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ORIGINAL RESEARCH

Short- and Long-Term Outcomes After Hepatectomy in Elderly Patients with Hepatocellular Carcinoma: An Analysis of 229 Cases from a Developing Country

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Background: The number of elderly patients with HCC who undergo liver resection is increasing. Because of the advanced age of the patients, increased postoperative morbidity and reduced overall survival are expected in this population. The study aim was to compare clinicopathologic and operative features, short- and long-term outcomes among hepatocellular carcinoma (HCC) patients from three age groups undergoing potentially curative liver resection in a developing country.

Methods: Prospectively collected data relating to 229 patients who underwent curative-intent liver resection from January 2009 until December 2018 were analyzed. The patients were divided into two age groups: G1 was below 70 years old (n=151) and G2 was 70 years old and older (n=78). Demographic, clinical, operative data, short- and long-term outcomes were compared between the two groups. Univariate and multivariate analyses of prognostic factors were performed.

Results: The mean overall morbidity rate of the patients was 31.1% (G1), and 46.2% (G2) by age group. Postoperative morbidity was significantly higher in the G2 group (p=0.03). There was no difference in major morbidity between the two groups (p=0.214). No significant difference in mortality rate and overall survival was found between the study groups (p=0.280, p=0.383). Both age ≥70 years (ie, G2 group) and liver cirrhosis were identified as prognostic factors for postoperative morbidity, and a Child-Pugh score B as a negative prognostic factor for overall survival. In subgroup analysis of patients with cirrhosis, age ≥70, diabetes mellitus and perioperative transfusion were identified as prognostic factors for postoperative morbidity.

Conclusion: The study confirmed the safety and feasibility of liver resection in elderly patients with HCC. However, appropriate patient selection among the elderly is mandatory in order to improve short- and long-term outcomes.

Keywords: hepatocellular carcinoma, elderly, hepatectomy

Introduction

A significant increase in life expectancy and the enhancement of medical knowledge and surgical techniques have led to extended indications for liver surgery for the elderly. This is notably evident in Japan, which has the most aging society worldwide. However, there is a similar situation in other civilized countries.[1] In Europe in 2011 the mean life expectancy exceeded 80 years; in the US, people older than 65 constitute 13% of the population.[2,3]

Hepatocellular carcinoma (HCC) is the fourth most common cancer and the third cause of cancer-related death worldwide and its incidence is still increasing.[4]

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The majority of HCCs develop in the frame of chronic liver disease and inflammation.[5] In elderly patients, age is the strongest risk factor for hepatocarcinogenesis, regardless of the stage of fibrosis.[6] In western countries, the leading risk factors for HCC development are chronic hepatitis C virus (HCV) infection, alcohol and metabolic syndrome, including obesity, diabetes and non-alcoholic steatohepatitis (NASH).[7] Contrarily, the majority of HCC cases in Eastern Asia are associated with chronic hepatitis B virus (HBV) infection.[8,9] The assessment of tumor burden, liver function and general health status that is often compromised in the elderly has crucial significance for selecting the best treatment modality for individual patients with HCC.[10] Hepatectomy, as a curative-intent procedure, is one of the most effective treatment modalities for HCC. The indications for HCC resection in elderly patients are increasing and this is a forthcoming problem for countries with a growing number of patients with viral hepatitis and metabolic syndrome.[11]

Despite recent studies showing that liver resection is feasible in elderly patients, it is expected to be designated a higher risk of compromised outcomes because of an age-associated deterioration of liver function and higher perioperative morbidity due to a higher incidence of co-morbidities.[12–15] Therefore, age should be considered an adverse factor for liver resection.[16]

Moreover, strict criteria for the selection of particular hepatectomy procedures in elderly patients are not yet established. In published literature, both mortality and morbidity associated with hepatectomy for HCC in elderly patients varied because of an inconsistent definition of "elderly".[17,18] In the presented study the cut-off value for elderly (≥70 years) was defined according to the recent national demographic trends, prolongation of the retirement age and increase in life expectancy evidenced in the last decade.[19,20]

There are limited data from developing countries about the outcomes of liver resection in elderly patients. This is important due to disparate quality of healthcare considering screening and surveillance programs; available treatment modalities and drugs; reimbursement policies of the state-funded health insurance. Moreover, higher rate of HCC occurring in non-cirrhotic livers is found in developing countries.[21] The majority of studies evaluating the outcomes of liver resection in elderly originate from Asia with hepatitis B as the prevailing etiology of the background liver disease (with an exception of Japan where hepatitis C is the leading etiology). According to the recent systematic review involving more than 17,000 patients, studies from the western world are scarce (1 from America, 6 from Italy, 1 from Spain and 2 from Germany).[22] However, data from developing countries are not reported in the literature.

The aim of the study was to compare clinicopathologic and operative features, and short- and long-term outcomes among HCC patients from the two age groups (<70 and ≥70 years) undergoing potentially curative liver resection in a developing country.

Methods

Study Population

Between January 2009 and December 2018, 1203 hepatectomies were performed for different benign and malignant tumors. The study population included all patients with HCC managed by curative-intent hepatectomy at the HPB unit of University Clinic for Digestive surgery, Clinical Center of Serbia, Belgrade. Data from the electronic, prospectively maintained database were retrospectively analyzed. Patients with prior transarterial chemoembolization (TACE), preoperative or concomitant radiofrequency ablation (RFA) and initial hepatectomy performed at another institution were excluded from the study (Figure 1). Thirteen patients underwent liver re-resection for recurrent HCC but data related to repeat hepatectomy were not included in the current analysis. All patients included in the study provided their written informed consent before the proposed type of treatment. The institutional review board, Ethics Committee of the Clinical Center of Serbia, approved the study protocol. The study was conducted in accordance with the Declaration of Helsinki.

Preoperative Assessment

Preoperative investigation included transabdominal ultrasound, chest radiography, computed tomography (CT) and/or magnetic resonance (MR). Diagnosis of HCC was established according to EASL clinical practice guidelines and was confirmed by histopathology of resected specimen.[23]

The following patient demographics and clinicopathologic characteristics were prospectively recorded: age, sex, alcohol intake, previously known inherited liver disorders and autoimmune liver diseases, comorbidities. In all patients, total blood count, biochemistry, coagulative status, α-fetoprotein (AFP) and hepatitis viral (B and C) serology were done as part of routine laboratory

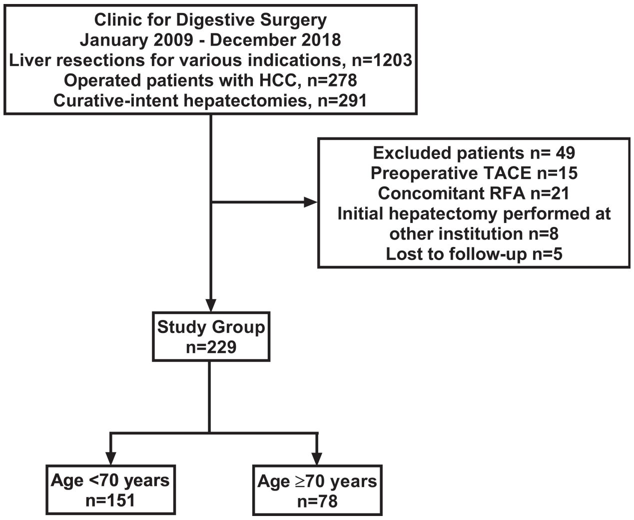


Figure 1 Study flowchart.

evaluation. Child-Pugh score was calculated to assess the functional liver capacity. The comorbidities were stratified according to American Society of Anesthesiologists and in all patients, ASA score was determined.

The presence of hepatic fibrosis/cirrhosis was retrieved from the histopathology report. In order to evaluate and compare comorbid conditions between the groups the Charlson Comorbidity Index (CCI) was calculated for all patients. The patients were divided into three groups based on their age: below 70 years old (group G1); 70 years old and older (group G2). Demographic, clinical, operative data, short- and long-term outcomes were compared between the study groups.

Surgical Technique

All patients were operated using the radiofrequency-assisted sequential "coagulate-cut" liver resection technique described in earlier publications.[24,25] Vascular occlusion techniques and low central venous pressure anesthesia were not used routinely. Terminology of liver anatomy and resections was determined according to the guidelines of the Brisbane 2000 Terminology of the International Hepato-Pancreato-Biliary Association.[26] Atypical resections were determined as non-anatomic. Major hepatectomy was defined as the removal of three and more liver segments.

Postoperative complications were assessed according to the Clavien–Dindo grading system and liver-specific complications were classified according to the definitions of the International study group of liver surgery.[27–30] Major morbidity was defined as any complication of grade 3 or more. Liver-specific complications included post-hepatectomy liver failure, bile leakage and hemorrhage. Perioperative mortality was defined as any death occurring within 30 days of surgery.

Patient Follow-Up

All patients underwent regular evaluations at the outpatient clinic. Routine laboratory test, α-feto protein measurement and transabdominal ultrasonography were performed every three months. An abdominal CT/MR was performed every six months. After the three-year follow-up patients were screened twice yearly and, after the 5th year, annually. Patients with the evidence of a recurrent disease limited to the remnant liver were managed by liver re-resection, RF ablation or transarterial chemoembolization. Long-term survival analysis included patients who died within 30 days of surgery, as well.

Statistical Analysis

Continuous variables are expressed as median (range) and were compared using Student's *t* test. Categorical variables are expressed as absolute numbers (percentages) and were compared between the groups using the chi-square test or Fisher's exact test as appropriate. Overall survival was estimated using the Kaplan–Meier method and compared using the Log-rank test. To identify potential prognostic factors of postoperative morbidity and long-term survival, univariate analysis was carried out using Fisher's exact test and the Log-rank test. Multivariate analysis of independent prognostic factors was carried out for all factors with $p \leq 0.05$ estimated in univariate analysis of postoperative morbidity and with $p \leq 0.1$ for overall survival. Prognostic factors associated with morbidity were assessed by logistic regression model and factors associated with overall survival were assessed by Cox regression model. Statistical analysis was performed using SPSS version 23.0 (SPSS Inc., Chicago, IL, USA). P value ≤ 0.05 was considered statistically significant.

Results

Study Population

During the study period, 278 patients with HCC underwent 291 curative-intent hepatectomies. (Figure 1) The following patients were excluded from the analysis: 15 patients were managed by prior transarterial chemoembolization, 21 with preoperative or concomitant RF ablation, and eight had initial hepatectomy at another institution. Five patients were lost to follow-up. Finally, 229 patients with HCC were included in the analysis. Of those, 151 patients (65.9%) were in G1, 78 patients (34.1%) were in

G2. In G2, seven patients were >80 years and none was >90 years old. Liver cirrhosis was present in the majority of study patients: 59.6%, and 50% of patients in G1 and G2, respectively. Chronic hepatitis C viral infection was a dominant cause of liver cirrhosis in all study groups without statistical difference between them. The majority of patients had preserved liver function (Child-Pugh score A): 91.1% and 92.3%, respectively. There was no statistical difference between the study groups regarding their ASA score. Charlson Comorbidity Index was statistically different (p<0.001) between the groups, with the median values 6 and 8 in G1 and G2, respectively. Among different comorbid conditions, no statistically significant difference was found between the study groups. Demographic and clinicopathological data are summarized in Table 1.

In regard to laboratory analysis (bilirubin and ALT values are presented only), tumor size and tumor numbers and lobar distribution of tumors there was no statistically significant difference between the study groups.

Surgical Procedures

In the majority of study patients, anatomic liver resection was performed (60.9% and 60.3% of patients in G1 and G2, respectively) without statistically significant difference between the groups. No difference was found for the extent of hepatectomies and the majority of patients received minor liver resection. Operative data are shown in detail in Table 2.

Postoperative Morbidity

The mean overall morbidity rate of the 229 patients was 31.1% (G1) and 46.2% (G2) by age group. Postoperative morbidity was significantly higher in G2 group (p=0.03). There was no difference in major morbidity between the two groups (p=0.214). Infected perihepatic collection occurred more frequently in G2 group (p=0.028) (Table 3).

Operative Death and Overall Survival

Eight (3.5%) patients died during their hospital stay and nine within 30 days of surgery. The thirty-day mortality rate in G1 and G2 was 2.6% (four patients) and 6.4% (five patients), respectively, without significant difference (p=0.28). The causes of death were the following: G1 (posthepatectomy liver failure in three patients and sepsis in one patient) and G2 (posthepatectomy liver failure in two patients, sepsis in one patient, and pulmonary embolism in two patients). Short-term results are summarized in Table 3.

The median survival was 49 and 28 months in G1 and G2, respectively. There was no difference in overall survival between the three groups (p=0.383) (Figure 2).

Analysis of Prognostic Factors

By univariate analysis, the following factors were identified as potential prognostic factors for postoperative morbidity: age ≥70, HCV infection, liver cirrhosis, other comorbidities, major resection, operative time ≥240min and perioperative transfusion. In regard to survival, only the Child-Pugh score was identified as potential prognostic factor according to univariate analysis (Table 4).

In subgroup analysis of patients with cirrhosis, the following factors were identified as potential prognostic factors for postoperative morbidity: age ≥70, diabetes mellitus and perioperative transfusion. Univariate analysis showed that, in regard to survival, only the Child-Pugh score was identified as potential prognostic factor (Table 4).

Age ≥70 (p=0.013, odds ratio (OR)=2.178, 95% CI: 1.176–4.033) and liver cirrhosis (p=0.007, OR=3.861, 95% CI: 1.456–10.239) were independent prognostic factors for postoperative morbidity. Child-Pugh score B (p=0.023, Hazard ratio (HR)=2.259, 95% CI: 1.119–4.560) was an independent negative prognostic factor for overall survival (Table 5).

In subgroup of patients with cirrhosis, diabetes mellitus (p=0.054, odds ratio (OR)=0.423, 95% CI: 0.177–1.015) and perioperative transfusion (p=0.024, odds ratio (OR) =6.272, 95% CI: 1.275–30.853) were independent prognostic factors for postoperative morbidity. No particular prognostic factor has been identified for overall survival (Table 5).

Discussion

The study aim was to compare short- and long-term outcomes among HCC patients from the two age groups (<70 and ≥70 years) who underwent curative-intent liver resection. The study results indicate no significant difference in the 30-day mortality rate between the two age groups and no difference in overall survival between them. The presented study identified both age ≥70 and liver cirrhosis as independent negative prognostic factors for postoperative morbidity, and Child-Pugh score B as a negative prognostic factor for overall survival.

In recent years the number of elderly patients rendered for liver resection has increased substantially as numerous studies confirmed the safety and feasibility of liver surgery

Table 1 Demographic and Clinico-Pathological Data

	All Patients n=229	Age <70 Years n=151 (65.9%)	Age ≥70 Years n=78 (34.1%)	*p* value
Age (years)	66 (36–83)	62 (36–69)	74 (70–83)	<0.001
Sex, n (%)				
Male	135 (59)	85 (56.3)	50 (64.1)	0.262
Female	94 (41)	66 (43.7)	28 (35.9)	
Background liver disease, n (%)				
HBV	61 (26.6)	39 (25.8)	22 (28.2)	0.753
HCV	88 (38.4)	61 (40.4)	27 (34.6)	0.474
ARLD	14 (6.1)	9 (6.0)	5 (6.4)	1.000
NAFLD	23 (10.0)	17 (11.3)	6 (7.7)	0.490
Metabolic disorders	10 (4.4)	6 (4.0)	4 (5.1)	0.738
Undetermined	35 (15.3)	20 (13.2)	15 (19.2)	0.249
Cirrhosis, n (%)				
Yes	129 (56.3)	90 (59.6)	39 (50)	0.206
No	100 (43.7)	61 (40.4)	39 (50)	
Child-Pugh score, n (%)				
A	118 (91.5)	82 (91.1)	36 (92.3)	1.000
B	11 (8.5)	8 (8.9)	3 (7.7)	
A5	103 (79.8)	73 (81.1)	30 (76.9)	0.850
A6	15 (11.6)	9 (10.0)	6 (15.4)	
B7	7 (5.4)	5 (5.6)	2 (5.1)	
B8	4 (3.1)	3 (3.3)	1 (2.6)	
BCLC stage, n (%)				
O	14 (10.9)	11 (12.2)	3 (7.7)	0.379
A	99 (76.7)	70 (77.8)	29 (74.7)	
B	16 (12.4)	9 (10.0)	7 (17.9)	
ASA, n (%)				
I/II	95 (41.5)	68 (45.0)	27 (34.6)	0.157
III/IV	134 (58.5)	83 (55.0)	51 (65.4)	
Charlson comorbidity index	7 (2–13)	6 (2–10)	8 (5–13)	<0.001
Comorbidities, n (%)	209 (91.3)	139 (92.1)	70 (89.7)	0.623
Cardiovascular	144 (62.9)	90 (59.6)	54 (69.2)	0.194
Respiratory	21 (9.2)	12 (7.9)	9 (11.5)	0.469
Diabetes mellitus	55 (24)	34 (22.5)	21 (26.9)	0.515
Other	161 (70.3)	111 (73.5)	50 (64.1)	0.170
Total bilirubin (mmol/L)	14 (3.7–636)	13.7 (3.7–49.4)	14.2 (4.1–636)	0.250
ALT (IU/L)	38 (8–220)	37 (8–220)	42.5 (11–166)	0.627
Lesion number, n (%)				
Solitary	186 (81.2)	123 (81.5)	63 (80.8)	1.000
Multiple	43 (18.8)	28 (18.5)	15 (19.2)	
Major lesion size (mm)	50 (14–300)	50 (14–250)	57.5 (15–300)	0.196
Lobar distribution, n (%)				
Unilobar	199 (86.9)	132 (87.4)	67 (86.9)	0.837
Bilobar	30 (13.1)	19 (12.6)	11 (14.1)	

Note: Values are presented as median (range) unless indicated otherwise.

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; ARLD, alcohol-related liver disease; NAFLD, nonalcoholic fatty liver disease; ASA, American Society of Anesthesiologists; ALT, alanine transaminase; BCLC, Barcelona Clinic Liver Cancer.

Table 2 Operative Data

	All Patients n=229	Age <70 Years n=151	Age ≥70 Years n=78	*p* value
Type of resection, n (%)				
Anatomic	139 (60.7)	92 (60.9)	47 (60.3)	1.000
Nonanatomic	90 (39.3)	59 (39.1)	31 (39.7)	
Extent of resection, n (%)				
Minor	201 (87.8)	135 (89.4)	66 (84.6)	0.296
Major	28 (12.2)	16 (10.6)	12 (15.4)	
Operative time (min)	190 (55–480)	190 (55–480)	210 (65–420)	0.246
Transection time (min)	50 (10–230)	50 (15–210)	50 (10–230)	0.822

Note: Values are presented as median (range) unless indicated otherwise.

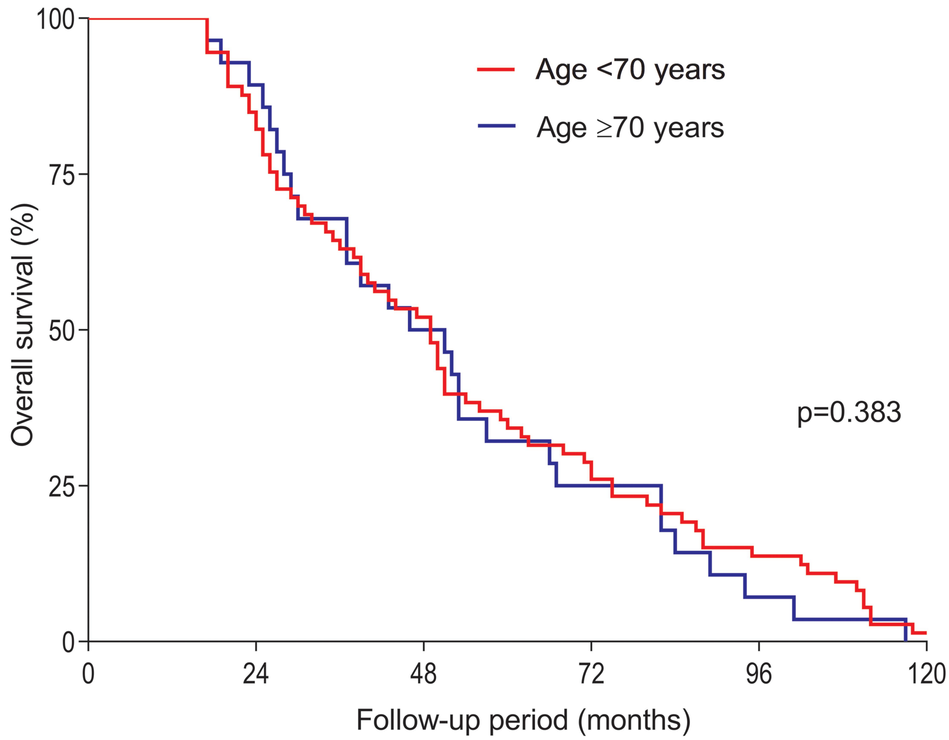
Table 3 Postoperative Outcome

	All Patients n=229	Age <70 Years n=151	Age ≥70 Years n=78	*p* value
Overall morbidity	83 (36.2)	47 (31.1)	36 (46.2)	0.030
Major morbidity	19 (8.3)	10 (6.6)	9 (11.5)	0.214
Liver related complications				
Liver insufficiency	48 (21)	29 (19.2)	19 (24.4)	0.394
Biliary leakage	11 (4.8)	7 (4.6)	4 (5.1)	1.000
Hemorrhage	8 (3.5)	4 (2.6)	4 (5.1)	0.449
Non-infected perihepatic collection	8 (3.5)	4 (2.6)	4 (5.1)	0.449
Infected perihepatic collection	21 (9.2)	9 (6.0)	12 (15.4)	0.028
General complications				
Cardiopulmonary	38 (16.6)	21 (13.9)	17 (21.8)	0.137
Renal failure	19 (8.3)	11 (7.3)	8 (10.3)	0.456
Perioperative transfusion rate	21 (9.2)	11 (7.3)	10 (12.8)	0.226
In-hospital mortality	8 (3.5)	3 (2.0)	5 (6.4)	0.125
30-day mortality	9 (3.9)	4 (2.6)	5 (6.4)	0.280
Postoperative hospital stay (days), median (range)	9 (2–55)	8 (2–52)	10 (3–55)	0.161

Note: Values are presented as absolute number (percentage) unless indicated otherwise.

in this patient population.[31–33] From the oncological standpoint, elderly people may benefit equally as well as younger patients from hepatectomies indicated for the treatment of HCC.[34,35] However, an increased perioperative risk – because of a higher rate of respiratory complications and aggravation of pre-existing comorbidities – explains the reluctance for upfront liver resection in aged patients. Numerous studies have reported that advanced age is associated with a higher prevalence of pre-existing comorbidities.[13,36,37] Moreover, the prognosis of HCC is still poor as it is compromised by the coexistence of chronic liver disease and malignancy, both potentially life-threatening conditions. There is currently an unmet need to identify age-specific risk factors for compromised perioperative outcome in order to select the elderly HCC patients who may benefit the most from liver resection.

Menon and co-workers have found a higher prevalence of ASA score >2 and CCI >2 among elderly patients being associated with an increased perioperative morbidity and reduced survival.[38] Similar findings were reported by Schiergens and co-workers.[17] Fong and co-workers have linked poor outcome of liver surgery in the elderly with a high ASA score.[39] However, Ijtsma and co-workers have shown that the ASA score is not a suitable indicator for predicting postoperative complications.[33] The same finding was evidenced by Andert and co-workers.[40] In the presented study, there was no difference in ASA score between the study groups; nor was a high ASA score



	0	12	24	36	48	60	72	84	96	108	120
Age <70 years	151	121	92	65	51	31	23	16	11	6	0
Age ≥70 years	78	56	40	29	19	16	11	7	3	3	1

Figure 2 Overall survival of the two age cohorts.

identified as a negative prognostic factor. Patients older than 70 had significantly higher CCI. However, CCI had no prognostic value in the presented study. Diabetes mellitus was the only comorbid condition found to have higher incidence in patients aged ≥70 compared to other study groups.

In the presented study nine patients died within thirty days of surgery: four patients in G1 (posthepatectomy liver failure in three patients and sepsis in one patient) and five patients in G2 (posthepatectomy liver failure in two patients, sepsis in one patient and pulmonary embolism in two patients) without significant difference between the groups (p=0.280).

The most common reported causes of operative death in elderly patients are hepatic failure, acute coronary syndrome, respiratory failure, and gastrointestinal bleeding.[38,41,42] Schiergens and co-workers reported the following causes of 30-day mortality: acute coronary syndrome in 55% of elderly patients, primary hepatic failure in 19% and primary respiratory failure in 10%, and they found a higher mortality rate in elderly patients compared to younger patients.[17] Andert and co-workers reported higher postoperative mortality in elderly patients due to a higher incidence of pneumonia but without statistical significance.[40] In the available literature, a large variation in mortality rates, ranging from below 5% to more than 40%, can be found.[43–48]

The overall morbidity rate in the presented study was 36.2%. The overall morbidity was significantly higher in patients aged ≥70 years compared to other study groups (p=0.030). However, there was no difference in major morbidity between the two groups (p=0.214). Among liver-specific complications, only infected perihepatic collection occurred more frequently in G2 group (p=0.028). In the available literature, the overall complication rates

Table 4 Univariate Analysis for Postoperative Morbidity and Overall Survival

	All Patients n=229		Patients with Cirrhosis n=129	
	Morbidity (*p* value)	**Survival (*p* value)**	**Morbidity (*p* value)**	**Survival (*p* value)**
Age ≥70	0.018	0.383	0.034	0.482
Sex	0.549	0.488	0.476	0.687
HBV	0.331	0.240	0.575	0.307
HCV	0.008	0.992	0.217	0.992
Cirrhosis	<0.001	0.943	NA	NA
Child-Pugh score	0.403	0.021	0.754	0.021
ASA >2	0.296	0.351	0.587	0.910
Charlson comorbidity index >2	0.065	0.359	NA	NA
Comorbidities	0.087	0.145	NA	NA
Cardiovascular	0.065	0.158	0.073	0.500
Respiratory	0.514	0.734	1.000	0.714
Diabetes mellitus	0.204	0.507	0.024	0.298
Other	0.015	0.524	1.000	0.647
Major lesion size ≥50mm	0.141	0.323	0.258	0.492
Anatomic resection	0.298	0.915	0.484	0.828
Major resection	0.036	0.582	0.187	0.526
Operative time ≥240min	0.024	0.472	0.193	0.787
Perioperative transfusion	0.034	0.438	0.012	0.378
Overall morbidity	NA	0.061	NA	0.237
Major morbidity	NA	0.734	NA	0.975

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; NA, not applicable; ASA, American Society of Anesthesiologists

range from 30% to 50%.[33,38,39,48] In the study by Schiergens and co-workers, an overall complication rate was 44% and elderly patients were at higher risk for non-surgical but not for surgical complications.[17] The same finding is reported by Shirabe and co-workers and Duron and co-workers.[45,49] In the study by Santambrogio and co-workers older patients had more complications in Clavien class II or higher.[48] It is stipulated that comorbidities may increase the risk for non-surgical complications, whereas surgical morbidity occurs because of age-independent factors. Although no significant difference in general complications (cardiopulmonary and renal) was found between the two study groups, better outcome in younger patients is expected because of higher perioperative compensatory capacities. This again emphasizes the importance of a thorough preoperative cardiac and pulmonary assessment in elderly patients.

In the presented study all patients were operated on using the radiofrequency-assisted (RF) liver resection technique (presented in detail in earlier publications), which has the advantage of minimal blood loss and no need for any vascular occlusion procedure prior to the liver transection.[24,25,49–51] There was no difference in the perioperative transfusion rate between the study groups (p=0.226) and the overall transfusion rate was 9.2%. Perioperative transfusion was not identified as a negative prognostic factor when all patients were analyzed. However, in the subgroup analysis of patients with cirrhosis perioperative transfusion was identified as negative prognostic factor for postoperative morbidity. Minimizing blood loss is particularly important in elderly patients because of reduced cardiopulmonary compensatory mechanisms.[45] It is reported that blood loss affects early and late outcomes in elderly patients who underwent liver

Table 5 Multivariate Analysis for Postoperative Morbidity and Overall Survival

	All Patients n=229			Patients with Cirrhosis n=129		
	Postoperative Morbidity					
	Odds Ratio	CI 95%	*p* value	Odds Ratio	CI 95%	*p* value
Age ≥70	2.178	1.176–4.033	0.013	2.133	0.952–4.777	0.066
HCV	1.275	0.670–2.427	0.459			
Cirrhosis	3.861	1.456–10.239	0.007			
Other comorbidity	0.933	0.344–2.531	0.892			
Diabetes mellitus				0.423	0.177–1.015	0.054
Major resection	2.086	0.785–5.543	0.140			
Operative time ≥240min	1.836	0.885–3.807	0.103			
Perioperative transfusion	1.661	0.594–4.641	0.333	6.272	1.275–30.853	0.024
	Overall Survival					
	Hazard Ratio	CI 95%	*p* value			
Child-Pugh score B	2.259	1.119–4.560	0.023			
Overall morbidity	1.327	0.841–2.095	0.224			

Abbreviation: HCV, hepatitis C virus.

resection and it is identified as an independent risk factor for both morbidity and reduced survival.[17,45,48,49]

In the presented study, age ≥70 years and liver cirrhosis were identified as independent prognostic factors for postoperative morbidity, and a Child-Pugh score B was identified as a negative prognostic factor for overall survival. It is important to highlight that the study cohorts included a high proportion of patients with HCC developing in non-cirrhotic livers (40.4% and 50% in G1 and G2, respectively), which is distinctive for developing countries.

In the subgroup analysis of patients with cirrhosis diabetes mellitus and perioperative transfusion were identified as independent prognostic factors for postoperative morbidity emphasizing again that minimizing blood loss during hepatectomy has a critical impact on the postoperative outcome of patients with cirrhosis.

In the study by Okinaga and co-workers male gender, being aged over 70 years, lower hospital volume (<23 cases/year), preoperative comorbidities ≥2, and the type of surgery were significantly associated with higher in-hospital mortality within 90 days.[52] Another study highlighted that age >70 years, pre-existing comorbidities, major liver resection, increased blood loss, and postoperative complications were independent risk factors for reduced overall survival while comorbidities and major blood loss were independent predictors of postoperative morbidity.[17]

Unlike studies from Asia comprising HCC patients with prevailing hepatitis B in the background liver disease or studies from the western world with HCC patients having HCV-related liver cirrhosis mostly, the presented study is comprised of HCC patients who had various etiology factors in the background liver disease and high proportion of non-cirrhotic patients. The presented results are important for more comprehensive understanding of the outcomes of hepatectomy in elderly worldwide. Moreover, this study confirmed that major liver resection is feasible in elderly with preserved liver function and sufficient liver volume as 15.4% of patients older than 70 years had major hepatectomy.

This study has several limitations. One is the retrospective methodology that may be associated with selection bias, and the other is a long study period that may result in a heterogeneous management. However, all data that were analyzed were collected prospectively and the same operative technique was used in all patients.

In conclusion, the presented study confirmed the safety and feasibility of liver resection in elderly patients with HCC, because no significant difference in mortality rate and overall survival was found between the study groups. Age ≥70 years and liver cirrhosis were both identified as prognostic factors for postoperative morbidity, and a Child-Pugh score B as a negative prognostic factor for overall survival. In patients with cirrhosis diabetes mellitus and perioperative transfusion were identified as prognostic factors for postoperative morbidity. A patient's advanced age should not be considered an exclusive contraindication for liver resection; appropriate patient selection among the elderly is mandatory in order to improve short- and long-term outcomes.

Disclosure

The authors declare no conflicts of interest in this work.

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