Arch Iran Med. May 2019;22(5):236-241

http www.aimjournal.ir

ARCHIVES OF IRANIAN MEDICINE

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Original Article

Is the Charlson Comorbidity Index a Prognostic Indicator for Toxicity and Mortality in Elderly Patients with Locally Advanced Rectal Cancer?

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Abstract

Background: Aging is significantly related to multiple comorbidities. Even with a good performance score, some elderly patients may have poor survival outcomes. We aimed to evaluate the prognostic value of the Charlson comorbidity index (CCI) for mortality and toxicity in elderly patients with locally advanced rectal cancer (LARC).

Methods: Seventy-two elderly patients with LARC who were treated with neoadjuvant chemoradiotherapy (CRT) were included. Based on their CCI score, severity of the comorbidity was categorized into 2 groups: CCI<7 and CCI≥7.

Results: The overall survival (OS) at 5 years was 54.4 percent in patients treated with neoadjuvant CRT. Median OS was not reached for all patients as well as patients with CCI score <7, but median OS was 25 (95% CI 1.0–62.1) months in patients with CCI≥7 ($P=0.002$). The OS at 2 years was 79.1 percent in the patients with CCI <7 and 50.0 percent in the patients with CCI score ≥7 ($P=0.002$). Moreover, there was a trend toward, patients with higher CCI score who had more treatment related to grade 3 or 4 toxicity compared to those with CCI score <7 (33.3% vs 13.3%, respectively, $P=0.09$). Multivariable analysis indicated that the CCI score ≥7, presence of down-staging after therapy and clinical stage (III) independently predict mortality (HR 6.14, 95%CI 2.45–15.35, $P<0.001$) in patients with LARC .

Conclusion: Although CCI score was not significantly associated with both toxicity and disease-free survival (DFS), we suggest that baseline CCI score might be a valuable prognostic indicator for physicians to evaluate elderly patiens with LARC for optimal treatment.

Keywords: Charlson comorbidity index, Elderly patients, Locally advanced rectal cancer, Mortality, Toxicity

Cite this article as: Köstek O, Bozkaya Y, Hacıoğlu MB, Özdemir NY, Yılmaz E, Demircan NC, et al. Is the Charlson comorbidity ındex a prognostic ındicator for toxicity and mortality in elderly patients with locally advanced rectal cancer? Arch Iran Med. 2019;22(5):236–241.

Received: June 5, 2018, Accepted: April 7, 2019, ePublished: May 1, 2019

Introduction

Colorectal cancer (CRC) is the fourth most frequently diagnosed cancer and its prevalence in patients aged 65 years and over is increasing due to improving life expectancy.[1,2] Approximately 65 percent of patients with CRC are aged 65 years and older.[3] Standard treatment approach of locally advanced rectal cancer (LARC) is neoadjuvant chemoradiotherapy (CRT) following by surgery. The management of LARC in fit elderly patients is similar to those in younger patients.

Aging is significantly related to prognosis as well as higher incidence of treatment complications.[4] Since higher chronic disease burden in elderly patients with CRC makes it difficult to achieve optimal therapy benefit. Eastern Cooperative Oncologic Group (ECOG) scale has been widely used by oncologists to evaluate suitability of the patient for systemic treatment. Elderly patients with good ECOG-PS scores are generally able to receive standard intensive therapy comparable to younger patients. Due to the heterogenecity of geriatric patients, even with good ECOG-PS, some patients have poor survival outcomes. ECOG does not always reflect the functional status of the elderly cancer patients.[5]

Polymorbidity also has significant effect on heterogenecity and plays an important role to assess prognosis in elderly patients. The Charlson comorbidity index (CCI) has been widely utilized by physicians to measure burden of disease and predict mortality.[6] There is limited data to evaluate the predictive value of CCI in elderly LARC patients.[7] In this study, we aimed to assess the prognostic value of the CCI for mortality and toxicity in elderly patients with LARC.

Material and Methods

Study Patients

This study was a retrospective descriptive study. Seventy-2 geriatric patients with locally advanced rectum cancer, who underwent neoadjuvant chemotherapy followed by surgery were received between September 2009 and

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December 2016 at Trakya University and Ankara Numune Training and Research Hospital. The study was approved by the institutional review board and the scientific review comittee. Demographic and clinical data were obtained from medical records of the patients. Patients were recruited in the study according to the following criteria: 91) Pathologically proven rectal adenocarcinoma, (2) Localized tumor within the first 15 cm from anal verge, (3) Clinical stage both II or III, (4) Patients without distant metastasis, and (5) Curative surgery following nCRT. Rectum was defined as the 0 to 15th cm segment from the anal verge; inferior rectum as the 0–4.99 cm from the anal inlet, midrectum as 5.0–9.99 cm portion, superior rectum as 10th to 15th cm portion. All patients had histologically proven rectal adenocarcinoma, clinically staged by contrast-enhanced computed tomography and/or magnetic resonance as T3-T4 with or without lymph node involvement and no evidence of metastasis. In order to determine performance status and co-morbidities of the patients ECOG and CCI scores were utilized.

CCI was calculated according to the scoring system established by Charlson et al and Radovanovic et al.[8,9] Cardio-cerebrovascular disease of the comorbidities in CCI was defined as a history of cardiac arrhythmia, diabetes mellitus, liver disease, malignancy, AIDS, moderate to severe chronic kidney disease, chronic obstructive pulmonary disease, peripheral vascular disease, cerebral vasculopathy, ischemic heart disease, or chronic heart failure, dementia, hemiplegia, connective tissure disorder and peptic ulcer. CCI scores of the patients were detected from 4 to 8 scores. According to multiple comordidity situations, patients were clinically grouped as <7 and ≥7.

Neoadjuvant Chemoradiotherapy and Surgery

Radiotherapy was performed to primary tumor site and perirectal metastatic lymph nodes in 42–54 Gy dose range, as 1.8–2 Gy fractions, 5 days a week for 30–35 days. Patients had one out of 2 different chemotherapy regimens simultaneously with radiotherapy: 225 mg/m^2/day of 5-Fluorouracyl (5 days a week) was introduced through central venous catheter with a pomp; 825 mg/m^2 oral capecitabine (2 times a day) was performed the whole week during the radiotherapy period.

All patients were underwent surgery after 6–9 weeks after the completion of neoadjuvant CRT and total mesorectal excision was performed according to standart technique. Adjuvant chemotherapy was planned by the medical oncologists. Adjuvant (FOLFOX or FUFA or capecitabine) chemotherapy regimen was introduced in 3rd–6th weeks following the surgery.

Pathological Assessment

The pathological findings of tumoral lesions after neoadjuvant CRT were evaluated and categorized as complete pathological response, if primary tumor was absent. Down-staging was defined as a reduction in the pathological stage (ypTNM), primary tumoral stage (ypT) and nodal involvement(ypN) compared with the pre-treatment clinical, tumor and lymph node stages, respectively (cTNM, cT, cN).

Statistical Analysis

Statistical analyses were performed using SPSS 18.0 for Windows (SPSS; Chicago, IL, USA). Categorical variables were presented as the frequency with percentages. Categorical variables were analyzed using the chi-square or Fisher exact test, as appropriate. Survival data were analyzed using the Kaplan-Meier method and compared using the log rank test. Progression free survival was defined as the amount of relapsed time from the date of surgery until the first event (recurrence or death from any cause) or the most recent follow up. Overall survival (OS) was defined as the amount of relapsed time from the date of surgery until death from any cause or the most recent follow up. The effects of various clinical parameters on survival were evaluated using univariate analysis, and adjusted influences were assessed using multivariable Cox proportional hazards analysis to determine which explanatory variables were independently associated with mortality and to estimate hazard ratio and 95% confidence interval (CI) for mortality. The presence of down-staging, relapse and clinically stage III and CCI (≥7), ECOG (=2) were significantly associated with mortality in the univariable analysis. In multivariable analysis, HR were adjusted for age, gender, ECOG and CCI scores, presence of down-staging, relapse and clincal stage III. In addition, treatment compliance, incidence of toxicity and survival outcomes were compared with Fisher's test between CCI score <7 versus CCI score ≥7. A two-sided *P* value less than 0.05 was considered as statistically significant.

Results

Patients Characteristics

A total of 72 patients with a Charlson score from 4 to 8 were enrolled. The median age was 72 years (minimum = 65, maximum = 85) and 45 patients were male, with female to male ratio of 3:5. Table 1 shows the clinical characteristics of study subjects. Chief complaints for applying to endoscopic assessment were rectal bleeding (47.2%), and primary tumor were largely localized on distal (40.3%) and middle (38.9%) rectum, respectively**.** The predominant colonoscopic appearance was ulcerovegetan lesion (59.7%) and 69.4% (n = 50) of the lesions was grade 2 and 3 differentiated. Clinical stage of cancer were II and III in 43 (II A/B = 34/9) and 29 (III B/C = 25/4) patients, respectively.

Treatment Compliance

All patients received programmed neoadjuvant CRT with prescribed RT total dose. Of these, RT was interrupted in

Table 1. Demographic and Clinical Characteristics of the Patients

	All Patients	Patients with CCI <7	Patients with CCI≥7	*P*
Age, No. (%)				0.04
65-69	25 (34.7)	23 (38.3)	2 (16.7)	
70-74	22 (30.6)	18 (30.0)	4 (33.3)	
75-79	20 (27.8)	17 (28.3)	3 (25.0)	
80-85	5 (6.9)	2 (3.3)	3 (25.0)	
Gender, F/M	27/45	22/38	5/7	0.49
ECOG, No. (%)				0.98
0-1	60 (83.3)	50 (83.3)	10 (83.3)	
2	12 (16.7)	10 (16.7)	2 (16.7)	
Smoking, No. (%)				0.52
Ex-smoker	26 (36.1)	23 (54.8)	8 (66.7)	
Current	12 (16.7)	19 (45.2)	4 (33.3)	
Comorbidity, No. (%)				
Hypertension	18 (25.0)	15 (25.0)	3 (25.0)	0.96
Diabetes mellitus	9 (12.5)	5 (8.3)	4 (33.3)	0.03
CCI, No. (%)				
4–6 points	60 (83.3)			
7–8 points	12 (16.7)			
Chief complaint, No. (%)				0.06
Rectal bleeding	34 (47.2)	27 (45.0)	7 (58.3)	
Constipation	14 (18.4)	11 (16.3)	3 (33.4)	
Diarrhea	10 (13.8)	8 (8.3)	2 (16.3)	
Abdominal pain	5 (6.9)	4 (6.7)	1 (8.3)	
Others	10 (13.8)	8 (8.3)	2 (16.3)	
Primary tumor site, No. (%)				0.13
Proximal rectum	15 (20.8)	10 (16.7)	5 (41.7)	
Middle rectum	28 (38.9)	24 (40.0)	4 (33.3)	
Distal rectum	29 (40.3)	26 (43.3)	3 (25.0)	
Colonoscopic appearance, No. (%)				0.91
Ulcerovegetan	43 (59.7)	36 (60.0)	7 (58.3)	
Polypoid	15 (20.8)	12 (20.0)	3 (25.0)	
Infiltrative	14 (19.4)	12 (20.0)	2 (16.7)	
Clinical stage, n/n				
cT2/cT3/cT4	0/56/14	0/46/10	0/14/2	0.47
cN0/cN+	43/29	37/23	6/6	0.52
c II A/B	34/9	28/9	6/0	0.31
c III A/B/C	0/25/4	19/4	6/0	
Type of resection, No. (%)				
LAR	56 (77.8)	48 (80.0)	8 (66.7)	0.78
APR	16 (22.2)	12 (20.0)	4 (33.3)	0.68
Completeness of local resection, No. (%)				
Complete	71 (98.6)	59 (98.3)	12 (100)	0.73
With distant metastasis	1 (1.4)	1 (1.6)		

Abbreviation: CCI, Charlson comorbidity index.

2 patients due to grade 3–4 toxicity. On the other hand, 64 (88.9%) patients received bolus 5FU and 8 patients received capecitabine. After neoadjuvant CRT, 56 patients underwent LAR and 16 patients underwent APR. All patients were resected with complete resection and 1 patient had distant metastasis. Therefore, 64 patients (88.9%) received adjuvant chemotherapy with 4 cycles (median = 4, minimum = 2 and maximum = 5 cycles). Postoperative chemotherapy protocols were FOLFOX (n = 37, 51.3%), FUFA (n = 19, 26.3%) and capecitabine (n = 8, 11.1%).

Treatment Response

The rate of complete pathologic response to neoadjuvant CRT is %11.1 (8/72). According to ypTNM, down-staging response to nCRT was observed in 45 (62.5%) patients. In addition, down-staging of ypT were observed in 40 (55.5%) patients. The ratio of down-staging of ypN were (25%) lower than those of ypT and ypTNM. Although down-staging of ypTNM was higher in distal rectum than middle and proximal rectum, there was no significant association between tumor localization and down-staging (P = 0.48). On the other hand, down-stagings of ypT and ypN were similar in all rectal parts (p = 0.46 and P = 0.81, respectively).

Toxicity

All patients had acute toxicity associated with chemoradiation therapy. There was no patient required hospitalization to palliate treatment, febrile neutropenia or toxicity related death. On the other hand, there was no grade 3 or 4 hematologic toxicity associated with chemoradiation therapy. Table 2 shows non-hematologic toxicities. Of these, acute non-hematologic toxicities were mainly gastrointestinal, dermatologic and genitourinary. Proctitis (70.8%) was the most common acute toxicity. One patient had fecal incontinence as treatment related long term toxicity, not required to a permanent colostomy.

Survival Outcomes

The OS at 5 years was 54.4 percent in patients treated with neoadjuvant CRT. CCI score was calculated (minimum = 4 and maximum = 8) and categorized as 2 groups, CCI score <7 and ≥7. Median OS was not reached for all patients as well as patients with CCI score <7, but median OS was 25 (95% CI 1–62.1) months in patients with CCI≥7 (P = 0.002, Figure 1). The OS at 2 years was 79.1 percent in the patients with CCI <7 and 50.0 percent in the patients with CCI score ≥7 (P = 0.002). The hazard ratio for death in the patients with CCI score ≥7, as compared with the patients with CCI <7, was 3.45 (95% CI, 1.49 to 7.95, P = 0.004). The disease-free survival (DFS) at 5 years was 20.9 percent in patients treated with neoadjuvant CRT. In

Table 2. Acute Non-hematologic Toxicity

	Grade 1–2	Grade 3–4
Proctitis	45 (62.5)	6 (8.3)
Diarrhea	37 (51.4)	4 (5.6)
Vomiting	12 (16.6)	—
Dermatitis	42 (58.3)	2 (2.7)
Dysuria	21 (29.1)	—
Fatigue	24 (33.3)	—

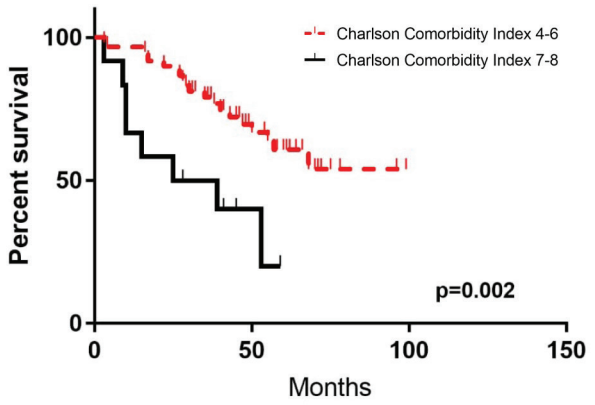

Figure 1. Kaplan-Meier plots shows that edian OS was not reached for patients with CCI score <7.

addition, there was no difference in terms of DFS between 2 groups (P = 0.21). Although, patients with CCI score ≥7 had more grade 3 or 4 acute toxicity, it was not statistically significant (33.3% vs 13.3%, P = 0.09). Univariate analyses showed that CCI score ≥7, ECOG = 2, presence of relapse and down-staging after therapy and clinical stage (III) were associated with survival. Multivariable analysis indicated that the that CCI score ≥7, presence of down-staging after therapy and clinical stage (III) independently predict mortality in patients with LARC (Table 3).

Discussion

The results of this study confirmed that outcomes in trimodality treatment for elderly patients with LARC is based not only on the expected survival benefit achieved with the treatment but also on the potential hazards of multiple comorbidities. Beside that, downstaging response to CRT and baseline stage III compared to stage II also had independent prognostic value in patients with LARC.

CRC is largely diagnosed in old age, at which time comorbidity is common and over half of CRC patients have at least one comorbid condition.[10] Since comorbidity is associated with an increased mortality risk in cancer patients, it plays an important role in CRC prognosis. There is not enough data about the potential effects of polymorbidity on prognosis in elderly LARC patients treated with neoadjuvant CRT following surgery. Firstly, De Felice et al revealed that increased comorbid conditions were not associated with a negative impact on survival in geriatric patients with LARC treated with neoadjuvant CRT.[11] Elderly patients with LARC who received intensified neoadjuvant CRT with concomitant oxaliplatin and 5-fluorouracil were enrolled and their comorbidity score was calculated by the ACE-27 index. Compared to our study, smaller population and different comorbidity scale were used to assess the possible association between comorbidity and survival in patients with LARC who received neaoadjuvant CRT. On the other hand, a recent meta-analysis showed both poor short- and long-term prognosis in CRC patients with comorbidity. It has been shown that the presence of comorbidity (CCI≥3) was associated with increased overall mortality compared to absence of comorbidity (CCI<2) in patients with CRC.[12] However, studies including only rectal cancer patients were not included in this review and also the treatments and patient groups were not homogeneous. All of our patients had comorbidities (CCI>3) and according to score distribution (min-max = 4–8), we evaluated the effect of severity of the comorbidity on mortality by dividing into our study populatin into 2 groups (CC <7 and CCI 7–8). Baseline CCI score of patients with LARC who aged above 65 years was calculated at least 4 and maximum 6 of those aged above 80 years. According to median age of our population, if one comorbid condition was present, total score was calculated as 7 points and clinically detected 7 points was the cut-off value. As expected, we found a higher risk of mortality in elderly LARC patients with CCI ≥7 (higher CCI score (≥7) which had significant prognostic value (HR = 6.14 95%CI 2.45–15.35, P < 0.001) than those with CCI<7. Noteworthy, we revealed that not only presence of comorbidity, but also increased severity of comorbidity has potential hazard impact on mortality.

Only the age factor should not be used as a selection criterion for foregoing neoadjuvant CRT in elderly patients.[12] There are several factors that are also associated with prognosis and important for making treatment decisions. The severity of comorbidity may influence tolerability of treatment and ultimately patient outcomes. There is still a gap to adapt the clinical trial data to our treatment decisions of older patients with cancer because

Table 3. Univariable and Multivariable Analysis of Prognostic Factors for Survival in Patients with LARC

	Univariate Analysis			Multivariable Analysis		
	Hazard Ratio	95% CI	*P*	HR	95% CI	*P*
Age, year	1.01	0.93–1.07	0.89			
Female	1.10	0.51–2.40	0.80			
CCI ≥7	3.44	1.49–7.94	0.004	6.14	2.45–15.35	<0.001
ECOG =2	2.41	1.02–5.70	0.04			
Down staging (+)	0.38	0.18–0.82	0.01	0.17	0.07–0.40	<0.001
Relapse (+)	2.39	1.05–5.44	0.033			
Clinical stage III	2.81	1.17–6.75	0.02	6.48	2.43–17.23	<0.001

the underlying health status of older (aged 65 and above) individuals included within clinical trials is not well characterized.[13] Moreover, more fit elderly patients were included the trials. Data from real-world settings in the geriatric population may not correspond to clinical trials. More fragile patients can take part in routine practice. On the other hand, due to the heterogeneity of the geriatric population, data about severity of multiple comorbidities in patients with elderly LARC who were treated with neoadjuvant CRT will be valuable to predict the prognosis of elderly LARC patients.

Performance status of elderly cancer patients defined by using ECOG score is commonly used in younger (<65 years) cancer patients. It is known that ECOG score does not estimate the functional limitations that are predictive of morbidity and mortality in the geriatric population.[14] Elderly patients with good ECOG-PS score are generally considered fit and able to receive standard intensive therapy comparable to younger patients. However, these elderly patients are also heterogeneous. Some patients, even with good ECOG-PS, have poor survival outcomes. ECOG does not always reflect the functional status of the elderly cancer patients.[5] We demonstrated that both ECOG performance score and CCI was significantly related to mortality in univariate analysis, but only CCI was independently associated with mortaliy in multivariable analysis. We suggested that CCI score together with ECOG can be preferable to assess the functional status of elderly patients.

Neoadjuvant chemoradiation has become the preferred treatment of LARC because of evidence demonstrating improved outcomes and better tolerability.[15] We also demonstrated that, even patients who had multiple comorbidity, who achieved downstaging response to therapy, had favourable outcome (HR = 0.17, 95% CI 0.07–0.40, $P < 0.001$). As expected, baseline clinical stage III (HR = 6.48 95% CI 2.43–17.2, $P < 0.001$) had worse prognosis than stage II. Fortunately, all patients had received total prescribed RT dose and perioperative chemotherapy was admistered to 88.9% of the patients without required hospitalization to palliate treatment and death associated with toxicity. In addition, Italian and French studies showed that neoadjuvant CRT in elderly LARC was well tolerated[16–18] whereas Margalit et al and Cai et al revealed that CRT should be performed with caution in elderly patients due to acute and late toxicities.[19,20] In contrast, De Felice et al showed that patients with pre-existing comorbidities did not associate with increased frequency of acute and late complication.[11] In our study, there was a trend toward patients with higher CCI score who had more treatment related to grade 3 or 4 toxicity compared to those with CCI score <7 (33.3% vs 13.3%, respectively, $P = 0.09$).

There are some major limitations. First, retrospective clinical data of a geriatric population from medical records has disadvantages to control for all potential confounding bias that may influence the morbidity and mortality. Second, the number of patients was small. Then, data about toxicity profile may have missing data due to incomplete identification of adverse events considering the limitation of the retrospective study. In addition, cT3 tumor on CT imaging has limitation to define as T3 due to the fact that clear definition is based on histologically proven invasion through the muscularis propria into the subserosa. Despite these limitations, a noteworthy strength of our study is that CCI score above 7 showed prognostic indicator independent from disease stage and treatment benefit in elderly LARC patients. Therefore, we believed that CCI score may help physician to predict mortality when added to ECOG-PS score in routine clinical setting in elderly cancer patients. Further randomized prospective studies are required to clarify the validated CCI score impact on LARC patients' survival.

In conclusion, although CCI score was not significantly associated with both toxicity and DFS, we suggest that baseline CCI score might be a valuable prognostic indicator for physicians to evaluate elderly patiens with LARC for optimal treatment.

Authors' Contribution

All authors contributed equally to this study

Conflict of Interest Disclosures

No conflict of interest was declared by the authors.

Financial Disclosure

The authors declared that this study received no financial support

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