The Clinical Impact of the Age-adjusted Charlson Comorbidity Index on Esophageal Cancer Patients Who Receive Curative Treatment

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Abstract. *Background/Aim:* We investigated the impact of the age-adjusted Charlson comorbidity index (ACCI) on esophageal cancer survival and recurrence after curative treatment. *Patients and Methods:* This study included 122 patients who underwent curative surgery followed by adjuvant chemotherapy for esophageal cancer between 2005 and 2017. The risk factors for the overall survival (OS) and recurrence-free survival (RFS) were identified. *Results:* An ACCI of 5 was regarded as the optimal critical point of classification considering the survival rates. The OS rates at 3 and 5 years after surgery were 64.2% and 54.4% in the low-ACCI group, respectively, and 42.3% and 29.2% in high-ACCI group, respectively ($p=0.035$). The RFS rates at 3 and 5 years after surgery were 50.2% and 43.6% in the low-ACCI group, respectively, and 28.5% and 21.3% in high-ACCI group, respectively ($p=0.021$). A multivariate analysis demonstrated that ACCI was a significant independent risk factor for both the OS and RFS. *Conclusion:* ACCI is a risk factor for survival in patients who undergo curative treatment for esophageal cancer. An effective plan for the perioperative care and surgical strategy should be developed according to ACCI.

Esophageal cancer is the seventh-most common cancer and the sixth leading cause of cancer-related mortality. An

estimated 470,000 new esophageal cancer cases and 400,000 deaths occurred worldwide every year (1, 2). Esophagectomy with perioperative chemotherapy is the standard treatment for locally advanced esophageal cancer (3-5). However, almost half of patients suffer recurrence, even after curative surgery.

Recently, the number of the elderly esophageal cancer patients has been rapidly growing. Elderly esophageal cancer patients generally have co-morbidities and age-related physiological problems (6-8). Previous reports have shown that the postoperative surgical complication rates after esophagectomy are 30% to 70%, and the mortality rate is 1%-5% (9-12). Given this situation, perioperative management might be difficult in elderly esophageal cancer patients. To improve the outcomes of locally advanced esophageal cancer patients, it is necessary to establish an optimal treatment strategy.

The Charlson comorbidity index (CCI) was first proposed by Charlson *et al.* in 1987 (13). The CCI was initially developed to account for the influence of patients' adverse medical conditions and is useful for prognostic prediction by weighing and scoring each comorbidity disease. This scoring index is widely used to evaluate the impact of comorbidities on a variety of conditions. In addition, the age-adjusted CCI (ACCI) includes the age of the patient as a correction variable in the final score, and several studies have shown ACCI to be a useful tool for predicting both the short- and long-term outcomes of various cancers (14-16). Given the above, ACCI might be a useful tool for establishing the optimal treatment strategy of esophageal cancer patients.

In the present study, we evaluated the clinical impact of ACCI on both the overall survival (OS) and recurrence-free survival (RFS) in esophageal cancer patients who underwent curative treatment.

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Table I. Comparison of survival rates stratified by patient characteristics.

Characteristics	No. of patients (%)	1-year survival rate (%)	3-year survival rate (%)	5-year survival rate (%)	p-Value
Age (years)					0.0024
<75	98 (80.3)	84.0	69.5	54.5	
≥75	24 (19.7)	62.5	39.5	14.8	
Gender					0.3772
Male	16 (13.1)	85.7	77.9	64.9	
Female	106 (86.9)	78.6	54.2	46.4	
Site of tumor					0.9167
Upper	86 (70.5)	71.4	58.8	44.1	
Middle or lower	36 (29.5)	78.0	49.9	45.7	
Age adjusted Charlson comorbidity index					0.0352
3-4	74 (60.7)	84.9	64.2	54.4	
5-6	27 (22.1)	68.5	41.2	41.2	
7-8	21 (17.2)	75.0	43.1	17.3	
UICC T status					0.0001
T1	43 (35.2)	93.0	75.1	71.3	
T2 to T3	79 (64.8)	68.1	39.6	30.8	
Lymph vascular invasion					0.0427
Negative	38 (31.1)	89.0	69.9	64.1	
Positive	84 (68.9)	75.4	49.7	41.1	
Pathological lymph node status					0.0219
Negative	62 (50.8)	85.1	66.4	60.4	
Positive	60 (49.2)	74.2	45.4	35.9	
Neoadjuvant therapy					0.7701
Yes	71 (58.2)	84.5	58.8	49.5	
No	51 (41.8)	76.1	61.0	46.6	

UICC: Union for International Cancer Control.

Patients and Methods

Patients. Patients who underwent esophagectomy for esophageal cancer at Yokohama City University between 2005 and 2017 were selected from the medical records. The patients had histologically proven primary esophageal squamous cell or adenocarcinoma, clinical stage IB to III, as evaluated using the 7th edition of the Union for International Cancer Control (UICC), and they underwent complete resection of the esophageal cancer with lymph node dissection.

Surgical procedure. Our standard procedures consisted of open subtotal esophagectomy *via* right thoracotomy. Reconstruction was performed with a gastric tube through the posterior mediastinal or retrosternal route. Anastomosis was performed *via* cervical incision. Three-field dissection was performed for upper thoracic tumors, while two-field lymph node dissection was indicated when tumors were located at the middle thoracic to lower thoracic esophagus.

Calculation of ACCI. In the present study, the ACCI was evaluated as defined by Charlson. A score of 1 was assigned for congestive heart failure, myocardial infarction, cerebrovascular disease, dementia, peripheral vascular disease, connective tissue disease, chronic obstructive pulmonary disease (COPD), mild liver disease, ulcer disease, or diabetes mellitus without end-organ damage, a score of 2 for moderate-to-severe chronic kidney disease, hemiplegia, solid tumor, diabetes with end-organ damage, lymphoma, or leukemia, a score of 3 for moderate-to-severe liver

disease, and a score of 6 for acquired immunodeficiency syndrome and metastatic solid tumors (1 point added for each decade over 40 years of age).

Evaluations and statistical analyses. The significance of correlations between ACCI and clinic pathological parameters was determined using Fisher's exact test or the χ^2 test. The OS and RFS were evaluated by univariate and multivariate analyses. The OS and RFS curves were calculated using the Kaplan-Meier method and compared by the log-rank test. A Cox proportional hazards model was used to perform the univariate and multivariate survival analyses. *p*-Values of <0.05 were considered to indicate statistical significance. The SPSS software program (v11.0 J Win; SPSS, Chicago, IL, USA) was used for all of the statistical analyses. This study was approved by the Institutional Review Board of Yokohama City University.

Results

Patients. We evaluated 122 patients in the present study. The median age was 68 years old (range=40-82 years); 106 patients were male, and 16 were female. The median follow-up period was 72.5 months (range=13.9-125.2 months). The median length of the operation was 573 min (range=236-911 min). The median blood loss was 541 ml (range=70-3000 ml). The median number of harvest lymph nodes was 37 (range=3-118).

Table II. Uni- and multi-variate Cox proportional hazards analysis of clinicopathological factors for overall survival.

Factors	No	Univariate analysis			Multivariate analysis		
		OR	95% CI	p-Value	OR	95% CI	p-Value
Age (years)				0.121			0.002
<75	98	1.000			1.000		
≥75	24	1.507	0.898-2.529		2.598	1.424-4.740	
Gender				0.139			
Female	16	1.000					
Male	106	2.153	0.780-5.949				
Age adjusted Charlson comorbidity index				0.011			0.017
≤4	74	1.000			1.000		
≥5	48	1.982	1.168-3.364		1.932	1.126-3.313	
Site of tumor				0.392			
Middle or lower	86	1.000					
Upper	36	1.331	0.691-2.564				
UICC T status				0.006			0.001
T1	43	1.000			1.000		
T2 or T3	79	2.387	1.286-4.430		2.158	1.589-2.931	
Pathological lymph node status				0.019			
Negative	62	1.000					
Positive	60	1.885	1.111-3.196				
Lymph vascular invasion				0.020			
Negative	38	1.000					
Positive	84	2.182	1.131-4.210				
Neoadjuvant therapy				0.881			
Yes	71	1.000					
No	51	1.041	0.612-1.771				

UICC: Union for International Cancer Control.

Survival analyses and patient's characteristics. The OS stratified by each clinical factor was compared using the log-rank test, and a significant difference was observed in age (<75 vs. ≥75 years old), UICC T factor (T1 vs. T2 to T3), lymphovascular invasion (positive vs. negative), and ACCI (3-4 vs. 5-6 vs. 7-8) (Table I). An ACCI of 4 was regarded as the optimal critical point for classification, considering the 1- to 5-year survival rate.

Each clinicopathological factor was categorized as shown in Table II and was analyzed for its prognostic significance. The univariate analyses for the OS showed that ACCI was a significant prognostic factor. The ACCI was therefore selected for the final multivariate analysis model. The OS rates at 3 and 5 years after surgery were 64.2% and 54.4% in the low-ACCI group, respectively, and 42.3% and 29.2% in the high-ACCI group, respectively, which amounted to a statistically significant difference ($p=0.035$). The OS curves are shown in Figure 1.

The univariate analyses for RFS showed that ACCI was a significant prognostic factor. ACCI was therefore selected for the final multivariate analysis model (Table III). The RFS rates at 3 and 5 years after surgery were 50.2% and 43.6% in the low-ACCI group, respectively,

and 28.5% and 21.3% in the high-ACCI group, respectively, which amounted to a marginally statistically significant difference ($p=0.021$). The RFS curves are shown in Figure 2.

When comparing the patients' demographic and clinical characteristics between the low- and high-ACCI groups, the incidence of postoperative anastomosis leakage (AL) was significantly different between the two groups. The incidence of AL was 27% in the low-ACCI group and 54% in the high-ACCI group. In addition, when comparing the sites of first relapse, the incidence of lung metastasis was significantly higher in the high-ACCI group than in the low-ACCI group (Table IV).

Discussion

The present study evaluated the clinical influence of ACCI on the survival of esophageal cancer patients who received curative surgery. The major finding was that ACCI was a significant risk factor for both the OS and RFS in esophageal cancer patients, indicating that age-related physiological problems and preoperative co-morbidities affected cancer treatment outcomes. To improve the survival of esophageal cancer patients who

Figure 1. A comparison of the overall survival in patients with an ACCI ≥ 5 and those with an ACCI ≤ 4 .

receive curative surgery, assessing ACCI might be useful for establishing an ideal treatment strategy for esophageal cancer.

First, we want to discuss the clinical influence of ACCI for esophageal cancer patients. In the present study, we showed that the OS rates at 5 years after surgery were 54.4% in the low-ACCI group and 29.2% in the high-ACCI group [hazard ratio (HR)=1.932, 95% confidence interval (CI)=1.126-3.313, $p=0.035$]. A few studies have described the relationship between ACCI and survival for gastrointestinal cancer patients. Maezawa *et al.* investigated the survival impacts of ACCI in 2254 patients who received radical gastrectomy for gastric cancer (17). They divided the patients into two groups: low-ACCI group ($n=1656$) and high-ACCI group ($n=598$). They found that the 5-year OS rate was 85.4% in the low-ACCI group and 74.1% in the high-ACCI group, showing a significant difference between the groups (HR=1.80, 95%CI=1.46-2.23, $p<0.001$). In addition, the 5-year RFS was 83.1% in the low-ACCI group and 73.4% in the high-ACCI group (HR=1.44, 95%CI=1.15-1.80, $p=0.001$). Lin *et al.* evaluated the clinical impact of ACCE in 1476 gastric cancer patients who received curative surgery (18). They reported that there were significant

differences in the OS between the low- and high-ACCI groups. The 1-, 3-, and 5-year OS rates were 82.7%, 62.4%, and 56.4% in the low-ACCI group, respectively, and 81.6%, 57.2%, and 47.5% in the high-ACCI group, respectively. In addition, Lin *et al.* also evaluated the clinical impact of ACCI in 2257 patients who received curative gastrectomy for gastric cancer (19). They found that ACCI was an independent risk factor in gastric cancer. They reported that the HR for the OS increased with increasing ACCI score [ACCI score 0-1; reference; ACCI score 2: HR=1.324 (95%CI=1.612-2.382), $p=0.003$; ACCI score 3-10: HR=1.894 (95%CI=1.612-2.382), $p<0.001$]. These previous findings indicate that ACCI has some clinical impact on the survival of gastrointestinal cancer, including esophageal cancer.

One possible explanation for the reason why did ACCI affect esophageal cancer patients' survival could be that it might be associated with postoperative surgical complications. In the present study, the incidence of AL was 27% in the low-ACCI group and 54% in the high-ACCI group. Similar results have been observed in other studies. In the colorectal cancer field, Tian *et al.* evaluated the

Table III. Uni- and multi-variate Cox proportional hazards analysis of clinicopathological factors for recurrence free survival.

Factors	No	Univariate analysis			Multivariate analysis		
		OR	95% CI	p-Value	OR	95% CI	p-Value
Age (years)				0.742			
≤75	98	1.000					
≥75	24	1.091	0.651-1.828				
Gender				0.282			
Female	16	1.000					
Male	106	1.590	0.683-3.702				
Age adjusted Charlson comorbidity index				0.010			0.001
≤4	74	1.000			1.000		
≥5	48	1.863	1.158-2.998		2.241	1.375-3.651	
Site of tumor				0.853			
Middle or lower	86	1.000					
Upper	36	1.032	0.737-1.447				
UICC T status				<0.001			0.001
T1	43	1.000			1.000		
T2 or T3	79	4.623	2.265-9.434		1.980	1.527-2.567	
Pathological lymph node status				<0.001			
Negative	62	1.000					
Positive	60	2.664	1.546-4.590				
Lymph vascular invasion				0.005			
Negative	38	1.000					
Positive	84	2.588	1.341-4.995				
Neoadjuvant therapy				0.089			
Yes	71	1.000					
No	51	1.620	0.928-2.827				

UICC: Union for International Cancer Control.

Table IV. Patterns of recurrence between the patients with age adjusted Charlson comorbidity index <4 and those with age adjusted Charlson comorbidity index ≥5.

Recurrence site	Age adjusted Charlson comorbidity index						p-Value
	All cases		<4 (n=74)		≥5 (n=48)		
	Number	%	Number	%	Number	%	
Lymph node							
Regional	23	18.9	13	17.6	10	20.8	0.6523
Distant	7	5.7	3	4.1	4	8.3	0.3208
Local site	12	9.8	8	10.8	4	8.3	0.6535
Distant site							
Lung	12	9.8	3	4.1	9	18.8	0.0078
Liver	11	9.0	7	9.5	4	8.3	0.8320
Bone	5	4.1	3	4.1	2	4.2	0.9755
Others	9	8.0	4	5.4	5	10.4	0.3009
Disseminated	3	2.5	1	1.3	2	4.2	0.3267

association of the ACCI score and the incidence of postoperative ileus in 11,397 colorectal cancer patients (20). They found that the incidence of postoperative ileus after rectal cancer surgery was 1.2% in the ACCI score 0-1 group,

1.6% in the ACCI score 2-3 group, 2.5% in the ACCI 4-5 group, and 2.7% in the ACCI ≥6 group. Furthermore, the incidence of postoperative ileus after colon cancer surgery was 7.8% in the ACCI score 0-1 group, 7.0% in the ACCI

Figure 2. A comparison of the recurrence-free survival in patients with an ACCI ≥ 5 and those with an ACCI ≤ 4 .

score 2-3 group, 7.6% in the ACCI 4-5 group, and 11.8% in the ACCI ≥ 6 group. We have previously found that postoperative anastomotic leakage was a significant independent risk factor for esophageal cancer patients who received curative treatment. In a previous study, the 5-year survival rate was 40.2% in patients with AL and 53.2% in the patients without AL (21). Therefore, postoperative surgical complications might occur in groups with high ACCI, resulting in a poor prognosis. Future studies should clarify the mechanism underlying the relationship between ACCI and prognosis.

We also want to discuss the cut-off value of the ACCI for cancer survival. In the present study, we set the cut-off value at 4 according to the 1- to 5-year survival rate. To utilize ACCI for esophageal cancer treatment, it is necessary to establish the optimal cut-off value. Several studies have previously explored the appropriate cut-off value of ACCI in several cancers. In the gastrointestinal region, Lin *et al.* set 3 as the cut-off value in 1476 gastric cancer patients, and Maezawa *et al.* set 6 as the cut-off value in 2254 gastric cancer patients (17, 18). In the hepato-biliary pancreatic

cancer region, Qu *et al.* set 4 as the cut-off value in 268 intrahepatic cholangiocarcinoma patients, and Takahara *et al.* set 5 as the cut-off value in biliary tract cancer (22, 23). Although it is difficult to establish a definitive cut-off value due to differences among cancer types, patients' background characteristics, and the number of patients, a cut-off value of 3-5 might be useful for ACCI. Future studies should focus on this issue to clarify the optimum cut-off value for the ACCI.

Several limitations associated with the present study should be mentioned. First, the present study was retrospective and conducted at a single institution. Therefore, there might have been some selection bias. Second, there might have been some time bias in our study. The patient records in the present study were collected between 2005 and 2017. During this period, the perioperative management and perioperative adjuvant treatment changed, and these changes might have affected the present study results. As such, the present study results should be validated in another cohort.

In conclusion, ACCI was a significant risk factor for both the OS and RFS in esophageal cancer patients. Age-related

physiological problems and preoperative co-morbidities affected cancer treatment outcomes. The assessment of ACCI might be useful for establishing the treatment strategy for esophageal cancer.

Conflicts of Interest

The Authors declare no conflicts of interest in association with the present study.

Authors' Contributions

Toru Aoyama and Yosuke Atsumi made substantial contributions to conception and design. Norio Yukawa, Kenki Segami, Toru Aoyama, Hiroshi Tamagawa, Ayako Tamagawa, Yosuke Atsumi, Shinnosuke Kawahara, Yukio Maezawa, Kazuki Kano, Kentaro Hara, Masaaki Murakawa, Keisuke Kazama, Masakatsu Numata, Takashi Oshima, Munetaka Masuda, and Yasushi Rino made substantial contributions to acquisition of data, or analysis and interpretation of data. Norio Yukawa, Toru Aoyama, Hiroshi Tamagawa, Ayako Tamagawa, Yosuke Atsumi, and Shinnosuke Kawahara have been involved in drafting the manuscript or revising it critically for important intellectual content. Norio Yukawa, Toru Aoyama, Hiroshi Tamagawa, Ayako Tamagawa, Yosuke Atsumi, and Shinnosuke Kawahara have given final approval of the version to be published. Each Author participated sufficiently in the work to take public responsibility for appropriate portions of the content, and agreed to be 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 resolved. All Authors read and approved the final manuscript.

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