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ORIGINAL ARTICLE

The prognostic significance of the age-adjusted Charlson comorbidity index in the prediction of postoperative outcome after liver resection for colorectal cancer metastases

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Summary

Introduction: The prognostic value of the age-adjusted Charlson comorbidity index (ACCI) for patients with colorectal liver metastases (CRLM) undergoing liver resection is still unclear. The aim of this study is to analyze the impact of ACCI in the prediction of short- and long-term outcomes after liver resection in patients with CRLM.

Material and methods: Data related to 101 patients who underwent liver resection for CRLM at the University Clinic for Digestive Surgery between October 2019 and October 2022 were analyzed in this cohort retrospective study. ACCI was determined according to an established point scale. Patients were further divided into two groups: group 1, ACCI <7, and group 2, ACCI ≥7.

Results: There was no statistically significant difference in the length of postoperative ICU stay (p=0.9670), semi-ICU stay (p=0.627), and hospital stay (p=0.243). Overall morbidity was higher in group 1 (60%) than in group 2 (39.3), p=0.042, while major morbidity (grade ≥3) was similar between groups, p=0.127. Biliary fistula was more common in group 1 compared to group 2 (12.5% vs 1.6%), p=0.035. In-hospital mortality, 30-day, and 90-day mortality were similar between the study groups (p=1; p=0.517 and p=0.517). During the follow-up period, recurrence was registered in 48.5% of patients. There was no difference in recurrence-free survival between groups, p=0.430. The overall survival was similar between the groups, p=0.141.

Conclusion: ACCI can be used to predict postoperative morbidity after liver resection for CRLM. The postoperative mortality and recurrence-free survival are similar regardless of age and comorbidity.

Keywords: colorectal cancer, liver metastases, Charlson comorbidity index

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INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer and the second leading cause of cancer-related death worldwide (1). In 2020, the prevalence of CRC was 1.9 million, while 0.9 million people died of this disease.

Colorectal liver metastases (CRLM) are present in about 17% of patients at the time of diagnosis of CRC (synchronous metastases) (2). An additional third of patients with CRC will develop CRLM during their disease (metachronous metastases) (3) Liver resection is currently the only potentially curative treatment option.

Comorbidities are chronic diseases affecting the patient's quality of life. The impact of comorbidities on the treatment plan and prognosis was previously confirmed. In 1987, anesthesiologist Mary Charlson introduced a new prognostic parameter – the Charlson comorbidity index (CCI) (4). The authors performed a longitudinal study, analyzing the impact of 17 most common comorbidities on one-year survival. A certain point was assigned to each disease according to the relative risk of dying from the disease under investigation, whereby a higher number of points meant a more severe degree of comorbidity. A few years later, the age-adjusted Charlson Comorbidity Index (ACCI) was introduced as a clinical predictor of the short-and long-term survival (5). The modified CCI considers age as an additional risk of postoperative complications.

Traditionally, ACCI was demonstrated as an optimal predictor of treatment outcomes of benign diseases including renal, heart, and pulmonary diseases (6-8). The prognostic impact of ACCI was also confirmed in patients with malignant conditions (9-10). Previous studies analyzed the predictive value of ACCI in terms of short- and long-term outcomes after surgery for primary cancers of the digestive system (11-12). There is a lack of literature data about the predictive value of ACCI in patients with CRLM treated by liver resection. However, patients suffering from CRLM were at an advanced age with one or more coexisting comorbidities, which may affect treatment outcomes and long-term prognosis. Furthermore, patients with CRLM are usually presented with a more advanced stage of disease at the initial diagnosis, requiring perioperative chemotherapy. Aggressive onco-surgical management combined with a high level of comorbidities may lead to a poorer prognosis.

The aim of this study was to analyze the significance of ACCI in the prediction of short- and long-term postoperative outcomes after liver resection in patients with CRLM.

MATERIAL AND METHODS

Between October 2019 and October 2022, 101 patients who had undergone liver resection for CRLM at the University Clinic for Digestive Surgery, were included in this study. Patients with extrahepatic metastatic disease were excluded. All data were collected retrospectively from medical histories, and analyzed within this cohort retrospective study. The present research was approved by the Ethics Committee of the University Clinical Center of Serbia (N° 87/13). Informed consent was obtained prior to surgical treatment.

Preoperative patient preparation included a detailed physical examination, laboratory analyses, transabdominal ultrasound, and computed tomography or magnetic resonance imaging. All patients were examined by cardiologists and anesthesiologists. Demographic and clinical-laboratory parameters included sex, age, body mass index (BMI), ASA score, localization of the primary tumor, involvement of regional lymph nodes, preoperative chemotherapy (HT), total bilirubin, aspartate aminotransferase values (AST) and alanine aminotransferase (AST), prothrombin time (PT), number of tumors and their size were recorded.

Table 1. Comorbidities included in the Charlson Comorbidity Index (CCI)

Points	Comorbidity	n (%)
1	Myocardial infarction	3 (2.9)
	CHF	
	CVA or TIA	
	Peripheral arterial disease	3 (2.9)
	Dementia	
	Chronic obstructive lung disease	
	Connective tissue disease	
	Peptic ulcer	
	Liver disease	
	Age	
2	Diabetes mellitus	2 (1.9)
	Hemiplegia	
	Leukemia	
	Lymphoma	
	Moderate to severe chronic kidney disease/ Solid tumor	4 (3.9)
3	Moderate to severe liver disease	
6	Metastatic disease	101 (100)
	AIDS	

*for every decade > 40 years, 1 point is assigned to each patient (up to 4 points)
CHF, congestive heart failure, CVA, cerebral vascular accident, TIA, transient ischemic attack, AIDS, acquired immunodeficiency syndrome

Operative details included the type and extent of resection, the duration of surgery, cumulative liver ischemia time, blood loss, and the need for intraoperative transfusion. Postoperative transfusion requirements, intensive and semi-intensive care unit stay, postoperative hospital stay, postoperative morbidity, and mortality were registered. The Clavien-Dindo classification was

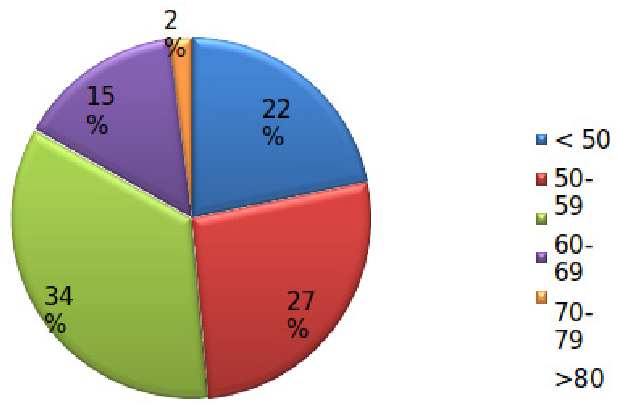

Figure 1. Age distribution

used for grading adverse events after surgery (13). Severe complications were defined as a score of 3 or more. Liver-specific complications including posthepatectomy liver failure, hemorrhage, and bile leakage were defined by the International Study Group of Liver Surgery (14-16). Mortality was defined as any death in the hospital, or within 30 and 90 days after surgery (hospital, 30-days, and 90-days mortality rate).

ACCI was calculated according to the established scale **(Table 1)**. Age distribution is presented in **Figure 1**. Based on ACCI score, the patients were divided into two groups: group 1 (ACCI <7) and group 2 (ACCI ≥7). The two groups were compared according to preoperative, intraoperative, and postoperative data.

Patients were followed up every three months for two years after surgery. Abdominal CT or MRI was performed during the visit, while thoracic CT was performed annualy. Any appearance of metastatic disease during follow-up was defined as recurrence.

STATISTICAL ANALYSIS

Continuous variables are presented using median values (range) and were compared using Student's t-test. Nominal variables are presented as percentages and they were compared using the Pearson chi-squared test or Fisher's exact test, as appropriate. Two-tailed $P < 0.05$ was considered statistically significant. All statistical analyses were performed with SPSS for Windows, version 19.0. (SPSS Inc, Chicago, IL).

RESULTS

All 101 patients who underwent liver resection for CRLM at the University Clinic for Digestive Surgery were included in this study. Patients in group 2 were older than those in group 1 (66.7 years (range, 50-84) vs 49 years (range, 33-59), respectively), (p<0.001). The number of metastases was higher in group 1 than in group 2, p=0.02. Other demographic and clinical laboratory parameters are summarized in **Table 2**.

Table 2. Demographic and clinical characteristics

	Total (n=101)	Group 1 (n=40)	Group 2 (n=61)	p
Age	60 (33-84)	49 (33-59)	66.7 (50-84)	**<0.001**
Sex, n (%)				
Male	62 (61.4)	23 (57.5)	39 (63.9)	0.516
Female	39 (38.6)	17 (42.5)	22 (36.1)	
ASA score, n (%)				
I/II	99 (98)	40 (100)	59 (96.7)	0.247
III/IV	2 (2)	0	2 (3.3)	
BMI (kg/m2)	24.5 (18.7-167.7)	24.4 (18.7-167.7)	24.8 (18.7-34.2)	0.489
Tumor localization				
Colon	52 (51.5)	20 (50)	32 (52.5)	0,809
Rectum	49 (48.5)	20 (50)	29 (47.5)	
T stadium				
T1/2	12 (11.9)	2 (5)	10 (16.4)	0.118
T3/4	89 (88.1)	38 (95)	51 (83.6)	
N stadium				
N0	22 (21.8)	6 (15)	16 (26.2)	0.181
N1	79 (78,2)	34 (85)	45 (73.8)	
Preoperative CHT, n (%)	41 (40.59)	18 (45)	23 (37.7)	0.465
Total bilirubin (mmol/L)	15 (4.2-35.4)	14.9 (4.2-35.4)	15.1 (4.9-25)	0.295
AST (IU/L)	21 (11-67)	20.5 (12-67)	22.2 (11-65)	0.574
ALT (IU/L)	22 (10-187)	24,8 (10-187)	20 (10-115)	0.158
PT (INR)	0.9 (0.8-1.2)	0.9 (0.8-1.2)	0.9 (0.8-1.1)	0.289
Tumor size (mm)	30 (7-190)	30 (12-190)	30 (7-150)	0.511
Number of tumors	2 (1-21)	2 (1-21)	2 (1-10)	**0.020**

Bolded values are statistically significant. Data are presented as median (range) unless indicated otherwise.
BMI, body mass index; PT, prothrombin time, CHT, chemotherapy, ASA score, American Society of Anesthesiologists, AST, aspartate aminotransferase, ALT, alanine transaminas

Table 3. Operative details

	Total (n=101)	Group 1 (n=40)	Group 2 (n=61)	p
Extent of resection, n (%)				
Minor	79 (78.2)	28 (70)	51 (83.6)	0.105
Major	22 (21.8)	12 (30)	10 (16.4)	
Resection type, n (%)				
Atypical resection	70 (69.3)	29 (72.5)	41 (67.2)	0.843
Segmentectomy	17 (16.8)	7 (17.5)	10 (16.4)	
Sectorectomy	7 (6.9)	2 (5)	5 (8.2)	
Hepatectomy	7 (6.9)	2 (5)	5 (8.2)	
Type of resection, n (%)				
Non-anatomical	88 (87.1)	36 (90)	52 (85.2)	0.485
Anatomical	13 (12.9)	4 (10)	9 (14.8)	
Surgery duration (min)	290 (30-780)	300 (60-780)	270 (30-650)	**0.035**
Total ischemia time (min)	45 (10-240)	49 (10-240)	45 (10-175)	0.155
Blood loss (ml)	200 (0-4000)	275 (0-2000)	200 (40-4000)	0.447
Intraoperative transfusion, n (%)	9 (8.91)	6 (15)	3 (4.91)	0.150

Bolded values are statistically significant. Data are presented as median (range) unless indicated otherwise.

The operative time was longer in group 1 (median 300 min, range 60-780) compared to group 2 (median 270 min, range 30-650), p=0.035. All other operative data are listed in **Table 3**.

Postoperative transfusion rate was higher in group 1 (27.5%) compared to group 2 (9.8%). Overall perioperative transfusion rate was higher in group 1 (32.5%) than in group 2 (13.1%). There was no statistically significant difference in the length of postoperative ICU stay (p=0.9670), semi-ICU stay (p=0.627), and hospital stay (p=0.243).

Overall morbidity was higher in group 1 (60%) than in group 2 (39.3), p=0.042. Major morbidity (grade ≥3) was similar between the groups, p=0.127. Biliary fistula was more common in group 1 compared to group 2 (12.5% vs 1.6%), p=0.035. No statistical difference was observed in the incidence of liver failure and postoperative bleeding between the two groups: 10% vs 4.9% and 20% vs 6.6 %, respectively, p=0.430 and p=0.059, respectively.

Of the 61 patients with an ACCI score >7 (group 2), one (1.6%) patient died at hospital during postoperative recovery. There was no in-hospital mortality in patients with an ACCI score ≤7. In-hospital mortality was similar between the groups (p=1). No death occurred within 30 and 90 days after surgery in group 1, while two patients died within 90 days after surgery in group 2. The difference in 30-day and 90-day mortality was not statistically significant (p=0.517 and p=0.517, respectively).

The median follow-up was 10 (range, 1-33) months. One- and 2-year survival was 96% and 77% in group 1, respectively, and 81% and 65% in group 2. The overall survival was similar between the groups, p=0.141 **(Figure 2a)**. The median time to recurrence was 7 (range, 1-33) months. During the follow-up period, recurrence was registered in 48.5% of patients. Two-year recurrence-free survival was 31% in group 1 and 28% in group 2. There was no difference in recurrence-free survival between groups, p=0.430 **(Figure 2b)**.

DISCUSSION

The prognosis of various benign and malignant diseases is affected by age and comorbidities. This fact is particularly important for public health systems because the

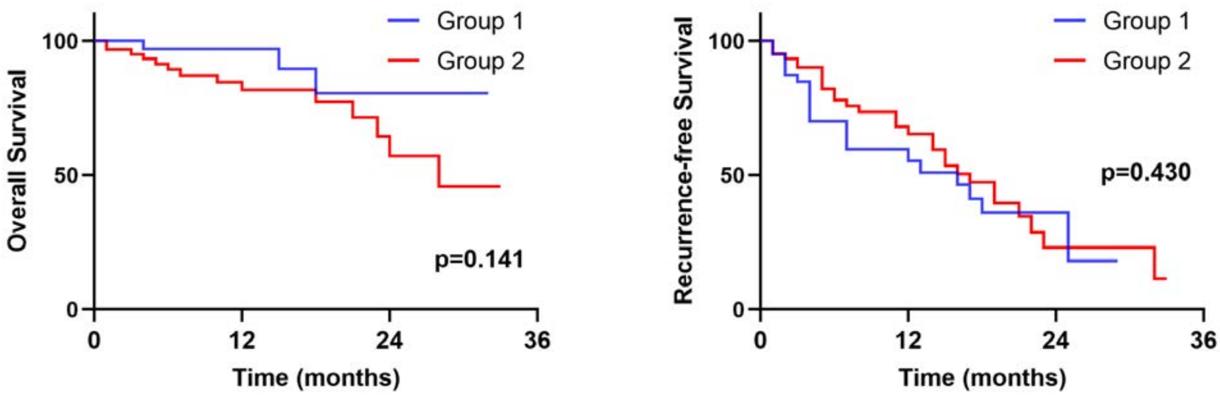

Figure 2. Overall (a) and recurrence-free survival (b)

proportion of the elderly population is gradually increasing. The present study is one of the rare reports of correlation analysis between ACCI score and postoperative outcomes in patients undergoing liver resection for metastatic disease.

Table 4. Postoperative parameters

	Total (n=101)	Group 1 (n=40)	Group 2 (n=61)	p
Postoperative transfusion, n (%)	17 (16.8)	11 (27.5)	6 (9.8)	**0.020**
Perioperative transfusion, n (%)	21 (20.8)	13 (32.5)	8 (13.1)	**0.019**
ICU stay, (days)	1 (0-11)	1 (0-3)	1 (0-11)	0.967
Semi-ICU stay, (days)	5 (2-28)	5 (3-26)	5 (2-28)	0.627
Postoperative hospitalization, (days)	7 (4-42)	8 (5-40)	7 (4-42)	0.243

Bolded values are statistically significant. Data are presented as median (range) unless indicated otherwise.
ICU, intensive care unit

The optimal cut-off value was determined using various methods in some previous studies designed to assess the association between ACCI scores and surgical outcomes after cancer treatment, including ROC curve analysis, X-tile software, or the value chosen from the literature (17-19). The threshold used in the current study was 7. Since all study participants had metastatic liver tumors, the minimal ACCI score was six in the entire cohort. Therefore, patients with additional points from comorbidity or age were classified in group 1, while those with more than one added point were classified in group 2.

Table 5. Postoperative morbidity and mortality

	Total (n=101)	Group 1 (n=40)	Group 2 (n=61)	p
Overall morbidity, n (%)	48 (47.5)	24 (60)	24 (39.3)	**0.042**
Major morbidity, n (%)	18 (17.8)	10 (25)	8 (13.1)	0.127
Liver-specific complications, n (%)				
Post-hepatectomy liver failure	7 (6.9)	4 (10)	3 (4.9)	0.430
Bile leakage	6 (5.9)	5 (12.5)	1 (1.6)	**0.035**
Postoperative bleeding	12 (12.9)	8 (20)	4 (6.6)	0.059
General complications, n (%)	10 (9.9)	4 (10)	6 (9.8)	1
In hospital mortality, n (%)	1 (1)	0 (0)	1 (1.6)	1
30-day mortality, n (%)	2 (2)	0 (0)	2 (3.3)	0.517
90-day mortality, n (%)	2 (2)	0 (0)	2 (3.3)	0.517

Bolded values are statistically significant. Data are presented as median (range) unless indicated otherwise

The present study showed that ACCI can predict postoperative overall morbidity and bile leakage. However, major morbidity and mortality were similar between the groups. Interestingly, patients with a lower ACCI score experienced higher overall morbidity and a higher percentage of bile fistula compared to those with a higher ACCI score. The result might be explained by the fact that younger patients with fewer comorbidities were selected for more extensive surgeries. Moreover, patients with lower ACCI scores had a higher number of tumor nodules in the liver, requiring more radical and more complex surgery related to a higher rate of postoperative complications. Different perioperative transfusion requirements between the groups were also the consequence of technically demanding liver resection in optimal surgical candidates.

The incidence of biliary fistula as a complication varies between 5.8 and 11% in different studies (20, 21). A study by Sadamori et al. showed that the duration of surgery ≥ 300 min is an independent risk factor for biliary fistula occurrence (22). In our study, patients who suffered from bile leakage also had prolonged operative time and were more often exposed to more complex resections where a higher percentage of bile leakage was expected.

The perioperative transfusion rate in the entire cohort was approximately 21%, while transfusion requirement was more common in patients with lower ACCI scores. According to the data of the National Surgical Quality Improvement Program of the American College of Surgeons, transfusion rates showed no statistically significant decreasing trends from 2014 to 2020 (18.13%-16.71%) (23). Prolonged operative time was associated with increased transfusion odds. Intraoperative transfusion was confirmed as an independent risk factor associated with a worse long-term prognosis (24). Furthermore, the restrictive policy of allogenic blood transfusion is recommended.

Similar major morbidity and postoperative mortality between the groups were highlights of the present study. Based on these findings, liver resection is an equally safe procedure in the elderly population weighted by comorbidity. Di Martino et al. reported similar major morbidity, liver-specific complications, and mortality among patients aged 75 and older characterized by higher ASA scores and patients younger than 75 (25). However, younger patients were presented with more intraoperative blood loss.

One- and 2-year overall survival and 2-year recurrence-free survival were similar between the groups. Despite higher overall morbidity, the two study groups showed no differences in long-term prognosis. In the study by Watanabe et al., early recurrence within 6 months after the initial hepatectomy was developed in 20.7% of patients undergoing resection for CRLM (26). In our cohort, approximately 49% of patients developed recurrence after the median follow-up of 10 months.

This study has several limitations. The strength of conclusions is decreased by the retrospective method and the relatively small sample size. A larger study is needed to improve the predictive potential of ACCI. Additionally, a relatively short follow-up period should be replaced in future by five-year follow-up data, as it is a better indicator of long-term prognosis.

CONCLUSION

ACCI can be used to predict postoperative morbidity after liver resection for CRLM. Postoperative mortality and recurrence-free survival are similar regardless of age and comorbidity.

Conflict of interest

None to declare

Autor contribution

AD, the conception or design of the work, the acquisition, preparing of the draft of the manuscript; AB, the conception or design of the work, analysis, or interpretation of data, preparing the draft of the manuscript; PZ, the acquisition, preparing of the draft of the manuscript, analysis; UD, the acquisition, preparing of the draft of the manuscript, interpretation of data; DB, the conception or design of the work, the acquisition, analysis, or interpretation of data; VD, the conception or design of the work, interpretation of data, interpretation of revised version of manuscript.

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PROGNOSTIČKI ZNAČAJ ČARLSONOVOG INDEKSA KOMORBIDITETA PRILAGOĐENOG STAROSTI U PREDVIĐANJU POSTOPERATIVNOG ISHODA NAKON RESEKCIJE JETRE USLED METASTAZA KOLOREKTALNOG KARCINOMA

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Sažetak

Uvod: Prognostički značaj Čarlsonovog indeksa komorbiditeta (ČIK) prilagođenog starosti za bolesnike sa metastazama kolorektalnog karcinoma koji su podvrgnuti resekciji jetre je još uvek nerazjašnjen. Cilj ove studije je da analizira uticaj ovog indeksa u predviđanju kratkoročnog i dugoročnog ishoda nakon resekcije jetre kod bolesnika sa metastazama kolorektalnog karcinoma u jetri.

Materijal i metode: U kohortnu retrospektivnu studiju je uključen 101 bolesnik koji je podvrgnut resekciji jetre zbog metastaza kolorektalnog karcinoma, na Klinici za digestivnu hirurgiju u periodu od oktobra 2019. do oktobra 2022. godine. ČIK prilagođen starosti je određen prema bodovnoj skali. Bolesnici su prema broju bodova podeljeni u dve grupe: grupa 1 (ČIK <7), i grupa 2 (ČIK ≥7).

Rezultati: Ne postoji statistički značajna razlika u vremenu provedenom u jedinici intenzivnog lečenja (p=0,9670), jedinici poluintenzivnog lečenja (p=0,627) i vremenu provedenom u bolnici (p=0,243) nakon operacije. Ukupni morbiditet je veći u grupi 1 (60%) u odnosu na grupu 2 (39,3), p=0,042, dok su teške komplikacije (stepen ≥3) bile slične učestalosti kod upoređenih grupa p=0,127. Bilijarna fistula je češća u grupi 1 u poredjenju sa grupom 2 (12,5% vs 1,6%), p=0,035. Mortalitet u bolnici, tridesetodnevni i devedesetodnevni mortaliteti su slični (p=1; p=0,517 and p=0,517). Tokom perioda praćenja, recidiv bolesti je utvrđen kod 48,5% bolesnika. Nema značajne razlike u periodu bez recidiva bolesti, p=0,430. Ukupno preživljavanje je slično između grupa, p=0,141.

Zaključak: ČIK prilagođen starosti se može koristiti kao prediktor postoperativnog morbiditeta nakon resekcije jetre zbog metastaza kolorektalnog karcinoma. Postoperativni mortalitet i period bez recidiva bolesti su slični bez obzira na starost i komorbiditete.

Ključne reči: kolorektalni karcinom, metastaze u jetri, Čarlsonov indeks komorbiditeta

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