



Outcome of Hepatectomy for Hepatocellular Carcinoma in Elderly Patients With Portal Hypertension

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The outcome of liver resection (LR) for elderly hepatocellular carcinoma (HCC) patients with portal hypertension (PHT) who may be excluded as liver transplantation candidates has not been fully evaluated. One hundred ninety-five patients who underwent initial curative LR for HCC with PHT were divided into 2 groups: age <70 years (n = 131) and age ≥70 years (n = 64). Clinicopathologic data and postoperative complications were compared. Preoperative characteristics and postoperative complications were similar in both groups. However, in-hospital mortality was significantly more frequent in elderly than in younger patients (11% versus 1%, $P = 0.002$). No significant intergroup differences were observed in the 5-year disease-free survival rate or recurrence rate (19.7% versus 17.2%; $P = 0.338$, 63% versus 56%; $P = 0.339$). Although LR for elderly HCC patients with PHT can be performed with curative intent and gives results comparable with those in younger patients, it is associated with higher in-hospital mortality.

Key words: Liver resection – Recurrence – Portal hypertension – Liver transplantation – Liver failure

Recently, the number of elderly patients with hepatocellular carcinoma (HCC) has been increasing with the increased proportion of the geriatric population in Japan.^{1,2} Thanks to recent advances in surgical techniques, perioperative management, and anesthesia, the indications for surgical treatment modalities such as liver resection (LR) or liver transplantation (LT) in elderly patients have

expanded.^{3,4} Thus, age itself is no longer a contraindication for liver surgery.

When considering the treatment of HCC, most patients already have existing liver dysfunction due to chronic hepatitis or liver cirrhosis, and portal hypertension (PHT) may be present at the time of diagnosis.^{5,6} The American Association for the Study of Liver Diseases (AASLD)/Barcelona Clinic

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for Liver Cancer (BCLC) Guidelines have been widely utilized for the management of HCC in Western countries.^{7,8} They recommend that only LT can be regarded as curative treatment for early-stage HCC (single nodule or up to 3 nodules measuring ≤ 3 cm) with PHT. However, LT for all HCC patients with PHT is impossible because of donor organ shortage, especially in Asian countries.⁹ In addition, expanding the indications of LT for elderly patients is still controversial. A previous study suggested that patients with PHT who underwent LR showed the same incidence of postoperative complications and survival rate as patients without PHT.¹⁰ In other words, LR still plays an important role as the mainstay of curative treatment for HCC patients with PHT, even if they are elderly. There have been several reports on the safety and feasibility of LR for elderly HCC patients, but there is little information on the outcome of elderly patients with PHT, who are considered to be at extremely high risk.^{11–16} Against this background, the aim of the present study was to examine the short- and long-term outcomes of LR in both elderly (age ≥ 70 years) and younger (age < 70 years) HCC patients with PHT at a single center over a 12-year period.

Patients and Methods

The database available to us comprised 435 patients who had undergone initial curative LR for HCC, without extrahepatic metastasis, at Dokkyo Medical University Hospital between April 2000 and March 2012. Among them, 195 patients who had PHT were included in the present study. Because the hepatic venous pressure gradient was not measured, PHT was defined as the presence of esophageal varices, a platelet count of $< 100,000/\mu\text{L}$ with splenomegaly, or both, in accordance with the BCLC group criteria.¹⁷ Based on this definition, 143 patients were diagnosed as having esophageal varices, 133 had a platelet count of $< 100,000/\mu\text{L}$, and 81 had both conditions. We classified the patients into 2 age groups, < 70 years ($n = 131$) and ≥ 70 years ($n = 64$), according to their age at the time of LR. Preoperative upper-gastrointestinal endoscopy was performed in all patients to evaluate the presence of esophageal varices. If patients had esophageal varices with a red color sign, they were preoperatively treated by endoscopic variceal ligation or sclerotherapy to prevent variceal rupture. Clinicopathologic parameters such as preoperative and postoperative liver function data, surgical data, perioperative data,

pathologic data, and postoperative complications were compared between the 2 groups.

The indications for LR and surgical procedures in our department were based on the Makuuchi criteria.^{18,19} The type of LR was classified according to the Brisbane 2000 Nomenclature of Hepatic Anatomy and Resections.²⁰ Major hepatectomy included hemihepatectomy, sectionectomy, and bisegmentectomy, while minor hepatectomy included segmentectomy and wedge resection with a sufficient margin. Splenectomy before or simultaneously with hepatectomy was additionally performed to prevent hemorrhagic complications in patients with a platelet count of $< 50,000/\mu\text{L}$, based on our departmental policy.

Postoperative complications were evaluated according to the Clavien grading systems²¹ (*i.e.*, grade-I and -II complications were classified as minor problems that did not require invasive intervention). Complications worse than grade III were considered to be major problems requiring invasive intervention: grade III required surgical, endoscopic, or radiologic intervention; grade-IV complications were life-threatening, requiring intermediate care/intensive care unit management; and grade V represented the death of a patient. The definition and severity grading of posthepatectomy liver failure formulated by the International Study Group of Liver Surgery was used.²²

Patients visited the hospital once a month for the initial 12 months and at 3-month intervals after surgery. The tumor markers alpha-fetoprotein (AFP) and protein induced by vitamin K antagonism-II (PIVKA-II) were examined at each visit, and ultrasonography was performed. Patients were monitored using contrast-enhanced computed tomography (CT) of the abdomen and noncontrast CT of the chest at 3-month intervals for the initial 12 months and at 6-month intervals thereafter.²³

Data are presented as mean \pm SD. The χ^2 test, Fisher's test, and Mann-Whitney *U* test were used for comparisons of categorical and continuous data between the 2 groups. Survival curves were calculated using the Kaplan-Meier method and compared using the log-rank test. Univariate and multivariate analyses were performed using the Cox proportional hazards model. Statistical analysis was performed using SPSS software Version 17.0 (SPSS Inc, Chicago, IL). Statistical significance was defined as $P < 0.05$.

Results

Preoperative characteristics in the patients aged < 70 years (younger) and ≥ 70 years (elderly) are shown

Table 1 Preoperative characteristics of hepatocellular carcinoma patients with portal hypertension

Variables	<70 y (n = 131)	≥70 y (n = 64)	P value
Age, y	61.2 ± 6.7	73.3 ± 2.9	<0.001
Sex, male	106 (81%)	41 (64%)	0.010
BMI, kg/m ²	23.5 ± 3.7	22.8 ± 3.7	0.111
HCV antibody, +	94 (72%)	53 (83%)	0.092
Child-Pugh class A	93 (71%)	50 (78%)	0.290
Total bilirubin, mg/dL	0.79 ± 0.38	0.73 ± 0.24	0.564
Albumin, g/dL	3.3 ± 0.5	3.3 ± 0.5	0.965
Prothrombin time, %	78 ± 12	80 ± 10	0.289
ICG-R15, %	21.3 ± 11.8	20.9 ± 9.5	0.838
Platelet count, ×10 ⁴ /μL	106 ± 57	96 ± 48	0.374
AST, U/L	44 ± 17	45 ± 18	0.620
ALT, U/L	43 ± 21	38 ± 17	0.226
Creatinine, mg/dL	0.72 ± 0.21	1.01 ± 2.42	0.498
AFP, ng/mL	1201 ± 4268	2294 ± 8688	0.055
PIVKA-II, mAU/mL	1749 ± 8577	2190 ± 8590	0.056
Esophageal varices, +	96 (73%)	47 (73%)	0.982
Hypertension, +	40 (31%)	41 (64%)	<0.001
Diabetes mellitus, +	47 (36%)	9 (14%)	0.002
Follow-up, mo	43.5 ± 34.7	34.8 ± 30.4	0.082

in Table 1. There were no significant differences between the 2 groups in terms of body mass index (BMI), hepatitis C virus positivity, Child-Pugh class A, total bilirubin, albumin, indocyanine green retention rate at 15 minutes (ICG-R15%), platelet count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine, AFP, PIVKA-II, presence or absence of esophageal varices, and follow-up period. However, with regard to comorbidity, hypertension was more frequent in the elderly patients, while diabetes mellitus was more frequent in the younger patients. Males accounted for a higher proportion of the younger patients. Table 2 summarizes the surgical and perioperative data in both groups. The type of LR employed, such as major or minor hepatectomy, splenectomy, operation time, blood loss, Pringle time, and hospital stay, did not differ significantly between the 2 groups. Postoperative liver function parameters such as ALT, total bilirubin, prothrombin time, and the amount of ascites showed no significant intergroup differences. Pathologic findings in the 2 groups are listed in Table 3. Maximum tumor size was significantly greater in elderly than in younger patients. However, no significant intergroup differences were found in tumor number, percentage of patients within the Milan criteria (MC), histologic grade, and presence of intrahepatic metastasis, vascular invasion, and liver cirrhosis. Postoperative complications according to the Clavien grading

Table 2 Surgical and perioperative data of hepatocellular carcinoma patients with portal hypertension

	<70 y (n = 131)	≥70 y (n = 64)	P value
Major hepatectomy	24 (18%)	17 (27%)	0.185
Right hemihepatectomy	6	2	
Left hemihepatectomy	2	5	
Sectionectomy	13	9	
Bisegmentectomy	3	1	
Minor hepatectomy	107 (82%)	47 (73%)	
Segmentectomy	25	19	
Wedge resection	82	28	
Splenectomy, +	19 (15%)	6 (9%)	0.314
Operative factors			
Operative time, min	299 ± 109	300 ± 101	0.851
Blood loss, mL	957 ± 1479	867 ± 730	0.222
Pringle time, min	53 ± 28	52 ± 23	0.722
Hospital stay, d	31.1 ± 20.3	38.3 ± 33.3	0.383
ALT, U/L			
POD 1	218 ± 334	171 ± 128	0.770
POD 3	196 ± 226	165 ± 108	0.999
POD 5	116 ± 103	98 ± 49	0.806
Total bilirubin, mg/dL			
POD 1	1.13 ± 0.52	1.08 ± 0.47	0.506
POD 3	1.10 ± 0.59	1.01 ± 0.36	0.530
POD 5	1.03 ± 0.52	1.03 ± 0.37	0.419
Prothrombin time, %			
POD 1	67 ± 11	68 ± 12	0.464
POD 3	72 ± 13	73 ± 14	0.561
POD 5	71 ± 13	72 ± 14	0.603
Ascites, mL			
POD 1	240 ± 283	215 ± 227	0.981
POD 3	273 ± 374	350 ± 450	0.109
POD 5	420 ± 445	485 ± 554	0.513

system are noted in Table 4. No significant differences were observed between the 2 groups in terms of grade-II, -III, and -IV complications. However, the frequency of grade-V complication (in-hospital mortality) was significantly higher in elderly than in younger patients, being mainly attributable to liver failure. The overall postoperative mortality and recurrence rates in the 2 groups are shown in Table 5. Eighty-three (63%) of the 131 younger patients developed recurrence, whereas 36 (56%) of the 64 elderly patients did so. No significant intergroup difference was observed in the time to recurrence (13 months versus 14 months, $P = 0.339$). The main cause of death in younger patients was HCC recurrence, whereas that in elderly patients was both HCC recurrence and liver failure. The results of univariate and multivariate analyses for overall

Table 3 Pathologic findings of hepatocellular carcinoma patients with portal hypertension

	<70 y (n = 131)	≥70 y (n = 64)	P value
Tumor size, mm	33 ± 22	41 ± 25	0.011
Tumor number, single	87 (66%)	44 (69%)	0.744
Milan criteria, within	93 (71%)	43 (67%)	0.587
Histologic grade ^a			
well/mod or poor	34/90 (73%)	10/53 (84%)	0.079
Intrahepatic metastasis, + ^a	22 (18%)	11 (17%)	0.925
Vascular invasion, + ^a	37 (30%)	28 (44%)	0.057
Liver cirrhosis ^a	101 (83%)	50 (81%)	0.720

Mod, moderate.

^aSome data were not available for all patients (n = 8, n = 7, n = 7, and n = 10, respectively, from top to bottom). The percentage was calculated according to available data.

survival (OS) of elderly patients are shown in Table 6. Univariate analysis showed that Child-Pugh class B or C ($P = 0.034$), PIVKA-II >100 mAU/mL ($P = 0.005$), tumor size >5 cm ($P < 0.001$), multiple tumors ($P = 0.044$), operation time >250 minutes ($P = 0.002$), and blood loss >400 mL ($P = 0.001$) were significant risk factors for OS. Multivariate analysis revealed that 3 independent risk factors: tumor size >5 cm ($P = 0.030$), multiple tumors ($P = 0.010$), and blood loss >400 mL ($P = 0.007$) were significant.

Figure 1 shows the OS and disease-free survival (DFS) curves for the 2 groups. Elderly patients showed a poorer 5-year OS than younger patients (36.0% versus 56.3%, $P = 0.010$). However, the difference in the 5-year DFS did not reach significance (19.7% versus 17.2%, $P = 0.338$).

The OS and DFS rates for younger patients and elderly patients within the MC are shown in Fig. 2. No significant intergroup differences were evident (65% versus 49%, respectively, $P = 0.212$; 22% versus 25%, respectively, $P = 0.826$). For patients outside the MC (Fig. 3), the 5-year OS and 1-year DFS rates were significantly higher in younger than in elderly patients (37% versus 9%, respectively, $P = 0.002$; 46% versus 37%, respectively, $P = 0.050$).

Discussion

There is no doubt that LT is a better therapeutic approach for HCC patients with a cirrhotic liver, as it can provide potential cure of both the cancer and underlying liver disease at the same time. In the United States and Europe, the AASLD/BCLC

Table 4 Postoperative complications according to the Clavien grading systems

Grade	<70 y (n = 131)	≥70 y (n = 64)	P value
II	n = 27 (21%)	n = 11 (17%)	0.571
Ascites/pleural effusion	15	9	
Wound/drain infection	12	1	
Biliary leakage	2	1	
Gastric ulcer	2		
Hyperglycemia	1		
Arrhythmia	1		
Anemia	1		
Delayed gastric empty	1		
Delirium	1		
Renal dysfunction	1		
Atelectasis		1	
III	n = 43 (33%)	n = 18 (28%)	0.506
IIIa			
Refractory ascites/ pleural effusion	36	17	
Wound/drain infection	7		
Acute renal failure	1	2	
Arrhythmia	2	1	
Intraperitoneal abscess	2		
Biliary leakage	1	1	
Atelectasis	1	1	
Ileus		2	
Gastric ulcer	1		
Gingival abscess	1		
Heart failure		1	
Portal vein thrombosis	1		
IIIb			
Wound dehiscence		1	
Postoperative bleeding	1		
IV	n = 2 (2%)	n = 1 (2%)	1.000
Postoperative bleeding		1	
Heart failure due to arrhythmia	1		
Respiratory failure due to pneumothorax	1		
V	n = 1 (1%)	n = 7 (11%)	0.002
Liver failure	1	6	
Aspiration pneumonia		1	

Guidelines have been widely utilized for the management of HCC.^{7,8} They recommend that LT can be applied for HCC patients with PHT, and LR can be applied for HCC patients without PHT who have a single nodule with or without cirrhosis, with preservation of liver function. Although LT has recently been used in an increasing number of

Table 5 Postoperative recurrence and mortality of hepatocellular carcinoma patients with portal hypertension

	<70 y (n = 131)	≥70 y (n = 64)	P value
Recurrence	83 (63%)	36 (56%)	
Time to recurrence (median)	13 mo	14 mo	0.339
Mortality	57 (44%)	39 (61%)	
HCC recurrence	41 (72%)	18 (46%)	0.033
Liver failure	12 (21%)	15 (38%)	
Others	4 (7%)	6 (16%)	

patients older than 65 years,^{4,24} it remains debatable whether the indications for LT in elderly patients should be expanded. In Japan, low availability of donated organs is a serious limitation to the use of LT as an initial treatment for patients with HCC,^{9,25} and therefore implementation of LR for HCC has been developed as the preferred initial treatment. LR still plays a crucial role as one of the curative treatment modalities in Japan for elderly HCC patients, irrespective of the presence of PHT. Clarification of the outcome of LR for elderly HCC patients with PHT may help to better define the indications for LT in such patients. However, to our knowledge, no reports have described the outcome of LR for elderly patients with PHT, who are considered to be at extremely high risk. Accordingly, in the present study, we compared the OS, DFS, recurrence rate, and postoperative complications between elderly patients and younger patients.

In the present study, values of preoperative liver function parameters such as total bilirubin, albumin, prothrombin time, and ICG-R15% in the 2 groups were similar. Operation time, blood loss, and Pringle time in elderly patients were comparable with those in younger patients, irrespective of whether major or minor hepatectomy was performed. Values of postoperative liver function parameters such as ALT, total bilirubin, and prothrombin time, the amount of drained ascites up to postoperative day 5, and the duration of hospitalization were generally equivalent between the 2 groups. Furthermore, there were no significant intergroup differences in the recurrence rate and time to recurrence after surgery. These results indicate that LR can be performed safely and curatively based on adequate selection criteria even in elderly patients with PHT. The feasibility of LR for elderly patients reflects the results of previous studies that show operative outcomes similar to those for younger patients in terms of the type of hepatectomy, operation time,

Table 6 Univariate and multivariate analyses for overall survival of age ≥70 years group in hepatocellular carcinoma patients with portal hypertension

Variable	Univariate		Multivariate	
	P value	HR	95% CI	P value
Sex, male	0.173			
BMI, >25 kg/m ²	0.598			
HCV antibody, +	0.350			
Preoperative hypertension, +	0.697			
Preoperative DM, +	0.544			
Child-Pugh class, B or C	0.034	1.797	0.742–4.350	0.194
ICG-R15%, >20	0.657			
AFP, >20 ng/mL	0.734			
PIVKA-II, >100 mAU/mL	0.005	0.690	0.282–1.687	0.416
Tumor size, >5 cm	<0.001	3.050	1.116–8.340	0.030
Tumor number, multiple	0.044	2.688	1.268–5.697	0.010
Tumor histology, mod or poor	0.274			
Vascular invasion, +	0.370			
Intrahepatic metastasis, +	0.445			
Major hepatectomy, +	0.480			
Splenectomy, +	0.868			
Operative time, >250 min	0.002	2.236	0.795–6.289	0.127
Blood loss, >400 mL	0.001	6.310	1.641–24.266	0.007

blood loss, requirement for blood transfusion, and hospital stay.^{11–16}

Our study demonstrated that the incidence of grade-II, -III, and -IV complications did not differ between the 2 age groups. Ascites, pleural effusion, wound infection, and drain infection frequently developed in both. Patients with cirrhosis who have PHT may have intestinal circulatory disturbance, causing bacterial translocation and thus increasing the levels of inflammatory cytokines.^{26,27} These background factors may contribute to such complications. Furthermore, it has been reported that platelets may play an important role in antimicrobial host defenses against bacterial and fungal pathogens.²⁸ Therefore, patients with thrombocytopenia due to PHT may be more susceptible to various infections than patients without thrombocytopenia. Elderly patients exhibited a higher incidence of grade-V complication (*i.e.*, in-hospital mortality) than younger patients (7 cases versus 1 case, $P = 0.002$). Among these 7 grade-V cases, 6 were due to postoperative liver failure. These results

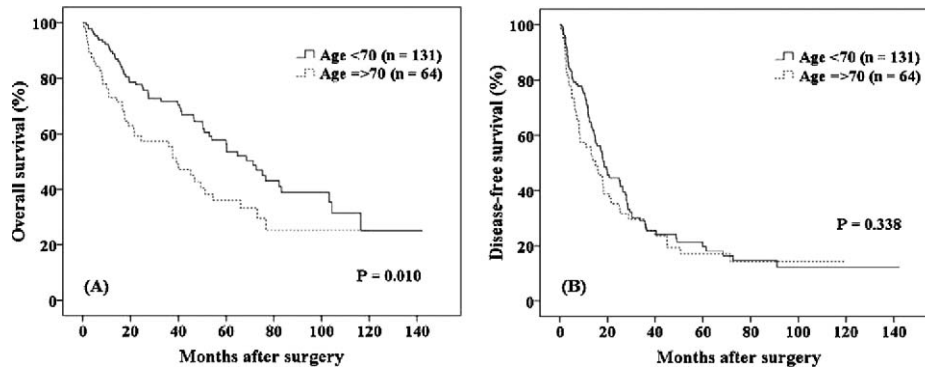


Fig. 1 The 5-year overall survival was significantly higher in the <70 years age group than in the ≥70 years age group (56.3% versus 36.0%, $P=0.010$) of HCC patients with portal hypertension. However, the difference in disease-free survival between the groups did not reach significance (19.7% versus 17.2%, $P=0.338$).

suggest that despite the similarity of preoperative values of liver function parameters between the 2 groups, the liver functional capacity of some elderly patients might not allow them to tolerate the metabolic demands after LR.

Both HCC recurrence and liver failure due to progression of underlying liver disease were often observed as part of the background contributing to overall mortality in elderly patients (Table 5). Wakabayashi *et al* demonstrated a discrepancy between the liver volume estimated by CT and actual functional hepatocyte volume examined using ^{99m}Tc -galactosyl-human serum albumin liver scintigraphy in elderly patients with liver tumors, who were awaiting surgery, and considered that this might have a critical impact on preoperative liver functional reserve prior to hepatic resection.²⁹ In the field of LT, donor age is a well-known risk factor affecting graft failure and patient survival. Grafts

from older donors are associated with slow recovery of liver function, a higher incidence of primary nonfunction, and a higher risk of early and long-term mortality.^{30–32} These findings suggest that liver functional capacity declines with aging, finally resulting in a difference of OS, as was observed between the 2 groups in this series.

Although the 5-year OS rate was significantly lower in elderly than in younger patients, it did not differ significantly between the groups for patients who were within the MC. In contrast, for patients outside the MC, the 5-year OS and 1-year DFS rates were significantly lower in the elderly. These results indicate that LR for elderly HCC patients with PHT is obviously preferable for patients within the MC.

In conclusion, although LR for elderly HCC patients with PHT can be performed safely and curatively, allowing outcomes comparable with those in younger HCC patients, it is associated with

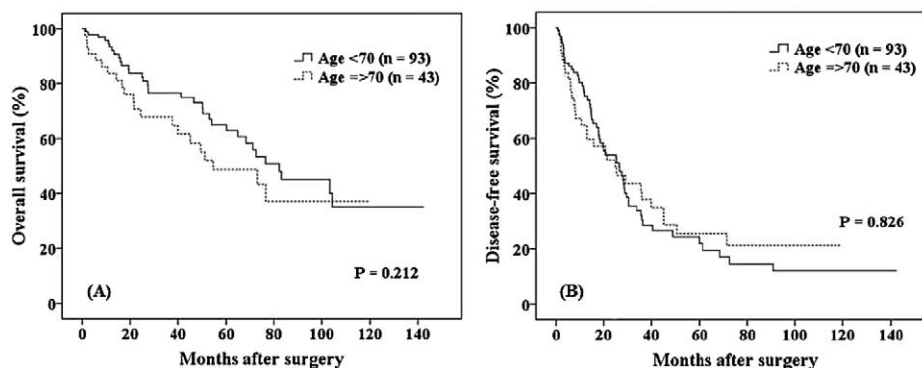


Fig. 2 For patients within the Milan criteria, no significant differences in the 5-year overall survival and disease-free survival rates were observed between younger and elderly patients (65% versus 49%, respectively, $P=0.212$; 22% versus 25%, respectively, $P=0.826$).

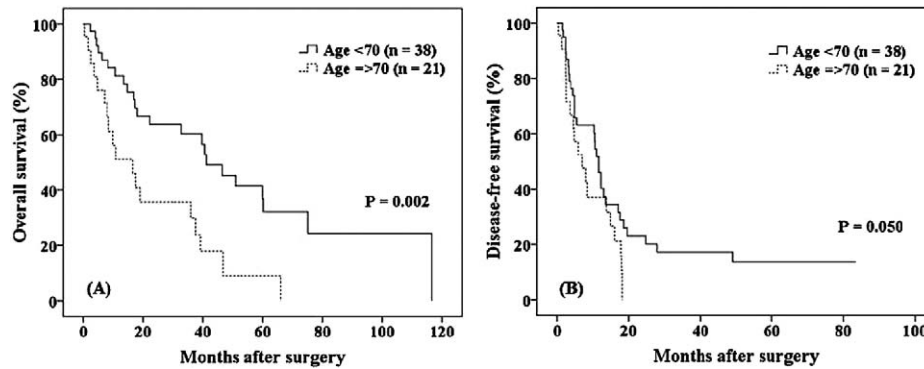


Fig. 3 For patients outside the Milan criteria, the 5-year overall survival and 1-year disease-free survival rates were significantly higher for younger than for elderly patients (37% versus 9%, respectively, $P = 0.002$; 46% versus 37%, respectively, $P = 0.050$). CI, confidence interval; DFS, disease-free survival; DM, diabetes mellitus; HCV, hepatitis C virus; HR, hazard ratio; POD, postoperative day.

a higher in-hospital mortality rate and a lower 5-year OS rate. Therefore, LR should be performed for patients within the MC while ensuring careful postoperative management.

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