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Analysis of Predictive Factors for Morbidity after Hepatectomy in Elderly Patients

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Abstract

Background: It is controversial whether hepatectomy is safe for the elderly, particularly the extreme elderly (older than 80 years). In this study, we analyzed risk factors for morbidity and the prognosis of elderly hepatectomy patients.

Methods: We retrospectively reviewed 81 patients of advanced age (>75 years) who had undergone hepatectomy for malignant tumors at our institution between 2010 and 2017. We evaluated morbidity according to Clavien-Dindo classification (greater than IIIa) and prognosis. Factors were compared between patients aged 75 to 79 years (Group I) and patients over 80 years (Group II).

Results: Thirty-nine patients (48%) were classified in Group II. Compared to Group I, Group II had higher female cases, transfusion during surgery, and discharge outcome (transferred to another hospital, rather than released) and a lower nutritional score. Meanwhile, there were no significant differences with performance status, number of comorbidities, surgical procedure, blood loss, operating time, hospitalization period, or frequency of delirium. The complications of those with grade IIIa or higher were significantly increased in Group II. Age, surgical procedure, liver function, respiratory function, operating time, and blood loss were risk factors for morbidities in the univariate analysis. Age was the strongest risk factor in the multivariate analysis (odds ratio, 10.4; 95% confidence interval, 1.44-74.7; P=0.020). However, no significant correlation between overall survival and age was found.

Conclusion: Age affected the morbidity of hepatectomy, but the prognosis was similar between extreme elderly patients and relatively elderly patients. Under appropriate perioperative care, hepatectomy can be safely performed in elderly patients.

Keywords: Hepatectomy; Elderly patients; Morbidity; Prognosis

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Introduction

For hepatic malignancies, surgical resection is the most effective procedure for curing patients [1-3]. Hepatocellular Carcinoma (HCC) is the sixth most common cancer worldwide [1], and Intrahepatic Cholangiocarcinoma (ICC) is the second most common hepatic malignancy [2,4]. Gallbladder Cancer (GBC) is the fifth most common neoplasm of the gastrointestinal tract and the most common cancer of the biliary tract [3,5]. Furthermore, approximately 50% to 60% of Colorectal Cancer (CRC) patients are diagnosed with metastases including liver [6]. Hepatectomy still remains the best treatment of choice for HCC, ICC, GBC and CRC metastases.

Given the rapid growth of the elderly population worldwide, the need for hepatectomy due to hepatic malignancy is increasing for patients in advanced age [7]. Indeed, the proportion of HCC in elderly patients tends to increase due to the rising incidence of cirrhosis related to hepatitis B or C virus, alcoholic hepatitis, and non-alcoholic steatohepatitis among other causes [7,8]. It is reported that advanced age is associated with shorter OS in ICC [3,4], and GBC was an aggressive malignancy with poor outcome, especially in elderly patients. Moreover, elderly patients tend to have more comorbidities, lower ECOG performance status [9,10], and less residual respiratory, hepatic, and renal function [11], conflicting findings exist. Some groups have found hepatectomy to be almost as safe in elderly patients as their younger counterparts [12,13]; however, other groups found that increasing age was associated with higher risk of in-hospital mortality [14]. In HCC patients, hepatectomy can be performed safely, and the short- and long-term outcomes following the procedure in the elderly were similar to those in younger patients [15]. However, another group reported that pre-existing comorbidities, major liver resection, increased perioperative blood loss, and postoperative complications were independent risk factors for reduced OS of elderly patients [11]. Therefore, some researchers recommend limiting extended or complicated liver resections for elderly patients to reduce postoperative complications [16]. Thus, the incidence of morbidities and the prognosis for elderly patients undergoing hepatectomy are controversial.

To further complicate matters, the number of patients aged 80 years or older, termed the "extreme elderly", is increasing, but few studies have reported the safety and prognosis following a hepatectomy in this age group. Therefore, it is questionable whether age is a prognostic factor. To solve this problem, we defined 75-79-year-old hepatectomy patients as the control group. In this study, we aimed to investigate the clinicopathological characteristics, morbidity, mortality, and prognosis of elderly hepatectomy patients aged 75 years or older.

Materials and Methods

Patients and data acquisition

In our institution between September 2010 and October 2017, we registered a total of 81 elderly patients (aged >75 years) who underwent hepatectomy for malignant tumors, such as HCC, ICC, GBC, and Metastatic Tumor (Met), for this study. Clinicopathological and perioperative data were retrospectively collected from patients' medical records. Preoperative variables were assessed including age, sex, diagnosis (HCC, ICC, GBC, or Met), ECOG Performance Status (PS), American Society of Anesthesiologist (ASA) class, body mass index, Total Lymphocyte Count (TLC), hemoglobin, platelets, total protein, Albumin (ALB), activated partial thrombin time, prothrombin time, cholinesterase, total cholesterol, C-reactive protein, value of Indocyanine Green (ICG) test, 99mTc-Galactosyl Serum Albumin (GSA) scintigraphy, comorbidities (diabetes, hypertension, cancer, cardiovascular disease, and cerebrovascular disease), spirometry [Vital Capacity (VC), and forced expiratory volume in 1 second (FEV 1.0)]. Intraoperative variables included intraoperative transfusion, operative time, and blood loss, procedure [partial resection (Hr-0), segmentectomy (Hr-S), staitonectomy (Hr-1), lobectomy (Hr-2) and extended lobectomy (Hr-3). Postoperative variables included incidence of delirium, length of stay, discharge outcome (home or transfer to another hospital), morbidity, and mortality.

Study approval

This study was performed in accordance with the ethical standards of the declaration of Helsinki and the ethical guidelines for medical and health research involving human subjects. This study was approved and reviewed by the ethics review board of Fukuyama Medical Center, Hiroshima, Japan (no. H30-21, Japan). We obtained written informed consent from all patients for participation in this study.

Definitions

Patients aged 75-79 years at the time of hepatectomy were defined as Group I, and Group II consisted of patients aged 80 years or older. The Child–Pugh score [Child–Pugh score included ascites, Hepatic Encephalopathy (HE), nutritional status, total bilirubin, ALB, and PT or international normalized ratio] [17], liver damage classification were applied to evaluate liver function. 99mTc-GSA scintigraphy was performed to investigate residual liver function, and values of uptake ratio of the heart at 15 min to that at 3 min, uptake ratio of the liver to the liver plus heart at 15 min, and uptake ratio of the liver to the whole body at 15 min were scored [18]. For ICG testing, the ICG Retention rate at 15 min (ICGR-15) and ICG plasma clearance rate were recorded. We evaluated nutritional condition using the modified Prognostic Nutritional Index (mPNI: =10x alb (g/dl)+0.005 × TLC (/mm^3)) and the Controlling Nutritional Status (CONUT) score: range 0-12) [19,20]. The CONUT score was calculated using serum ALB concentration, peripheral lymphocyte count, and total cholesterol concentration [20]. In this study, we set 3 as the cut-off value for the CONUT score and classified the patients into high CONUT (≥ 3) and low CONUT (≤ 2) groups. Postoperative morbidity was assessed by Clavien-Dindo classification [21]. In this study, a grade IIIa or higher was defined as morbidity-positive. OS was defined as the time from the date of the operation to the date of death or last follow-up. In surgical procedure, Hr-S was defined as segmentectomy regarding to segments 1-8 in the classification of Couinaud. Hr-1 was also defined as sectionectomy (left lateral, left medial, right anterior and right posterior resection) [22]. In discharge outcome, "transfer to another hospital" was defined as transferring to the specialized institution for rehabilitation or a medical treatment after hepatectomy.

Statistical analysis

Statistical analyses were performed using SPSS Advanced Statistics 19.0 (SPSS Inc., Chicago, IL, USA). Data are shown as mean or median (range). For categorical data, chi-square tests or Fisher's exact test was used, while the Mann-Whitney test or unpaired t-test was used for continuous data. OS was calculated using the Kaplan-Meier method, with the log-rank test used for two-group comparison. Hazard Ratio (HR) and 95% Confidence Intervals (CIs) for clinical variables were calculated using Cox proportional hazards regression. The risk factors for postoperative morbidities were calculated using a binary logistic regression model in univariate and multivariate analyses. P-values <0.05 were considered statistically significant.

Results

Preoperative clinicopathological characteristics of elderly patients

The preoperative clinicopathological characteristics are shown in Table 1. Of the 81 patients enrolled in this study, 42 were categorized as Group I and 39 patients as Group II. Between Group I and Group II, there was no significant correlation of sex, diagnosis, surgical procedure, PS, ASA score, number of comorbidities, liver function (Child-Pugh score, liver damage score, ICG examination, and 99mTc-GSA scintigraphy), or pulmonary function (%VC and %FEV1.0). Concerning comorbidities, more than half of the patients had a diagnosis of hypertension or other malignancies, and almost a quarter of patients had diabetes or cardio-/cerebrovascular disorders (Table 2). In laboratory data, there was no significant difference in Hb and PLT between groups, but Group I showed significantly lower ALB levels (3.82 g/dl *vs.* 4.14 g/dl; P=0.009) and TLC (1249/mm^3 *vs.* 1621/mm^3; P=0.011) (Table 3). To evaluate nutritional status, we used mPNI and CONUT score. The number of cases with CONUT score more than 3 was 22 (56%) in Group II, which was significantly higher than that in Group I (10 cases, 24%) (P=0.003), indicating that older patients had a reduced nutritional status in the preoperative period compared to their younger cohorts. However, there was no significant difference in mPNI score between the two groups.

Incidence of morbidities in the perioperative period

During the perioperative period, there were no significant

Table 1: Clinicopathological characteristics of patients who underwent hepatectomy.

Characteristic			Age (years) 75-79 (Group I)	>80 (Group II)	P
No. of patients			42	39	
Age	(mean, range)		76.5 (75-79)	82.9 (80-89)	
Sex					0.056
	Male		33 (79%)	22 (56%)	
	Female		9 (21%)	17 (44%)	
Diagnosis					0.759
	HCC		23 (55%)	20 (51%)	
	ICC		4 (10%)	7 (18%)	
	GBC		11 (26%)	8 (21%)	
	Met		4 (10%)	4 (10%)	
Procedure					0.233
	Hr-0		8 (19%)	4 (10%)	
	Hr-S		18 (43%)	15 (36%)	
	Hr-1		9 (21%)	10 (24%)	
	Hr-2		7 (17%)	9 (21%)	
	Hr-3		0 (0%)	1 (2%)	
ECOG Performance Status					0.401
	0-1		30 (71%)	31 (79%)	
	02-03		12 (29%)	8 (21%)	
ASA score					0.449
	01-02		28 (67%)	29 (74%)	
	03-04		14 (33%)	10 (26%)	
Child-Pugh					0.939
	A		40 (95%)	37 (95%)	
	B		2 (5%)	2 (5%)	
Liver Damage					0.885
	A		32 (76%)	29 (74%)	
	B		5 (12%)	5 (13%)	
	N/A		5 (12%)	5 (13%)	
Comorbidities					0.239
	0-2		29 (69%)	22 (56%)	
	3-		13 (31%)	17 (44%)	
BMI	(kg/m^2)				0.136
	22>		20 (48%)	25 (64%)	
	22 ≤		22 (52%)	14 (36%)	
Hb	(g/dl)				0.147
	13>		18 (43%)	23 (59%)	
	13 ≤		24 (57%)	16 (41%)	
PLT	(*10^3/µl)				0.181
	150>		19 (45%)	12 (31%)	
	150 ≤		23 (55%)	27 (69%)	
mPNI					0.345
	45>		12 (29%)	15 (38%)	
	45≤		30 (71%)	24 (62%)	
CONUT score					
	0-2		32 (76%)	17 (44%)	0.003
	3-		10 (24%)	22 (56%)	
ICG Examination (ICGR15)					
	15>		24 (57%)	19 (49%)	0.448
	15 ≤		18 (43%)	20 (51%)	
GSA scintigraphy					
	HH15				0.716
		0.60>	20 (48%)	17 (44%)	
		0.60 ≤	22 (52%)	22 (56%)	
	LHL15				0.742
		0.90>	22 (52%)	19 (49%)	
		0.90 ≤	20 (48%)	20 (51%)	
	LU15				0.099
		20>	13 (31%)	6 (15%)	
		20 ≤	29 (69%)	33 (85%)	
Spirometry					
	% VC				0.787
		80>	13 (31%)	11 (28%)	
		80 ≤	29 (69%)	28 (72%)	
	% FEV1.0				0.847
		70>	6 (14%)	5 (13%)	
		70 ≤	36 (86%)	34 (87%)	

Listed P values present chi-square tests or Fisher's exact test between the two groups (75-79 years old *vs.* over 80 years old).

ASA: American Society of Anesthesiologist; BMI: Body Mass Index; CONUT score: Controlling Nutritional Status score; ECOG: Eastern Cooperative Oncology Group; FEV1.0: Forced Expiratory Volume in one second; GBC: Gallbladder Cancer; GSA: 99mTc-Galactosyl Serum Albumin; HCC: Hepatocellular Carcinoma; ICC: Intrahepatic Cholangiocarcinoma; ICG: Indocyanine Green; Met: Metastatic tumor; mPNI: modified Prognostic Nutritional Index; VC: Vital Capacity

Table 2: The details of comorbidities in patients who underwent hepatectomy.

Characteristic	Age (years) 75-79 (Group I) n=42	>80 (Group II) n=39	P
Comorbidities			
cardiovascular	10 (24%)	7 (18%)	0.517
cerebrovascular	7 (17%)	7 (18%)	0.879
diabetes	14 (33%)	10 (25%)	0.449
hypertension	27 (64%)	24 (62%)	0.798
malignancies	22 (52%)	20 (51%)	0.921

*The total does not add up because of multiple responses

differences in blood loss during operation, operating time, or incidence of delirium between the two groups (Table 4). Group II received significantly more transfusions during the operation that did Group I (46% *vs.* 22%; P=0.018). The incidence of severe morbidities, which yielded Clavien-Dindo classification IIIa or higher, was strongly associated with age (4.8% *vs.* 26%; P=0.012). In the oldest age group (Group II), the complications included atelectasis or difficulty in expectoration, bile leakage, abdominal abscess, cholangitis requiring endoscopic retrograde cholangiography, malnutrition requiring enteral feeding, and brain infarction. However, we found no significant difference in the mortality rate between the two groups

Table 3: Laboratory data in patients who underwent hepatectomy.

Characteristic	Age (years)		P
	75-79 (Group I)	>80 (Group II)	
No. of patients	42	39	
APTT (sec)	32.01 (24.9-49.1)	30.67 (25.6-45.7)	0.168
PT (%)	97.62 (37-122)	97.10 (63.0-114)	0.882
TP (g/dl)	7.33 (6.2-8.5)	7.05 (5.4-8.8)	0.059
Alb (g/dl)	4.14 (3.0-5.2)	3.82 (1.7-5.0)	0.009
ChE (IU/l)	240.90 (140-357)	224.26 (58-573)	0.291
Tchol (mg/dl)	178.51 (94-253)	180.16 (109-282)	0.847
TLC (/µl)	1621.56 (378-4536)	1249.57 (606-2217)	0.011
CRP (mg/dl)	0.55 (0.00-10.5)	0.97 (0.01-24.18)	0.526

Listed P values present t-test between the two groups (75-79 years old *vs.* over 80 years old).
APTT: Activated Partial Thrombin Time; PT: Prothrombin Time; TP: Total Protein; ALB: Albumin ChE: Cholinesterase; Tchol: Total cholesterol; TLC: Total Lymphocyte Count; CRP: C-Reactive Protein

Table 4: Analyses of perioperative factors of patients who underwent hepatectomy.

Factors	Age (years)		P
	75-79 (Group I)	>80 (Group II)	
Blood loss (ml) (median, range)	475 (10-13080)	470 (20-13870)	0.751
Operating time (min) (median, range)	317 (117-696)	348 (122-923)	0.62
Transfusion			0.018
yes	9 (21%)	18	
No	33 (79%)	21	
Delirium			0.448
positive	24 (57%)	19	
negative	18 (43%)	20	
Length of stay in Hospital (days)	19.12 (8-62)	24.97 (8-127)	0.098
Discharge form			0.003
Home	39 (93%)	26 (67%)	
Transfer to another hospital	3 (7%)	13 (33%)	
Morbidity (Clavian-Dindo scale)			0.012
0-II	40 (95%)	29 (74%)	
IIIa-	2 (5%)	10 (26%)	
(*The details of morbidities)			
Aspiration sputum by bronchoscopy	1	3	
Bile leakage	1	1	
Abdominal abscess	0	1	
Cholangitis needed ERC	0	1	
Undernutrition needed enteral tube	0	1	
Brain infarction	0	1	
Mortality			0.229
alive	42 (100%)	37 (95%)	
dead	0 (0%)	2 (5%)	

Listed P values present chi-square tests or Fisher's exact test between two Groups (75-79 years old *vs.* over 80 years old)
P values present the Mann–Whitney test or unpaired t-test for continuous variable data
ERC: Endoscopic Retrograde Cholangiography

Table 5: Risk factors for postoperative morbidities in univariate and multivariate analysis.

Variable		Univariate			Multivariate		
		OR	95% CI	P	OR	95% CI	P
Age	75-79	Ref			Ref		
	80-	5.11	1.30-20.01	0.019	10.36	1.44-74.71	0.02
Sex	Male	Ref					
	Female	0.82	0.23-2.90	0.756			
Diagnosis	HCC	Ref					
	Non-HCC	0.57	0.17-1.89	0.36			
ECOG PS	0-1	Ref					
	02-03	1.25	0.31-5.01	0.756			
ASA score	01-02	Ref					
	03-04	1.4	0.42-4.73	0.585			
Procedure	Hr-0, S	Ref			Ref		
	Hr-1-3	6.16	1.57-24.22	0.009	2.31	0.87-6.13	0.094
Comorbidities	0-2	Ref					
	3-	1.34	0.42-4.33	0.621			
Child-pugh	A	Ref					
	B	5.42	0.69-42.26	0.107			
BMI	22>	Ref					
	22 ≤	0.44	0.13-1.54	0.197			
Hemoglobin	13>	Ref					
	13 ≤	1.03	0.33-3.26	0.956			
Platelet cell count	150>	Ref					
	150 ≤	1.26	0.39-4.05	0.698			
CONUT score	0-2	Ref					
	3-	0.82	0.25-2.73	0.75			
ICGR15	15>	Ref			Ref		
	15 ≤	4.01	1.03-15.68	0.046	4.53	0.68-30.06	0.118
% VC	80 ≤	Ref					
	80 >	2.04	0.62-6.70	0.239			
% FEV1.0	70 ≤	Ref			Ref		
	70 >	5.65	1.42-22.40	0.014	10.05	1.15-87.61	0.037
Blood loss in operation	500<	Ref			Ref		
	500 ≤	8.89	1.84-42.92	0.007	6.49	0.71-59.42	0.098
Operating time	350>	Ref			Ref		
	350 ≤	4.48	1.27-15.83	0.02	2.69	0.50-14.36	0.248
Delirium	Yes	Ref					
	No	0.61	0.19-1.95	0.402			

P values are calculated using a binary logistic regression model in univariate and multivariate analyses.
OR: Odds Ratio; 95% CI: 95% Confidence Intervals; ECOG: Eastern Cooperative Oncology Group; Ref: Reference; ASA: American Society of Anesthesiologist; BMI: Body Mass Index; CONUT score: Controlling Nutritional Status score; ICG: Indocyanine Green; GSA: 99mTc-Galactosyl Serum Albumin; HCC: Hepatocellular Carcinoma; VC: Vital Capacity; FEV1.0: Forced Expiratory Volume in one second

Table 6: Univariate analysis of overall survival in patients who underwent hepatectomy.

Variable		Univariate		
		HR	95% CI	P
Age	75-79	Ref		
	80-	1.29	0.555-2.989	0.555
Sex	Male	Ref		
	Female	0.81	0.315-2.069	0.655
Diagnosis	HCC	Ref		
	Non-HCC	2.48	1.016-6.062	0.046
ECOG PS	0-1	Ref		
	02-03	1.31	0.510-3.355	0.577
ASA score	01-02	Ref		
	03-04	2.64	1.129-6.166	0.025
Procedure	Hr-0, S	Ref		
	Hr-1-3	1.85	0.776-4.419	0.165
Comorbidities	0-2	Ref		
	3-	1.49	0.641-3.448	0.356
Child-Pugh	A	Ref		
	B	2.82	0.821-9.704	0.099
CONUT score	0-2	Ref		
	3-	1.09	0.465-2.552	0.845
Morbidity	0-II	Ref		
	IIIa-	1.98	0.804-4.879	0.137
Delirium	Yes	Ref		
	No	1.09	0.469-2.529	0.843

P values are calculated using Cox proportional hazards regression
HR: Hazard Ratio; 95% CI: 95% Confidence Intervals; Ref: Reference; ASA: American Society of Anesthesiologist; CONUT score: Controlling Nutritional Status score; ECOG: Eastern Cooperative Oncology Group

(P=0.229). Furthermore, length of hospital stay was not associated with age, but hospital transfer at discharge was significantly higher in Group II than Group I (7.1% *vs.* 33%; P=0.003).

Factors affecting morbidity after hepatectomy

To evaluate the predictive factors for morbidity, we calculated the odds ratios of morbidity according to different variables (Table 5). In the univariate analysis, age (Group I *vs.* Group II), procedure (Hr-0, -S *vs.* Hr-1, -2, and -3), ICGR-15 (>15 *vs.* ≤ 15), %FEV1.0 (>70 *vs.* ≤ 70), blood loss during operation, and operating time were risk factors for perioperative morbidities. Moreover, in the multivariate analysis, the older group (age ≥ 80) and poor respiratory function (%FEV1.0 <70) were significant independent risk factors for the incidence of morbidities (age: odds ratio, 10.36; 95% CI, 1.44-74.71; P=0.020, %FEV1.0: odds ratio, 10.05; 95% CI, 1.15-87.61; P=0.037).

Prognostic factors after hepatectomy

We investigated the predictive prognostic factors after hepatectomy (Table 6). In the univariate analysis, diagnosis (HCC *vs.* other malignancies) and ASA score (1-2 *vs.* 3-4) were the prognostic factors for hepatectomy in patients aged 75 or older. There was no significant correlation with age and prognosis (HR, 1.29; 95% CI, 0.56-2.99; P=0.555) (Figure 1). Using a cancer-specific death model, almost the same tendency was identified. These results indicated that the prognosis of hepatectomy patients aged >80 years (Group II) was approximately equivalent to that of patients aged 75-79 (Group I).

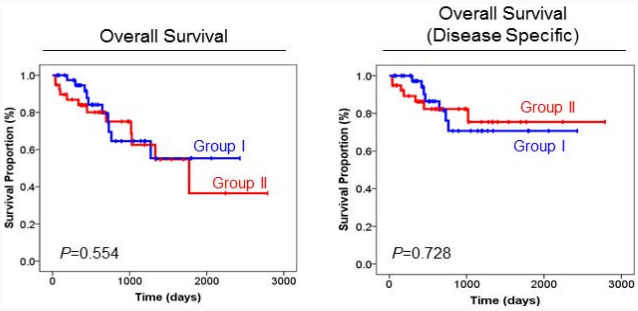

Figure 1: Survival curves according to age (Group I, 75-79 years and Group II, 80 years and older).
No significant correlation was detected either in the graph of overall survival (left panel) or in that of disease-specific overall survival (right panel) (left; P=0.554, right; P=0.728, log-rank test).

Discussion

In this study, multivariate analysis revealed that age was the most important risk factor of postoperative morbidities. However, there was no difference in mortality rate between the two groups. The finding that there were no significant differences between the two groups in terms of diagnosis, procedure, PS, ASA score, and comorbidities indicates that patient background was quite similar and that age did not affect the indication of hepatectomy. However, some differences should be noted, specifically higher LU 15 as liver function in Group II. This may be due to selection bias. Surgeons might not perform hepatectomy in patients with a lower residual liver function. All factors that were significantly lower in Group II were associated with nutrition. This suggested that elderly patients had inferior nutritional status even if selection bias was present. Moreover, this result indicates that the sarcopenia was potentially present in the oldest patients (Group II). Other researchers have reported that preoperative sarcopenia increased morbidity and mortality rates after major hepatectomy [23,24], which supports our results. Recently, sarcopenia is defined as a syndrome characterized by progressive and generalized loss of skeletal muscle mass for evaluating general conditions, and the prevalence is high in elderly people (5% to 13% in 60-70 year-olds; 11% to 50% in >80 years) [25]. Malnutrition is one of the causes of sarcopenia. Patients with a latent malnutrition or sarcopenia may have been included in the oldest group. Other researchers have reported that preoperative sarcopenia increased morbidity and mortality rates after major hepatectomy [23,24], which supports our results.

We defined elderly people as 75 years old or older, and analyzed the comparison with extreme elderly patients in this study. Recently, the population distribution of elderly people is changed with the aging of society, and surgical indication is not decided only for a reason of 80s. Several studies comparing outcomes from this procedure in younger and older patients exist; however, such studies have many limitations. First, selection bias may be present. For example, hepatectomy may have been limited to elderly patients with good nutritional status and little comorbidity. Further, when the control group is defined as non-elderly patients, the age variation of the population in the control group may be large. Therefore, we hypothesized that we could investigate the problem of extreme elderly patients by comparing the nearer population, 75-79 year-old hepatectomy patients.

Concerning morbidity, in this study, a significant difference was detected in the incidence of complications in patients with a

Clavien-Dindo classification IIIa or higher between the two groups. Decreased respiratory function prior to operation was one of the risk factors for severe morbidity and one of the complications found with the highest frequency (Table 4 and 5). Age was also a significant risk factor for severe complication. We hypothesize that for patients aged 80 years or older, the therapeutic window of safety and residual function is smaller than that for non-elderly people, even if the results of conventional examinations (e.g., laboratory data and physical examination) and general conditions (e.g., PS, ASA-score) are good. Physiologic changes in the liver such as a decrease in size and blood flow reduce the hepatic functional reserves in the elderly [26]. Thus, severe complications for oldest patients may occur because of low tolerance to adverse events in the peri- and postoperative period of hepatectomy.

On the univariate analysis, the factors affecting the prognosis of patients who had undergone hepatectomy were diagnosis and ASA-PS. Note that there was no significant difference between the prognoses of the two age groups. While patients in Group II did have a risk for severe morbidities, the prognosis in Group II was comparable to that in Group I. Similar results between the groups were identified in the analysis of disease-specific proportional hazards model (Figure 1). Moreover, liver regeneration after major hepatectomy was reported to be not affected by age [27]. This suggests that overcoming the perioperative period without complications is necessary to avoid mortality in extreme elderly patients undergoing hepatectomy for malignant hepatic tumors.

Our findings also showed that the patients in Group II were treated and considered carefully compared with those in Group I. We found that more transfusions were performed in Group II during the perioperative period, even though they did not have severe anemia. It appears that surgeons or anesthesiologists decided to perform transfusion to maintain general conditions of the patients. Additionally, a similar tendency was observed concerning the discharge from the hospital. Many patients in Group II transferred to another hospital for rehabilitation or required medical treatments postoperatively.

This study suggests that morbidities may be decreased by improving nutritional status and providing intensive care for the perioperative period. Minimally invasive surgery (e.g., laparoscopic surgery) may also help decrease the morbidities of elderly people [6,28]. Moreover, to achieve successful hepatectomy for extreme elderly patients, it is important to organize a perioperative team of multidisciplinary medical professionals and create a coherent treatment strategy from the pre- to post-operative period [29,30]. A comprehensive strategy implemented in the hospital, at rehabilitation facilities, and at home can be effective in achieving successful outcomes for elderly hepatectomy patients.

Our study had some limitations. We evaluated the morbidity and prognosis with various kinds of cancer, such as HCC, ICC, GBC, and Met. Therefore, these factors might confound our results. In addition, this was a retrospective and a single-institute study in Japan, so the number of patients was relatively small, and there is the question of generalizability of our findings to other population, particularly in regions outside of Japan. To address these problems, further investigation by multicenter design is warranted.

In conclusion, subjects aged 80 years or older were at a greater risk of severe complications following a hepatectomy. We posit that careful pre-, peri-, and post-operative management is essential in avoiding morbidities for these patients.

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