ANTICANCER RESEARCH *41*: 5213-5222 (2021)
doi:10.21873/anticanres.15340

Impact of Frailty on Treatment Outcome in Patients With Locally Advanced Esophageal Cancer Undergoing Concurrent Chemoradiotherapy

YUNG-HSIN HUANG[1], YU-SHIN HUNG[2], CHENG-CHOU LAI[3], MING-MO HO[2], KUN-YUN YEH[4], CHIEH YANG[5], CHANG-HSIEN LU[6], CHEN-KAN TSENG[7], NGAN-MING TSANG[7], CHIA-YEN HUNG[8], SHUN-WEN HSUEH[4], PEI-HUNG CHANG[4], YA-WEN HO[2], YU-CHING LIN[9] and WEN-CHI CHOU[2]

Departments of [1]Gastroenterology and Hepatology, [2]Hematology and Oncology, and [3]Colon and Rectal Surgery, Chang Gung Memorial Hospital at Linkou and College of Medicine, Chang Gung University, Taoyuan, Taiwan, R.O.C.;
Departments of [4]Oncology, and [9]Medical Imaging and Intervention, Chang Gung Memorial Hospital at Keelung, Keelung, Taiwan, R.O.C.;
[5]Department of Internal Medicine, En-Hua Hospital, New Taipei City, Taiwan, R.O.C.;
[6]Department of Oncology, Chang Gung Memorial Hospital at Chiayi, Chiayi, Taiwan, R.O.C.;
[7]Department of Radiation Oncology, Chang Gung Memorial Hospital at Linkou and College of Medicine, Chang Gung University, Taoyuan, Taiwan, R.O.C.;
[8]Division of Hema-oncology, Department of Internal Medicine, Mackay Memorial Hospital, Taipei, Taiwan, R.O.C.

Abstract. *Background/Aim: The clinical significance of frailty status on treatment outcome in patients with esophageal cancer (EC) has been seldom explored. This study aimed to evaluate the impact of pretreatment frailty on treatment-related toxicity and survival outcome in patients with EC undergoing concurrent chemoradiotherapy (CCRT). Patients and Methods: Patients aged ≥20 years and with newly diagnosed locally advanced EC receiving neoadjuvant radiotherapy and concurrent chemotherapy with weekly administration of carboplatin and paclitaxel for 5 weeks were prospectively enrolled. A pretreatment frailty assessment was performed within 7 days before CCRT initiation. The primary endpoint was treatment-related toxicity and complications of CCRT while the secondary endpoint was overall survival. Results: A total of 87 patients were enrolled, 41 (47%) and 46 (53%) of whom were allocated in the frail and fit group, respectively. Frail patients had a significantly higher incidence of having at least one severe hematological adverse event (63.4% vs. 19.6%, p<0.001), higher risk of emergent room visiting [relative risk 3.72; 95% confidence interval (CI)=1.39-9.91; p=0.009] and hospitalization (relative risk 3.85; 95% CI=1.03-11.2; p=0.013) during the course of CCRT, when compared to fit patients. Overall survival showed significant worsening in the frail group [adjusted hazard ratio (HR)=2.12; 95% CI=1.01-4.42; p=0.046]. Conclusion: Frailty is associated with increase of treatment-related toxicities and poor survival outcome in EC patients undergoing CCRT. Our study suggested that pretreatment frailty assessment is imperative to serve as a predictor and prognostic factor for all adult patients with EC undergoing CCRT.*

Correspondence to: Wen-Chi Chou, MD, Ph.D., Department of Hematology and Oncology, Chang Gung Memorial Hospital, No. 5, Fu-Hsing Street, Kwei-Shan Shiang, Taoyuan, Taiwan, R.O.C. Tel: +886 3281200 (Ext 2517), Fax: +886 33285818, e-mail: f12986@cgmh.org.tw

Key Words: Esophageal cancer, frailty, prevalence, survival outcome.

Esophageal cancer (EC) was the eighth most diagnosed cancer in 2020 and the sixth leading cause of death due to cancer worldwide (1). EC is one of the most difficult cancers to cure with a poor 5-year survival rate of approximately 20% (2). Surgical resection and definitive concurrent chemoradiotherapy (CCRT) are the most effective curative treatment options for patients with early-stage esophageal cancer (3). Despite the advances in surgical treatment, survival outcome of patients with EC remains dismal, especially for patients diagnosed with locally advanced disease (4).

Multimodality treatment including neoadjuvant CCRT followed by radical surgery is the treatment of choice in EC patients with locally advanced or nodal positive disease (5). Paclitaxel and carboplatin (PC) combination regimen is the optimal neoadjuvant chemotherapeutic agent in EC, based on the CROSS-trial (6). This phase III study reported that EC

patients who received CCRT with PC regimen experienced less than 7% and 13% of the hematological and non-hematological severe adverse events (sAEs; defined as grade III or higher toxicities), respectively (6). However, several phase II and retrospective studies reported the incidence of grade III or higher neutropenia that ranged from 25-47% in EC patients receiving the same treatment (7-14). While there is a noted wide range of prevalence of treatment-related toxicities, it is important to identify the EC patients who are vulnerable to sAEs while receiving CCRT with PC regimen.

Frailty is defined as a syndrome of increased vulnerability to external stressors due to decline in reserve and function across multiple physiologic systems (15-17). Although prevalence of frailty increases with age, it occurs independently from chronological age and is observed in all age groups (17-19). Recently, the concept of frailty has been widely utilized for selection of fit patients to receive antitumor therapy and to serve as a predictor of treatment-related complications, tolerance, or survival outcome in oncologic practice (20-22). Whether the frailty might utilize as a predictive or prognostic factor for treatment outcome in EC patients undergoing neoadjuvant CCRT has been seldom explored. This study aims to evaluate the impact of pretreatment frailty on treatment-related sAEs, treatment completion, and survival outcome in patients with locally advanced EC undergoing CCRT.

Patients and Methods

Patient selection. This is a multi-center prospective study to investigate the effectiveness of frailty status toward prediction of treatment-related sAEs and tolerance of CCRT for locally advanced EC patients. Patients were consecutively recruited between August 2016 and December 2017 from three medical institutes in Taiwan. Eligibility criteria included: patients aged 20 years or older with histological proven locally advanced EC and eligible for CCRT as the first-line antitumor treatment, Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2, and acceptable bone marrow function, liver function and renal function. Locally advanced tumor was defined as any non-metastatic tumor from cervical esophagus, ≥T2 classification, or any regional nodal positive tumor. Exclusion criteria included metastatic disease, inability to complete the frailty questionnaires for any reason, and treatment with chemotherapy or radiotherapy alone. Tumor staging was according to 7th edition American Joint Committee on Cancer (AJCC) staging system in this study. All patients provided written informed consent prior to inclusion. The study protocol was approved by the institutional review board (No: 1608080002). Figure 1 shows the study flowchart.

Neoadjuvant CCRT. All eligible patients received intensity modulated or arc technique radiotherapy at a conventional fractionated daily dose of 180 cGy for 5 consecutive days per week, with the total prescribed radiotherapy dose of 4,140 cGy over 5 weeks (6). The chemotherapy regimen with carboplatin (area under the curve of 2 mg per ml per min) and paclitaxel (50 mg per m^2 of body-surface area) were administered weekly up to 5 weeks concurrent with radiotherapy (6).

The patients underwent a computed tomography (CT) and esophagogastroduodenoscopy (EGD) for tumor restaging within 4 weeks after the completion of radiotherapy. After the completion of treatment, the resectability of tumor was evaluated by a specialized tumor board, based on the response of tumors and clinical condition of patients. If the residual tumor was deemed resectable by the board and the patient provided informed consent, the patient underwent minimally invasive transthoracic esophagectomy (Ivor-Lewis) (23) with mediastinal lymphadenectomy within 4-8 weeks after the completion of CCRT.

Local booster radiotherapy with 2,340 cGy was administered to the tumor bed and regional lymphatics area over 13 fractions, in patients who did not undergo surgical resection or those with positive pathological lymph node metastases after surgery (6).

Frailty assessment. A baseline frailty assessment was performed within 7 days before CCRT initiation and including the following 6 frail conditions: i) functional status as assessed by the activity of daily living (ADL) and instrumental activities of daily living (IADL), ii) nutritional status as assessed by mini-nutritional assessment short-form (MNA-SF), iii) comorbidity as assessed by the Charlson comorbidity index (CCI), iv) polypharmacy as assessed by types of medications being used, v) mood as assessed by the geriatric depression scale -4 questions (GDS-4), and vi) social support as assessed by living with others or alone (24). Because the majority of our patients aged less than 65 years, we modified the frailty assessment tool (excluded Mini-Mental State Examination from the original tool) that was used in our previous study (24). Frailty in this study was defined as the presence of two or more of frail conditions (24).

Study endpoints. The primary endpoint was CCRT-related toxicity and complications of CCRT. The vital status and grades for any adverse event of patients were evaluated at least weekly during CCRT treatment. CCRT-related toxicity was graded according to the common toxicity criteria (CTC) of the National Cancer Institute (NCI), version 3. A toxicity of grade III or higher was defined as sAE. Complications of CCRT were defined as incomplete treatment, emergency room visit, or hospitalization due to any reason during the CCRT period. All adverse events or treatment-related complications were recorded from CCRT initiation till one month after the end of CCRT. Adverse events that occurred during the booster radiotherapy were not included in the analysis. Patients who received less than 90% of the protocol specified radiotherapy dose or less than 5 times of chemotherapy dose due to any cause were considered as having undergone incomplete radiotherapy or chemotherapy (6), respectively.

The second endpoint was overall survival and disease-free survival. All enrolled patients were followed up until May 31, 2019 or until death. Overall survival time was determined from the first date of CCRT until death or until the last date on which the patient was known to be alive. Disease-free survival (DFS) time was calculated from the date of operation until tumor recurrence, death, or the last date of follow-up.

Statistical analysis. Descriptive analyses were performed to summarize patient and tumor characteristics. The Kruskal-Wallis test for continuous and ordinal variables, and chi-square (or the Fisher's exact test) for categorical variables were used for in-group comparison. Univariate and multivariate logistic regression analyses were performed to estimate the relative risk (RR) and 95% confidence

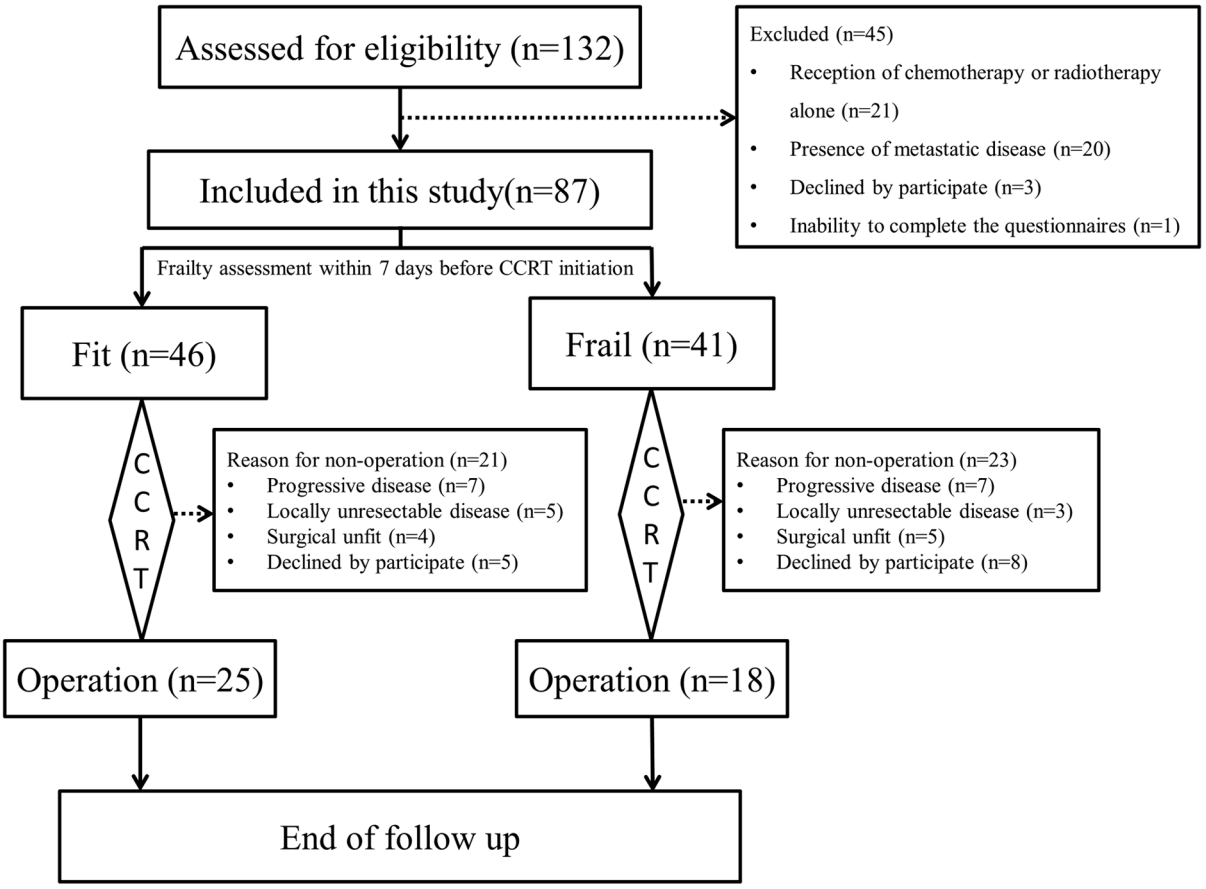

Figure 1. *Study flowchart*.

interval (CI) for variables associated with complications of CCRT. Survival outcome was calculated according to the Kaplan–Meier method. Log-rank tests were used to determine significant differences between the survival curves. Cox regression model was performed to estimate the hazard radio (HR) for variables associated with overall survival. SPSS 17.0 software (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. All statistical assessments were two-sided, and a p-value <0.05 was considered statistically significant.

Results

Frailty assessment results. The assessment tool and cut-off standard for each frail condition of the 87 patients is shown in Table I. Malnutrition was the most common frail condition (73.6%), followed by comorbidities (29.9%), and polypharmacy (25.3%). The median number of frail condition was 1 (range=0-5). No statistical difference was observed in each frail condition between patients aged <65 and those aged ≥65 years. Accordingly, 46 (52.9%) and 41 (47.1%) patients were allocated to fit and frail groups based on the frail assessment, respectively. *Patient demographics and tumor characteristics*. The median age was 56 years old (range=28-82), and 87.4% of patients were male in this study (Table II). Eighty-five (97.7%) patients were diagnosed as squamous cell carcinoma in histological type, while the other 2 (2.3%) patients had adenocarcinoma. The median length of tumor was 5.0 cm (range=1.2-13). The distribution of the T- and N-classification was 1.1%, 13.8%, 55.2%, 29.9% for T1, T2, T3, T4 and 6.9%, 23.0%, 47.1%, 23.0% for N0, N1, N2, N3, respectively. The patient numbers with ECOG performance 0, 1, and 2 were 50 (57.5%), 35 (40.2%), and 2 (2.3%), respectively. Forty-three (49.4%) patients received radical-intent surgery for esophageal cancer after CCRT. The major reasons for not undergoing surgical resection in fit group were progressive disease (n=7), locally unresectable disease (n=5), and decline by patients (n=5). In the frail group, the surgery was not performed if patients declined (n=8), had progressive disease (n=7), or were surgically unfit (n=5) (Figure 1).

Unemployment was prevalent among patients in the frail group they had less history of cigarette smoking and alcohol drinking. No statistical differences were observed between

Table I. *Definition of frailty domain and its prevalence in the patient cohort studied.*

Frail condition	Definition (scale)	Overall, n (%)	Age <65, n (%)	Age ≥65, n (%)	*p*-Value
Patient number		87	68	19	
MNA-SF	Normal nutrition (12-14)	23 (26.4)	19 (27.9)	4 (21.1)	0.77
	Malnutrition (<12)	64 (73.6)	49 (72.1)	15 (78.9)	
CCI	No comorbidity (0-1)	61 (70.1)	49 (72.1)	12 (63.2)	0.57
	Comorbidity (2+)	26 (29.9)	19 (27.9)	7 (36.8)	
Polypharmacy	Intact (0-3 types of medication)	65 (74.7)	52 (76.5)	13 (68.4)	0.53
	Defect (4+ types of medication)	22 (25.3)	16 (23.5)	6 (31.6)	
GDS-4	Intact (0-1)	77 (88.5)	62 (91.2)	15 (78.9)	0.22
	Defect (2+)	10 (11.5)	6 (8.8)	4 (21.1)	
Social support	Intact (Living with others)	79 (90.8)	62 (91.2)	17 (89.5)	0.99
	Defect (Living alone)	8 (9.2)	6 (8.8)	2 (10.5)	
ADL	Intact (100)	79 (90.8)	63 (92.6)	16 (84.2)	0.36
	Defect (<100)	8 (9.2)	5 (7.4)	3 (15.8)	
IADL	Intact (7-8)	84 (96.6)	67 (98.5)	17 (89.5)	0.12
	Defect (<7)	3 (3.4)	1 (1.5)	2 (10.5)	

MNA-SF, Mini Nutritional Assessment-short from; CCI, Charlson comorbidity index; GDS-4, Geriatric Depression Scale-4 questions; ADL, activities of daily living; IADL, instrumental activities of daily living.

the fit and the frail groups with respect to age, gender, educational level, tumor location, length of tumor, tumor stage, and surgical resection rate after CCRT.

Completion and complication of concurrent chemo-radiotherapy. Overall, 5.7%, 11.5%, 29.9%, and 24.1% of the total number of patients had experienced incomplete radiotherapy, incomplete chemotherapy, emergency room visiting, and hospitalization, respectively (Table III). There were no significant differences of incomplete radiotherapy or chemotherapy related to frailty status. Frail patients had a significantly higher relative risk (RR) of emergency room visits (crude RR=3.72, 95% CI=1.39-9.91, p=0.009) and hospitalization (crude RR=3.85, 95% CI=1.03-11.2, p=0.013) during the course of CCRT as compared to fit patients. Notably, frailty status maintained itself as a significant risk factor for emergency room visiting and hospitalization, independent of age, gender, ECOG performance, and tumor stage.

Severe adverse events of chemoradiotherapy. At least one hematologic and non-hematological sAE occurred in 40.2% and 51.7% of patients, respectively (Table IV). The most common hematological sAEs were leukopenia (32.2%), anemia (17.2%), and neutropenia (17.2%) while the most common non-hematological sAEs were mucositis (23.0%), non-neutropenic infection (17.2%), and fatigue (9.1%).

Frail patients had a significant higher incidence of having at least one grade III or higher hematological toxicities (63.4% *vs.* 19.6%, p<0.001), anemia (29.3% *vs.* 6.5%, p=0.009), and leukopenia (51.2% *vs.* 15.2%, p<0.001) as compared to fit patients. No statistical differences were observed between the fit and the frail groups with regard to non-hematological sAEs, although frail patients had a trend toward higher incidence of mucositis than fit patients (31.7% *vs.* 15.2%, p=0.07).

Survival outcomes. After a median follow-up duration of 21.5 months (range=6.8-29.6), 33 (37.9%) patients from the total number had died, and the 1- and 2-year survival rates were 71.2% and 56.9%, respectively. Figure 2A shows the survival curve according to the frailty status of the patients. The 1- and 2- year survival rates were 74.9% and 67.9% for fit patients, respectively, and were 66.9% and 44.7% for frail patients (log-rank p=0.045), respectively. The HR was 2.12 (95% CI=1.01-4.42, p=0.046) when comparing the fit and frail patients after adjustment for gender, age, ECOG performance, tumor stage and receipt status of surgical resection.

Disease-free survival was analyzed for 43 patients who underwent surgery (Figure 2B). Twenty-two patients experienced tumor recurrence (51.2%) by the end of the study. The 1- and 2- year DFS were 61.6% and 53.9% for fit patients, respectively, and 29.5% and 29.5% for frail patients (log-rank p=0.036), respectively. The HR was 4.61 (95% CI=1.75-12.1, p=0.002) when comparing the fit and frail patients after adjusting for gender, age, ECOG performance, and tumor stage.

Discussion

An effective method to predict treatment-related toxicities and complications in EC patients receiving CCRT is important to identify vulnerable patients, to increase treatment compliance, and, most importantly, to improve survival outcome. Frailty

Table II. *Baseline characteristics of patients*.

Characteristics	Overall (n=87)	Fit (n=46)	Frail (n=41)	*p*-Value
Age*, years	56 (28-82)	55 (28-82)	58 (37-77)	0.31
≥65	19 (21.8)	8 (17.8)	11 (26.8)	
Male gender	76 (87.4)	42 (91.3)	34 (82.9)	0.34
BMI*, kg/m^2	22.4 (15.9-31.6)	22.0 (17.1-31.0)	22.6 (15.9-31.6)	0.37
Marriage				0.15
Married	72 (82.8)	41 (89.5)	31 (75.6)	
Others	15 (17.2)	5 (10.5)	10 (24.4)	
Education				0.66
Nil or elementary	24 (27.6)	11 (23.9)	13 (31.7)	
Junior high school	32 (36.8)	17 (37.0)	15 (36.6)	
Senior high school or high	31 (35.6)	18 (39.1)	13 (31.7)	
Occupation				0.022
No	29 (33.3)	10 (21.7)	19 (46.3)	
Yes	58 (66.7)	36 (78.3)	22 (53.7)	
Cigarette smoking				0.021
No	11 (12.6)	2 (4.3)	9 (22.0)	
Yes	76 (87.4)	44 (95.7)	32 (78.0)	
Alcohol consumption				0.004
No	7 (8.0)	0	7 (17.1)	
Yes	80 (92.0)	46 (100)	34 (82.9)	
Betel quid chewing				0.24
No	26 (29.9)	11 (23.9)	15 (36.6)	
Yes	61 (70.1)	35 (76.1)	26 (63.4)	
ECOG performance status				0.029
0	50 (57.5)	32 (69.6)	18 (43.9)	
1	35 (40.2)	14 (30.4)	21 (51.2)	
2	2 (2.3)	0	2 (4.9)	
Tumor location				0.26
Upper third	13 (14.9)	10 (21.7)	3 (7.3)	
Middle third	31 (35.6)	14 (30.4)	17 (41.5)	
Lower third	20 (23.0)	11 (23.9)	9 (22.0)	
Overlapping	23 (26.4)	11 (23.9)	12 (29.3)	
Length of tumor*, cm	5.0 (1.2-13.0)	5 (1.2-13.0)	5.1 (1.5-12.5)	0.38
Histological type				0.99
Squamous cell carcinoma	85 (97.7)	45 (97.8)	40 (97.6)	
Adenocarcinoma	2 (2.3)	1 (2.2)	1 (2.4)	
7th AJCC Stage				0.40
2	15 (17.2)	6 (13.0)	9 (22.0)	
3	72 (82.8)	40 (87.0)	32 (78.0)	
T-classification				0.47
1	1 (1.1)	0	1 (2.4)	
2	12 (13.8)	8 (17.4)	4 (9.8)	
3	48 (55.2)	26 (56.5)	22 (53.7)	
4	26 (29.9)	12 (26.1)	14 (34.1)	
N-classification				0.060
0	6 (6.9)	2 (4.3)	4 (9.8)	
1	20 (23.0)	15 (32.6)	5 (12.2)	
2	41 (47.1)	22 (47.8)	19 (46.3)	
3	20 (23.0)	7 (15.2)	13 (31.7)	
Surgical resection after chemoradiotherapy	43 (49.4)	25 (54.3)	18 (43.9)	0.39

BMI, Body mass index; ECOG, Eastern Cooperative Oncology Group; AJCC, American Joint Committee on Cancer. *Data presented as median (range).

is a commonly used assessment tool to predict treatment-related outcome in elderly cancer patients across different antitumor therapies (20-22). To the best of our knowledge, this is the first study focusing on the impact of frailty on treatment outcome of CCRT in patients with locally advanced EC. Our study provides novel findings about the high prevalence of frailty in all adult EC patients and identifies the association of frailty status with treatment-related sAEs,

Table III. *Completion and complications of concurrent chemoradiotherapy.*

Frailty status	Incomplete radiotherapy			Incomplete chemotherapy			Emergency room visiting			Hospitalization		
	N (%)	Crude RR	Adjusted# RR	N (%)	Crude RR	Adjusted# RR	N (%)	Crude RR	Adjusted# RR	N (%)	Crude RR	Adjusted# RR
Overall	5 (5.7)			10 (11.5)			26 (29.9)			21(24.1)		
Fit (n=46)	2 (4.3)	1	1	3 (6.5)	1	1	8 (17.4)	1	1	6 (13)	1	1
Frail (n=41)	3 (7.3)	1.74 (0.28-10.9)	1.67 (0.22-12.6)	7 (17.1)	2.91 (0.71-12.3)	3.16 (0.65-15.3)	18 (43.9)	3.72 (1.39-9.91)	3.75 (1.35-10.4)	15 (36.6)	3.85 (1.03-11.2)	3.40 (1.10-10.5)
p-Value		0.56	0.66		0.14	0.16		0.009	0.011		0.013	0.034

#Adjusted for age, gender, tumor stage, and ECOG performance. RR, Relative risk.

emergency room visiting and hospitalization, as well as survival outcome in EC patients undergoing CCRT.

In contrast to the CROSS study (5), our study reported higher incidences of treatment-related toxicities with 40% and 52% of the patients experiencing grade 3 or higher hematological and non-hematological adverse events, respectively. The treatment-related toxicity of PC-based therapy varied widely in patients with esophageal cancer; 13% to 78% of the patients had grade 3 or higher toxicities in the previously published literature (7-14). In addition to the innate differences among different studies, different treatment intensity with radiotherapy dosage, dosage of PC regimens, and infusion duration (triweekly or weekly schedule) also contribute to the wide variation of toxicity profiles in EC patients during CCRT (7-14). In line with previous phase II and retrospective reports (7-14), our study highlighted that a substantial number of EC patients are vulnerable to sAEs of CCRT with PC regimen. Furthermore, our study presented that pretreatment frailty assessment is an effective method to assist clinicians to identify vulnerable patients who are susceptible to sAEs while undergoing CCRT with PC regimen.

Frailty assessment is a well-established tool to predict antitumor treatment-related complications in geriatric patients with various solid cancers (25). Frailty, occurring independently from chronological age, is a syndrome due to cumulative decreased physiological reserve and results in increased vulnerability to external stressors, such as acute illness or complication of medical treatment (18-19, 26). For example, the prevalence of frailty was reported at approximately 5.3% to 7.4% among those aged 18-64 years in a healthy population (18). The prevalence of frailty was reported up to 13.1% for young adult survivors of childhood cancer (27) and was presented in about 20-33% of patients with critical illnesses who were aged <65 years (28-29). Therefore, we hypothesized that frailty might not only be prevalent among geriatric population but also in all adult patients with malignant disease. In accordance with the hypothesis, our study demonstrated that the distribution of impairment in each frail domain was similar between non-elderly (age <65) and elderly (age ≥65) patient groups. Our study highlighted that the physiological reserve, regardless of the chronologic age, is most pertinent to frailty.

Our study demonstrated the utility of frailty in predicting sAEs of CCRT in esophageal cancer. However, the frailty status was associated with hematological, but not non-hematological toxicity. In the Chemotherapy Risk Assessment Scale for the High-Age patients (CRASH) trial, based on 518 patients with various malignancies receiving chemotherapy, the authors created two different frailty-based models, one for hematological and one for non-hematological toxicity to predict treatment-related sAEs (30). This phenomenon hints that hematological and non-hematological toxicities might be

Table IV. *Grade 3 or higher adverse events of the concurrent chemoradiotherapy.*

Adverse events	Overall (n=87)	Fit (n=46)	Frail (n=41)	*p*-Value
Hematological toxicity, n (%)				
Any	35 (40.2)	9 (19.6)	26 (63.4)	<0.001
Leukopenia	28 (32.2)	7 (15.2)	21 (51.2)	<0.001
Anemia	15 (17.2)	3 (6.5)	12 (29.3)	0.009
Neutropenia	15 (17.2)	5 (19.9)	10 (24.4)	0.15
Thrombocytopenia	9 (10.3)	4 (8.7)	5 (12.2)	0.73
Neutropenic fever	4 (4.6)	1 (2.2)	3 (7.3)	0.34
Non-hematological toxicity, n (%)				
Any	45 (51.7)	27 (58.7)	18 (43.9)	0.20
Mucositis	20 (23.0)	7 (15.2)	13 (31.7)	0.07
Non-neutropenic infection	15 (17.2)	6 (13.0)	9 (22.0)	0.40
Fatigue	8 (9.1)	4 (8.7)	4 (9.7)	0.75
Hyponatremia	8 (9.2)	2 (4.3)	6 (14.6)	0.14
Emesis	7 (8.0)	5 (1.9)	2 (4.9)	0.44
Esophageal tumor bleeding	6 (6.9)	3 (6.5)	3 (7.3)	0.99
Hyperglycemia	5 (5.7)	2 (4.3)	3 (7.3)	0.66
Hypertension	5 (5.7)	2 (4.3)	3 (7.3)	0.67
Abnormal AST or ALT	4 (4.6)	3 (6.5)	1 (2.4)	0.62
Hypokalemia	4 (4.6)	1 (2.2)	3 (7.3)	0.34
Diarrhea	3 (3.4)	1 (2.2)	2 (4.9)	0.80

AST, Aspartate aminotransferase; ALT, alanine aminotransferase.

due to decline of different physical functions. As a result, different frailty assessment tools using various geriatric domains might only predict some aspects of treatment-related toxicities. Further investigation is necessary to select the optimal aspects and instruments of frailty assessment used for evaluating both hematological and non-hematological sAEs in patients with EC under CCRT.

The frailty impairment in patients with EC is reasonable in several aspects. First, malnutrition and loss of skeletal muscle caused by dysphagia and odynophagia in EC patients inevitably leads to poor physical reserve and functional decline (31). Second, cognitive impairment was prevalent in patients with EC (31). Finally, social isolation and depressive symptoms further increased risk for adverse health outcome (32). The accumulation of malnutrition with cognitive, mood, and social disorders constructed the main components for frailty in our EC patient cohort. All these aspects might happen in all EC patients and are not solely limited to geriatric patients. Awareness of these common domains of physiological deficits in EC patients might assist clinicians to provide effective intervention to improve patients' frailty status upon initiation of the antitumor treatment.

Frail patients had higher incidences of sAEs, emergency room visiting, and hospitalization than fit patients in our study. Due to the easy accessibility of medical services in Taiwan, patients could receive appropriate management and treatment after reaching out for medical help. After appropriate and timely management of treatment-related sAEs, patients could continue the CCRT schedule. Therefore, the higher incidences of sAEs in frail patients did not compromise their treatment completion in our study. Despite the similar CCRT completion rate in both frail and fit groups in our study; it was however observed that, frail patients had poorer survival rates as compared to non-frail patients. This phenomenon is possibly related to the endowed causes of frailty in each individual, for which malnutrition, comorbidities, functional dependences, and poor social support could directly impact the survival outcome. Our study presented the frailty, as the summation of these psycho- physiological deficits, and could serve as an independent prognostic factor even after adjustment with other concomitant clinical and tumor factors.

The clinical significance of frail assessment in adult patients with EC undergoing CCRT was seldom explored. The strength of this study is its prospective design to assess multiple physiological domains of frailty including daily activity, nutritional status, comorbidity, polypharmacy, mood, and social support, which are all important prognosticators in patients with cancer (32-33). However, there are some limitations to our study. First, only 87 patients were included in our study, these small patient numbers with a heterogeneous population by tumor stage might limit the power of statistical analysis. Second, the comparison of treatment-related sAEs remained at univariate analysis level because we did not adjust other confounding factors that might be due to existence of in-group differences in clinical characteristics. Third, as histology of EC is mostly squamous cell carcinoma predominant in the Asian

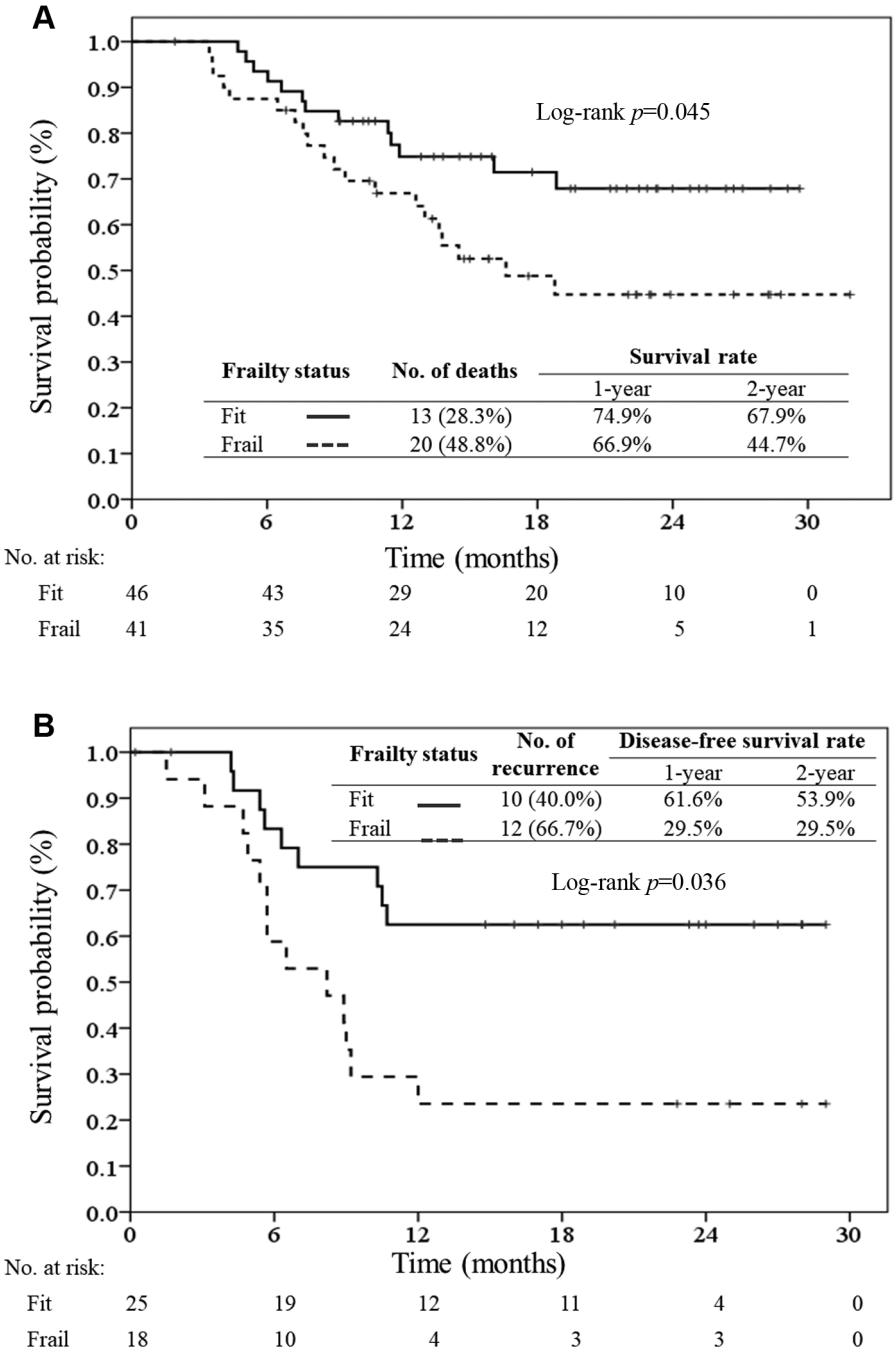

Figure 2. *Over survival curve (A) and disease-free survival curve (B) according to frailty status of the patients.*

population, which is different from that of adenocarcinoma in Western countries, the applicability of our findings to Western ethnic patients requires further validation (34). Fourth, there is neither consensus on the aspects and instruments of frail assessment tools nor the cutoff value of the numbers of frail domain impairment for frailty in oncologic practice. Our study used the same frail assessment tool and cutoff value for frailty that we previously validated in a Taiwanese adult population with primary head and neck cancer (24). The optimal instrument and cutoff value of numbers of frail domain impairment for frail assessment in patients with EC need further validation. Fifth, the poor DFS after operation might be due to

higher percentage of postoperative complications, more advanced pathological tumor stage, or poor tolerance to the postoperative adjuvant treatment. Unfortunately, we were unable to further analyze the key reason behind poor DFS in the frail patients as these factors were not included in our study. Finally, frail assessment tools were developed and utilized in the geriatric population (16). The application of these tools in non-elderly patients in our study may be an issue. While this study has shown that the features of frailty may be independent of age, we need more evidence to prove the practicality of frailty assessment in non-geriatric population and other cancers. Nevertheless, our findings present new avenues for further research of frailty assessment in non-elderly cancer populations.

Conclusion

This prospective observational cohort study found that frailty is associated with increase of treatment-related sAEs, incremental rate of emergency room visiting and hospitalization, as well as poorer survival outcome in EC patients undergoing CCRT with PC regimen. Our study highlighted that psycho-physiological reserve, regardless of the chronologic age, is most pertinent to the features of frailty in EC patients. The finding of this study suggested that pretreatment frailty assessment is imperative to serve as a predictor and prognostic factor for all adult patients with locally advanced EC undergoing CCRT.

Conflicts of Interest

The Authors declare that no competing interests exist regarding this study.

Authors' Contributions

Conception and design of study: SPH, HSW, CWC, TNM, HCY, HSW, CPH, HYW; Acquisition of data: HCY, HYS, LCC, LYC; Analysis and interpretation of data: HMM, YKY, YC; Drafting of the manuscript: LCH, TCK, SPH, HSW, HYS, HCY, CWC

Acknowledgements

The Authors gratefully acknowledge the support from the Cancer Center of Chang Gung Memorial Hospital, Taoyuan, Taiwan.

Ethics approval and consent to participate. This study was approved by the institutional review board of Chang Gung Memorial Hospital in August 2017 (ethic code: 1608080002) and has been conducted in compliance with the Helsinki Declaration (1996).

References

1 International Agency for Research on Cancer, World Health Organization. Available at: http://gco.iarc.fr/today/data/factsheets/cancers/6-Oesophagus-fact-sheet.pdf [Last Accessed on March 20, 2020]

2 American Cancer Society. Key Statistics for Esophageal Cancer. Available at: https://www.cancer.org/cancer/esophagus-cancer/about/key-statistics.html [Last Accessed on March 20, 2020]

3 Crosby T, Hurt CN, Falk S, Gollins S, Staffurth J, Ray R, Bridgewater JA, Geh JI, Cunningham D, Blazeby J, Roy R, Maughan T, Griffiths G and Mukherjee S: Long-term results and recurrence patterns from SCOPE-1: a phase II/III randomised trial of definitive chemoradiotherapy +/- cetuximab in oesophageal cancer. Br J Cancer *116(6)*: 709-716, 2017. PMID: 28196063. DOI: 10.1038/bjc.2017.21

4 D'Amico TA: Outcomes after surgery for esophageal cancer. Gastrointest Cancer Res *1(5)*: 188-196, 2007. PMID: 19262708.

5 Kidane B, Coughlin S, Vogt K and Malthaner R: Preoperative chemotherapy for resectable thoracic esophageal cancer. Cochrane Database Syst Rev *(5)*: CD001556, 2015. PMID: 25988291. DOI: 10.1002/14651858.CD001556.pub3

6 van Hagen P, Hulshof MC, van Lanschot JJ, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BP, Richel DJ, Nieuwenhuijzen GA, Hospers GA, Bonenkamp JJ, Cuesta MA, Blaisse RJ, Busch OR, ten Kate FJ, Creemers GJ, Punt CJ, Plukker JT, Verheul HM, Spillenaar Bilgen EJ, van Dekken H, van der Sangen MJ, Rozema T, Biermann K, Beukema JC, Piet AH, van Rij CM, Reinders JG, Tilanus HW, van der Gaast A and CROSS Group: Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med *366(22)*: 2074-2084, 2012. PMID: 22646630. DOI: 10.1056/NEJMoa1112088

7 Keresztes RS, Port JL, Pasmantier MW, Korst RJ and Altorki NK: Preoperative chemotherapy for esophageal cancer with paclitaxel and carboplatin: results of a phase II trial. J Thorac Cardiovasc Surg *126(5)*: 1603-1608, 2003. PMID: 14666040. DOI: 10.1016/s0022-5223(03)00710-4

8 El-Rayes BF, Shields A, Zalupski M, Heilbrun LK, Jain V, Terry D, Ferris A and Philip PA: A phase II study of carboplatin and paclitaxel in esophageal cancer. Ann Oncol *15(6)*: 960-965, 2004. PMID: 15151955. DOI: 10.1093/annonc/mdh230

9 Wang H, Ryu J, Gandara D, Bold RJ, Urayama S, Tanaka M, Goldberg Z, Follette D, Narayan S and Lau D: A phase II study of paclitaxel, carboplatin, and radiation with or without surgery for esophageal cancer. J Thorac Oncol *2(2)*: 153-157, 2007. PMID: 17410032. DOI: 10.1097/JTO.0b013e31802bff75

10 Münch S, Pigorsch SU, Devečka M, Dapper H, Weichert W, Friess H, Braren R, Combs SE and Habermehl D: Comparison of definite chemoradiation therapy with carboplatin/paclitaxel or cisplatin/5-fluoruracil in patients with squamous cell carcinoma of the esophagus. Radiat Oncol *13(1)*: 139, 2018. PMID: 30068371. DOI: 10.1186/s13014-018-1085-z

11 Ruppert BN, Watkins JM, Shirai K, Wahlquist AE, Garrett-Mayer E, Aguero EG, Sherman CA, Reed CE and Sharma AK: Cisplatin/Irinotecan *versus* carboplatin/paclitaxel as definitive chemoradiotherapy for locoregionally advanced esophageal cancer. Am J Clin Oncol *33(4)*: 346-352, 2010. PMID: 19841574. DOI: 10.1097/COC.0b013e3181aaca26

12 Haj Mohammad N, Hulshof MC, Bergman JJ, Geijsen D, Wilmink JW, van Berge Henegouwen MI and van Laarhoven HW: Acute toxicity of definitive chemoradiation in patients with inoperable or irresectable esophageal carcinoma. BMC Cancer *14*: 56, 2014. PMID: 24485047. DOI: 10.1186/1471-2407-14-56

13 Noronha V, Prabhash K, Joshi A, Patil VM, Talole S, Nakti D, Sahu A, Shah S, Ghosh-Laskar S, Patil PS, Mehta SA, Jambhekar N, Mahajan A and Purandare N: Clinical outcome in

definitive concurrent chemoradiation with weekly paclitaxel and carboplatin for locally advanced esophageal and junctional cancer. Oncol Res *23(4)*: 183-195, 2016. PMID: 27053347. DOI: 10.3727/096504016X14537290676865

14 Honing J, Smit JK, Muijs CT, Burgerhof JGM, de Groot JW, Paardekooper G, Muller K, Woutersen D, Legdeur MJC, Fiets WE, Slot A, Beukema JC, Plukker JTM and Hospers GAP: A comparison of carboplatin and paclitaxel with cisplatinum and 5-fluorouracil in definitive chemoradiation in esophageal cancer patients. Ann Oncol *25(3)*: 638-643, 2014. PMID: 24492674. DOI: 10.1093/annonc/mdt589

15 Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, McBurnie MA and Cardiovascular Health Study Collaborative Research Group: Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci *56(3)*: M146-M156, 2001. PMID: 11253156. DOI: 10.1093/gerona/56.3.m146

16 Xue QL: The frailty syndrome: definition and natural history. Clin Geriatr Med *27(1)*: 1-15, 2011. PMID: 21093718. DOI: 10.1016/j.cger.2010.08.009

17 Dent E, Kowal P and Hoogendijk EO: Frailty measurement in research and clinical practice: A review. Eur J Intern Med *31*: 3-10, 2016. PMID: 27039014. DOI: 10.1016/j.ejim.2016.03.007

18 Kehler DS, Ferguson T, Stammers AN, Bohm C, Arora RC, Duhamel TA and Tangri N: Prevalence of frailty in Canadians 18-79 years old in the Canadian Health Measures Survey. BMC Geriatr *17(1)*: 28, 2017. PMID: 28107813. DOI: 10.1186/s12877-017-0423-6

19 Hanlon P, Nicholl BI, Jani BD, Lee D, McQueenie R and Mair FS: Frailty and pre-frailty in middle-aged and older adults and its association with multimorbidity and mortality: a prospective analysis of 493 737 UK Biobank participants. Lancet Public Health *3(7)*: e323-e332, 2018. PMID: 29908859. DOI: 10.1016/S2468-2667(18)30091-4

20 Ethun CG, Bilen MA, Jani AB, Maithel SK, Ogan K and Master VA: Frailty and cancer: Implications for oncology surgery, medical oncology, and radiation oncology. CA Cancer J Clin *67(5)*: 362-377, 2017. PMID: 28731537. DOI: 10.3322/caac.21406

21 Ørum M, Gregersen M, Jensen K, Meldgaard P and Damsgaard EMS: Frailty status but not age predicts complications in elderly cancer patients: a follow-up study. Acta Oncol *57(11)*: 1458-1466, 2018. PMID: 30280625. DOI: 10.1080/0284186X.2018.1489144

22 Tsubata Y, Shiratsuki Y, Okuno T, Tanino A, Nakao M, Amano Y, Hotta T, Hamaguchi M, Okimoto T, Hamaguchi S, Kurimoto N, Nishiyama Y, Kimura T, Iwata H, Tsumoto S and Isobe T: Prospective clinical trial evaluating vulnerability and chemotherapy risk using geriatric assessment tools in older patients with lung cancer. Geriatr Gerontol Int *19(11)*: 1108-1111, 2019. PMID: 31746525. DOI: 10.1111/ggi.13781

23 van der Sluis PC, Schizas D, Liakakos T and van Hillegersberg R: Minimally invasive esophagectomy. Dig Surg *37(2)*: 93-100, 2020. PMID: 31096214. DOI: 10.1159/000497456

24 Chou WC, Chang PH, Chen PT, Wang HM, Yeh KY, Lu CH, Hung YS, Tung-Chieh Chang J, Tsang NM, Ho YW, Chen SY, Lee SH, Hung CY, Wang LJ, Liao KC, Lin CH, Tang WR and Lin YC: Clinical significance of vulnerability assessment in patients with primary head and neck cancer undergoing definitive concurrent chemoradiation therapy. Int J Radiat Oncol Biol Phys *108(3)*: 602-611, 2020. PMID: 31987971. DOI: 10.1016/j.ijrobp.2020.01.004

25 Chen X, Mao G and Leng SX: Frailty syndrome: an overview. Clin Interv Aging *9*: 433-441, 2014. PMID: 24672230. DOI: 10.2147/CIA.S45300

26 Järvinen T, Ilonen I, Kauppi J, Salo J and Räsänen J: Loss of skeletal muscle mass during neoadjuvant treatments correlates with worse prognosis in esophageal cancer: a retrospective cohort study. World J Surg Oncol *16(1)*: 27, 2018. PMID: 29433514. DOI: 10.1186/s12957-018-1327-4

27 Wilson CL, Chemaitilly W, Jones KE, Kaste SC, Srivastava DK, Ojha RP, Yasui Y, Pui CH, Robison LL, Hudson MM and Ness KK: Modifiable factors associated with aging phenotypes among adult survivors of childhood acute lymphoblastic leukemia. J Clin Oncol *34(21)*: 2509-2515, 2016. PMID: 27001572. DOI: 10.1200/JCO.2015.64.9525

28 Rockwood K, Song X and Mitnitski A: Changes in relative fitness and frailty across the adult lifespan: evidence from the Canadian National Population Health Survey. CMAJ *183(8)*: E487-E494, 2011. PMID: 21540166. DOI: 10.1503/cmaj.101271

29 Theou O, Brothers TD, Rockwood MR, Haardt D, Mitnitski A and Rockwood K: Exploring the relationship between national economic indicators and relative fitness and frailty in middle-aged and older Europeans. Age Ageing *42(5)*: 614-619, 2013. PMID: 23443511. DOI: 10.1093/ageing/aft010

30 Extermann M, Boler I, Reich RR, Lyman GH, Brown RH, DeFelice J, Levine RM, Lubiner ET, Reyes P, Schreiber FJ 3rd and Balducci L: Predicting the risk of chemotherapy toxicity in older patients: the Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score. Cancer *118(13)*: 3377-3386, 2012. PMID: 22072065. DOI: 10.1002/cncr.26646

31 van Deudekom FJ, Klop HG, Hartgrink HH, Boonstra JJ, Lips IM, Slingerland M and Mooijaart SP: Functional and cognitive impairment, social functioning, frailty and adverse health outcomes in older patients with esophageal cancer, a systematic review. J Geriatr Oncol *9(6)*: 560-568, 2018. PMID: 29680585. DOI: 10.1016/j.jgo.2018.03.019

32 Hamaker ME, Mitrovic M and Stauder R: The G8 screening tool detects relevant geriatric impairments and predicts survival in elderly patients with a haematological malignancy. Ann Hematol *93(6)*: 1031-1040, 2014. PMID: 24488257. DOI: 10.1007/s00277-013-2001-0

33 Agemi Y, Shimokawa T, Sasaki J, Miyazaki K, Misumi Y, Sato A, Aida S, Ishii M, Nakamura Y, Naoki K and Okamoto H: Prospective evaluation of the G8 screening tool for prognostication of survival in elderly patients with lung cancer: A single-institution study. PLoS One *14(1)*: e0210499, 2019. PMID: 30653558. DOI: 10.1371/journal.pone.0210499

34 He H, Chen N, Hou Y, Wang Z, Zhang Y, Zhang G and Fu J: Trends in the incidence and survival of patients with esophageal cancer: A SEER database analysis. Thorac Cancer *11(5)*: 1121-1128, 2020. PMID: 32154652. DOI: 10.1111/1759-7714.13311

Received June 9, 2021
Revised September 3, 2021
Accepted September 10, 2021