, these studies involved patients with various cancer types and treatment settings and predicted serious adverse events of chemotherapy, but rarely discussed their efficacy. The current study exclusively evaluated patients with unresectable gastrointestinal cancer and clarified whether GA, ST, and other factors at baseline could predict the PFS of first-line palliative chemotherapy. We found no significant association between baseline factors (PS, G8, and GA) and the regimen (combination therapy or monotherapy) or the dose reduction of the first-line treatment. Patients with G8 score ≤ 12 were more likely to receive monotherapy ($p = 0.06$). Due to the recent advances in chemotherapy, there are several chemotherapeutic options for treating colorectal cancer that have been shown to improve prognosis. However, in our study, there was no significant difference between the PFS of first-line therapy in colorectal cancer and that in non-colorectal cancers. Two randomized trials involving older patients with unresectable colorectal cancer reported that adding a molecular-targeted drug (bevacizumab) to chemotherapy was beneficial in terms of efficacy and safety, while adding irinotecan to infusional 5-fluorouracil-based chemotherapy did not significantly increase either PFS or overall survival (OS) [37,38]. It was considered that increasing the treatment intensity may be less beneficial to older patients than younger patients, especially by concomitant administration of cytotoxic drugs. This was possibly one of the reasons why there was no significant difference in the PFS between the patients with colorectal cancer and those with non-colorectal cancers in this study.

In our unspecified treatment regimen study, PFS tended to be longer in the group without initial dose reduction, but the choice of treatment method showed no significant difference in PFS. Further, both the choice of treatment method and the presence or absence of dose reduction revealed no significant difference in DCR. In younger patients, increasing the treatment intensity is often associated with therapeutic effects, such as PFS, ORR, and OS [39,40]. However, although one may hypothesize that treatment will be beneficial to healthy older patients as it is to younger patients, findings from previous studies and the present study suggested that the treatment intensity and treatment effect do not always correlate.

The Cancer and Aging Research Group score and the Chemotherapy Risk Assessment Scale for High-Age Patients score has been reported to be useful for predicting severe adverse events of chemotherapy in older patients with cancer [41,42]. However, these scoring systems are mainly used to predict grade ≥ 3 adverse events. Grade 4 hematologic toxicities do not always immediately lead to serious symptoms and can often be controlled with careful management, even in older patients with cancer. Moreover, hematologic toxicities have been reported to be correlated with the efficacy of chemotherapy in various cancers [43]. Similarly, we found a prolonged PFS and significantly higher DCR in the patients who developed grade ≥ 3 adverse events. Meanwhile, although there was no significant difference in the group that experienced adverse events requiring hospitalization, the PFS was shorter than that in the group that was not hospitalized. It is important to predict the possibility of serious symptoms during chemotherapy, especially those requiring hospitalization, in older patients.

G8 is useful for predicting OS [44,45,46], but not for severe adverse events, such as grade ≥ 3 adverse events or those requiring hospitalization, regardless of the cut-off value in our study. This indicates that G8 could not substitute GA with respect to the prediction of severe adverse events. As Mohile et al. described in the American Society of Clinical Oncology guidelines, the ST may be useful for predicting prognosis rather than adverse events [41].

Table 4-2
Association between baseline variables and Grade 3–4 toxicity.

				Univariate analysis				Multivariate analysis			
	Variable	n=	%	OR	95% CI		p-value	OR	95% CI		p-value
Age	< 80 years	46 / 61	75.4	1							
	≥ 80 years	25 / 32	78.1	1.165	0.420	3.232	0.770				
ECOG PS	0	45 / 65	69.2	1							
	1–2	26 / 28	92.9	5.778	1.249	26.73	0.010	6.145	1.287	29.34	0.023
G8	> 14 points	11 / 17	64.7	1							
	≤ 14 points	60 / 76	78.9	2.045	0.656	6.379	0.212				
	> 12 points	26 / 34	76.5	1							
	≤ 12 points	45 / 59	76.3	0.989	0.366	2.672	0.983				
Barthel Index	100 points	42 / 60	70.0	1							
	< 100 points	29 / 33	87.9	3.107	0.953	10.15	0.052				
IADL	no	51 / 65	78.5	1							
	yes	20 / 28	71.4	0.686	0.250	1.886	0.464				
Polypharmacy	0–4 types of medication	34 / 47	72.3	1							
	≥ 5 types of medication	37 / 46	80.4	1.57	0.596	4.143	0.358				
GDS-15	< 5 points	49 / 65	75.4	1							
	≥ 5 points	22 / 28	78.6	1.197	0.413	3.472	0.740				
MMSE	> 24 points	67 / 85	78.8	1							
	≤ 24 points	4 / 8	50.0	0.269	0.061	1.181	0.067				
Updated CCI	0	54 / 65	83.1	1							
	≥ 1	17 / 28	60.7	0.315	0.116	0.854	0.020	0.295	0.104	0.842	0.022
BMI	≥ 20	41 / 58	70.7	1							
	< 20	30 / 35	85.7	2.488	0.826	7.494	0.099				
Serum albumin	≥ 3.5 g/dl	49 / 65	75.4	1							
	< 3.5 g/dl	22 / 28	78.6	1.197	0.413	3.472	0.740				
Weight loss	≤ 3 kg	36 / 48	75.0	1							
	> 3 kg	35 / 45	77.8	1.167	0.447	3.046	0.753				
Geriatric condition	< 2 conditions	25 / 34	73.5	1							
	≥ 2 conditions	46 / 59	78.0	1.274	0.478	3.393	0.628				
Chemotherapy	doublet	36 / 50	72.0	1							
	mono	34 / 43	79.1	1.608	0.600	4.309	0.343				
Dose reduction	no	43 / 58	74.1	1							
	yes	28 / 35	80.0	1.395	0.505	3.853	0.519				

Abbreviations: G8: G8 Questionnaire, IADL: instrumental activities of daily living, GDS-15: geriatric depression scale 15, MMSE: mini mental state examination, Updated CCI: updated version of Charlson comorbidity index, BMI: Body mass index.

Table 5-1
ORR, DCR in patients with measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1).

	$n = 85$	%
ORR	22	25.9
DCR	60	70.6
Best overall response		
Complete response	0	0
Partial response	22	25.9
Stable disease	38	44.7
Progression disease	19	22.4
Not evaluated	6	7.1

Footnote: Stable disease without measurable disease: 7 patients. Progression disease without measurable disease: one patient.
Abbreviations: ORR: objective response rate, DCR: disease control rate.

In the present study, vulnerabilities could be ruled out in only 18% of the patients using the conventional G8 cut-off value of ≤14. However, when we used a cut-off value of ≤12, 37% of the patients were defined to be non-frail. A cut-off value of ≤12 could stratify PFS from first-line chemotherapy, whereas the conventional cut-off value of ≤14 points could not. This may be explained by the small sample size of the subjects for whom the vulnerability could be denied with a cut-off value of 14 points. It is common knowledge that gastrointestinal cancers have a strong effect on the nutritional status of the patient. When patients are screened using G8, which is mainly composed of nutritional status, most of them are suspected of being vulnerable at a cut-off value of 14 points. Therefore, it was suggested that lowering the cut-off value to 12 would help identify those who were less vulnerable and would benefit from first-line treatment. Using a G8 cut-off value of ≤12, we could stratify the PFS from first-line chemotherapy, similar to that in a retrospective study [15], and it was considered reasonable to adjust the optimal cut-off value of G8 depending on the subject. The optimal G8 cut-off values may vary by cancer type, country, or clinical stage [13,14,15], and it may be useful in clinical practice by adjusting the cut-off value of G8, which is a simple and popular tool.

This study had some limitations. First, although we exclusively evaluated patients with gastrointestinal cancer, the cancer types vary widely. For example, the prognosis of pancreatic cancer and colorectal cancer seems to be significantly different. However, in our study, there was no significant difference in PFS between colorectal cancer and other gastrointestinal cancers. Meanwhile, the prognosis in our study tended to differ according to stage, with the PFS being different between the localized group and the distant metastasis or recurrence group (HR: 1.728; 95% CI: 0.993–3.006; $p = 0.053$). Second, GA was primarily conducted by a clinical research associate or nurse after the attending physician screened the patient decided on a treatment regimen. Since the treatment is not specified in our study, it is likely that the treatment intensity was decided according to the impression of the attending physician in charge at the first visit. The reason for the significantly lower frequency of adverse events in patients with comorbidities was thought to be the tendency for less intense treatment (monotherapy for patients with a low CCI score vs. those with medium, high, and very high scores (OR: 2.00, 95% CI: 0.815–4.910, $p = 0.128$).

Both PFS and DCR were significantly more effective in the group with grade ≥ 3 adverse events; however, PFS tended to be shorter in the group with serious adverse events requiring hospitalization. This may imply that the appropriate intensity of individualized treatment will be beneficial during first-line treatment.

Table 5-2
Association between baseline variables and DCR.

			Univariate analysis				Multivariate analysis			
	Variable	n=	OR	95% CI		p-value	OR	95% CI		p-value
Age	< 80 years	44/59	1							
	≥ 80 years	15/26	0.465	0.176	1.231	0.120				
Site of cancer	CRC	12/21	1							
	Non CRC	47/64	2.074	0.743	5.790	0.986				
ECOG PS	0	46/59	1							
	1–2	13/26	0.283	0.106	0.757	0.010	0.227	0.051	1.017	0.053
Stage	localized	15/21	1							
	Rec / Mets	44/64	0.880	0.298	2.602	0.817				
G8	> 14 points	13/17	1							
	≤ 14 points	46/68	0.643	0.188	2.202	0.480				
	> 12 points	29/34	1							
	≤ 12 points	30/51	0.246	0.082	0.741	0.009	0.304	0.073	1.259	0.101
Barthel Index	100 points	42/57	1							
	< 100 points	17/28	0.552	0.211	1.442	0.223				
IADL	Normal	46/60	1							
	Abnormal	13/25	0.330	0.123	0.884	0.025	0.774	0.196	2.830	0.664
Polypharmacy	0–4 types	32/43	1							
	5 ≥ types	27/42	0.619	0.244	1.571	0.311				
GDS	< 5 points	45/60	1							
	≥ 5 points	14/25	0.424	0.159	1.133	0.083				
MMSE	> 24 points	55/78	1							
	≤ 24 points	4/7	0.558	0.116	2.691	0.462				
Updated CCI	0	45/58	1							
	≥ 1	14/27	0.311	0.117	0.825	0.017	0.484	0.137	1.705	0.258
BMI	≥ 20	37/53	1							
	< 20	22/32	0.951	0.368	2.460	0.918				
Serum albumin at baseline	≥ 3.5 g/dl	47/62	1							
	< 3.5 g/dl	12/23	0.348	0.128	0.950	0.036	0.472	0.132	1.691	0.249
Weight loss	≤ 3 kg	33/46	1							
	> 3 kg	26/39	0.788	0.312	0.613	0.613				
Geriatric condition	< 2 conditions	29/33	1							
	≥ 2 conditions	30/52	0.188	0.058	0.613	0.003	0.339	0.059	1.944	0.225
Chemotherapy	doublet	37/50	1							
	mono	22/35	0.595	0.234	1.511	0.273				
Dose reduction	no	39/53	1							
	yes	20/32	0.598	0.234	1.533	0.283				
Grade ≥ 3 adverse events	no	8/19	1							
	yes	51/66	4.675	1.592	13.73	0.003	16.70	3.007	92.64	0.001
Grade ≥ 3 adverse events requiring hospitalization	no	39/53	1							
	yes	20/32	0.598	0.234	1.533	0.283				

Abbreviations: G8: G8 Questionnaire, IADL: instrumental activities of daily living, GDS-15: geriatric depression scale 15, MMSE: mini mental state examination, Updated CCI: updated version of Charlson comorbidity index, BMI: Body mass index, non CRC: not colorectal cancer, CRC: colorectal cancer, Rec: Recurrence, Mets: Metastatic.

In conclusion, among older patients with advanced gastrointestinal cancer who undergo first-line chemotherapy, a modified G8 cut-off value of 12 points, occurrence of grade 3 or higher adverse events, and serum albumin level, rather than age or PS, were predictors of PFS prolongation. A G8 cut-off value of 12 points may help predict PFS before the start of first-line chemotherapy. Dose adjustments that can avoid serious adverse events that require hospitalization, rather than Grade 3 or higher adverse events, may be beneficial for chemotherapy in older patients.

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Data Statement

All data generated or analyzed during this study are included in this published article.

Declaration of competing interest

None.

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