

Major Hepatectomy in Elderly Patients with Large Hepatocellular Carcinoma: A Multicenter Retrospective Observational Study

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Zheng-Liang Chen,^{1,*} Cheng-Wu Zhang,^{2,*} Lei Liang,^{2,*} Han Wu,^{3,*} Wan-Guang Zhang,⁴ Yong-Yi Zeng,⁵ Wei-Min Gu,⁶ Ting-Hao Chen,⁷ Jie Li,⁸ Yao-Ming Zhang,⁹ Hong Wang,¹⁰ Ya-Hao Zhou,¹¹ Chao Li,² Yong-Kang Diao,² Wan Yee Lau,^{3,12} Meng-Chao Wu,³ Feng Shen,³ Tian Yang,³ Ying-Jian Liang¹

¹Department of Hepatobiliary Surgery, The First Affiliated Hospital of Harbin Medical University, Heilongjiang, People's Republic of China; ²Department of Hepatobiliary, Pancreatic and Minimal Invasive Surgery, Zhejiang Provincial People's Hospital, People's Hospital of Hangzhou Medical College, Zhejiang, People's Republic of China; ³Department of Hepatobiliary Surgery, Eastern Hepatobiliary Surgery Hospital (Navy Medical University), Second Military Medical University, Shanghai, People's Republic of China; ⁴Department of Hepatic Surgery, Tongji Hospital, Huazhong University of Science and Technology, Wuhan, People's Republic of China; ⁵Department of Hepatobiliary Surgery, Mengchao Hepatobiliary Hospital, Fujian Medical University, Fujian, People's Republic of China; ⁶The First Department of General Surgery, The Fourth Hospital of Harbin, Heilongjiang, People's Republic of China; ⁷Department of General Surgery, Ziyang First People's Hospital, Sichuan, People's Republic of China; ⁸Department of Hepatobiliary Surgery, Fuyang People's Hospital, Anhui, People's Republic of China; ⁹The 2nd Department of Hepatobiliary Surgery, Meizhou People's Hospital, Guangdong, People's Republic of China; ¹⁰Department of General Surgery, Liuyang People's Hospital, Hunan, People's Republic of China; ¹¹Department of Hepatobiliary Surgery, Pu'er People's Hospital, Yunnan, People's Republic of China; ¹²Faculty of Medicine, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong, SAR, People's Republic of China

*These authors contributed equally to this work

Correspondence: Ying-Jian Liang
Department of Hepatobiliary Surgery, The First Affiliated Hospital of Harbin Medical University, No. 23, Youzheng Road, Heilongjiang 150006, People's Republic of China
Email genomeliang@hotmail.com

Tian Yang
Department of Hepatobiliary Surgery, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University (Navy Medical University), No. 225, Changhai Road, Shanghai 200438, People's Republic of China
Email yangtiantdgd@hotmail.com

Background: With an increase in life expectancy and improvement of surgical safety, more elderly patients with hepatocellular carcinoma (HCC), even with large tumors, are now considered for hepatectomy. This study aimed to clarify the impact of age on short- and long-term outcomes after major hepatectomy (≥ 3 segments) for large HCC (≥ 5 cm).

Patients and Methods: Using a multicenter database, patients who underwent curative-intent major hepatectomy for large HCC between 2006 and 2016 were identified. Postoperative morbidity and mortality, overall survival (OS) and recurrence-free survival (RFS) were compared between the elderly (≥ 65 years) and younger (< 65 years) patients. Univariable and multivariable Cox-regression analyses were performed to identify the risk factors of OS and RFS in the entire and elderly cohorts, respectively.

Results: Of 830 patients, 92 (11.1%) and 738 (88.9%) were elderly and younger patients, respectively. There were no significant differences in postoperative 30-day mortality and morbidity between the two groups (5.4% vs 2.6% and 43.5% vs 38.3%, both $P > 0.05$). The 5-year OS and RFS rates in elderly patients were also comparable to younger patients (35.0% vs 33.2% and 20.0% vs 20.8%, both $P > 0.05$). In the entire cohort, multivariable Cox-regression analyses identified that old age was not independently associated with OS and RFS. However, in the elderly cohort, preoperative alpha-fetoprotein level > 400 $\mu\text{g/L}$, multiple tumors, macrovascular invasion and microvascular invasion were independently associated with decreased OS and RFS.

Conclusion: Carefully selected elderly patients benefited from major hepatectomy for large HCC as much as younger patients, and their long-term prognosis was determined by preoperative alpha-fetoprotein level, tumor number and presence of macro- or microvascular invasion.

Keywords: hepatocellular carcinoma, hepatectomy, survival, recurrence, elderly

Introduction

Hepatocellular carcinoma (HCC) is the fourth leading cause of cancer-related mortality in adults,¹ and is the most common cancer affecting the elderly worldwide.² The overall prognosis of HCC remains dismal. For a subset of patients receiving curative therapies including local ablation, liver transplantation and partial hepatectomy,³ long-term survival is still possible. Local ablation, albeit less invasive, is only suitable for small HCC, generally considered to be less than 5 cm. Liver transplantation is the treatment of choice for early HCC that meets the Milan criteria. However, the lack of donors limits its application in elderly patients, especially in Asia. Thus, for patients with a large HCC (≥ 5 cm), especially in elderly patients, the only possible cure is partial hepatectomy.

Advances in surgical techniques, perioperative assessments, anesthesia and medical care have led to notably decrease in postoperative morbidity and mortality following hepatectomy for HCC. In general, selected elderly patients, although having more associated comorbidities and compromised organ reserve, can still well tolerate hepatectomy for HCC with short- and long-term outcomes similar to younger patients. Age by itself did not have any significant negative impact.^{4–10} Major hepatectomy (≥ 3 Couinaud segments) for large HCC intrinsically has a higher surgical risk.¹¹ However, so far there have been few studies on whether this operation in elderly patients is safe, efficacious and having long-term oncological outcomes similar to younger patients.^{12,13}

The aim of the present study was to determine safety and efficacy in elderly patients undergoing major hepatectomy for large HCC using a large multicenter database. The short- and long-term outcomes, including long-term overall (OS) and recurrence-free survival (RFS), in elderly patients (≥ 65 years old) were compared with younger patients (< 65 years old).

Patients and Methods

Study Population

Using a multicenter database, patients who underwent curative-intent hepatectomy for HCC at 11 medical institutions in China from January 2006 to December 2016 were identified. These institutions included the First Affiliated Hospital of Harbin Medical University, Zhejiang Provincial People's Hospital, Eastern Hepatobiliary Surgery Hospital, Tongji Hospital, Mengchao Hepatobiliary Hospital, the Fourth Hospital of Harbin, Ziyang First People's Hospital, Fuyang People's Hospital, Meizhou People's Hospital, Liuyang People's Hospital, and Pu'er People's Hospital. Major hepatectomy was defined as partial hepatectomy of three or more Couinaud's segments. Curative hepatectomy was defined as the removal of all microscopic and macroscopic tumors with a microscopically clear margin (R0 resection). The exclusion criteria included: 1) patient ≤ 18 years old, 2) combined HCC-cholangiocarcinoma, 3) recurrent HCC, 4) palliative hepatectomy (R1 or R2 resection), 5) HCC with a maximum tumor size < 5 cm, 6) minor hepatectomy (< 3 segments), 7) loss to follow-up within 3 months after surgery, and 8) missing data on important prognostic variables. Informed consent was obtained from all the patients for their data to be used for clinical research. The data were censored on June 30, 2019. The study was performed according to the Declaration of

Helsinki and the Ethical Guidelines for Clinical Studies. Approval from Ethics Committees of each of the individual hospital was obtained.

Preoperative Evaluation

Preoperative evaluation was generally consistent at each participating institution. Liver function was evaluated by biochemistry and Child–Pugh classification. Upper gastrointestinal endoscopy was routinely employed for all HCC patients who were scheduled for operation. Patients older than 60 years and those with significant co-morbid illnesses were routinely sent for formal cardiopulmonary evaluation.^{14,15} Child–Pugh grade C was considered an absolute contraindication for HCC resection. Resection criteria were constant over the study period, including the number of resectable tumors, presence or absence of gross tumor thrombus, and adequate liver function reserve, as reported in our previous study.^{14,16}

Clinicopathologic Characteristics and Operative Variables

The following patients' clinicopathologic characteristics were collected, including: age, sex, co-morbidities, American Society of Anesthesiologists (ASA) score, etiology of liver diseases, presence of cirrhosis or portal hypertension, Child–Pugh grading, preoperative alpha-fetoprotein (AFP) level, maximum tumor size, tumor number, presence of satellite nodules, tumor differentiation, presence of macroscopic or microscopic vascular invasion, tumor encapsulation, and resection margin status. Co-morbidities included hypertension, diabetes mellitus, chronic obstructive pulmonary disease, renal dysfunction, and cardiovascular disease. Cirrhosis was confirmed by histopathological examination. Portal hypertension was defined as the presence of either splenomegaly with a decreased platelet count ($\leq 100 \times 10^9/L$) or esophageal varices. Operative variables collected included intraoperative blood loss and intraoperative blood transfusion.

Follow-Up

Patients were followed-up at each participating institution. The routine postoperative surveillance strategy for recurrence included serum AFP level, ultrasonography or contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) of the chest and abdomen once every 2 months for the first 6 months, once every 3 months thereafter for the next 18 months, and then once every 6 months at 2 years and later after resection. When HCC

recurrence was suspected, contrast-enhanced CT or MRI, chest CT, bone scan or positron emission tomography were performed as clinically indicated. Tumor recurrence was defined as a new appearance of intra- or extra-hepatic tumor nodule(s) with or without a rise in serum AFP level, as well as the presence of intrahepatic nodules that had typical imaging features with characteristic features of HCC on contrast-enhanced CT or MRI examination. Treatment of HCC recurrence was based on the pattern of recurrence, residual hepatic functional reserve, and general condition of patient.

Study Endpoints

As the present study focused on perioperative safety and long-term survival outcomes of hepatectomy for HCC, the primary endpoints were OS and RFS, while the secondary endpoints were postoperative 30-day mortality and morbidity. OS was defined as the time from surgery to death from any cause, and RFS as the time from surgery to HCC recurrence or death. Postoperative morbidities were classified into five grades based on the Clavien-Dindo classification,¹⁷ and minor and major morbidities were defined as Clavien-Dindo <3 and ≥3, respectively.

Statistical Analysis

Statistical analyses were performed using SPSS software version 25.0 (SPSS, Chicago, IL, USA). Categorical variables were expressed as number (n) or proportion (%), while continuous variables were expressed as mean ± standard deviation or median (range). Categorical and continuous covariates were compared using the χ^2 test with Yates correction or Fisher's exact test, and Student's *t* test or Mann-Whitney ranked *U*-test, respectively. The OS and RFS rates were estimated using the Kaplan-Meier curves and compared with the Log-rank test. Univariable and Multivariable Cox-regression analyses were performed to identify risk factors which were independently associated with decreased OS and RFS in the entire cohort, as well as in the elderly cohort. The variable of age, as the most important variable, was forced into the multivariable Cox-regression model. Other variables with a *P* value <0.1 in univariable analysis were subjected to the multivariable Cox-regression model using a forward stepwise selection. All tests were two-tailed, and a significant *P* value was defined as <0.05.

Results

The multicenter database contained details of 2133 patients from 11 institutions who underwent partial hepatectomy with the curative intention for HCC during the study period. Using the inclusion criteria, 830 patients who underwent curative major hepatectomy for large HCC were enrolled in this study (Figure 1). Among all the 830 patients identified in the entire cohort, there were 92 elderly patients (≥65 years old, 11.1%) and 738 younger patients (<65 years old, 88.9%), with a median age of 68 (range: 65 to 83) and 49 (range: 21 to 64) years, respectively. Patients' clinicopathologic characteristics and operative variables among the elderly versus the younger were notable for several differences (Table 1): proportion of male patients, patients with co-morbidities, ASA score > 2, chronic hepatitis B virus (HBV) infection and satellite nodules were significantly higher in the elderly group (all *P* < 0.05).

Comparisons of Postoperative Morbidity and Mortality

Postoperative short-term outcomes of the elderly and younger patient groups are summarized in Table 1. The postoperative 30-day mortality and morbidity rates were comparable in the two groups (5.443.5% vs 2.6% and 38.3%, *P* = 0.173 and 0.365, respectively). The postoperative major and minor morbidity rates were also comparable (17.426.1% vs 17.6% and 20.7%, *P* = 1.000 and 0.280, respectively). Univariable and multivariable logistic regression analyses of risk factors associated with postoperative 30-day morbidity are shown in Table 2.

Comparisons of Long-Term Survival and HCC Recurrence

After excluding 24 patients who suffered from postoperative 30-day death, long-term outcomes of the remaining 806 patients were compared between the two groups (Table 3). At a median follow-up of 26.4 months (mean follow-up: 36.8 months), 569 of 806 patients (70.6%) had died and 622 (77.2%) had developed HCC recurrence. The overall mortality and recurrence rates among the elderly versus the younger groups were 72.4 and 70.1% versus 77.7 and 70.7%, respectively (both *P* > 0.2). The median OS and RFS in the elderly group were 30.6 and 9.8 months, while the median OS and RFS in the younger group were 25.6 and 8.8 months, and there was no significant difference between these two groups (*P* = 0.739 and 0.632, respectively). As

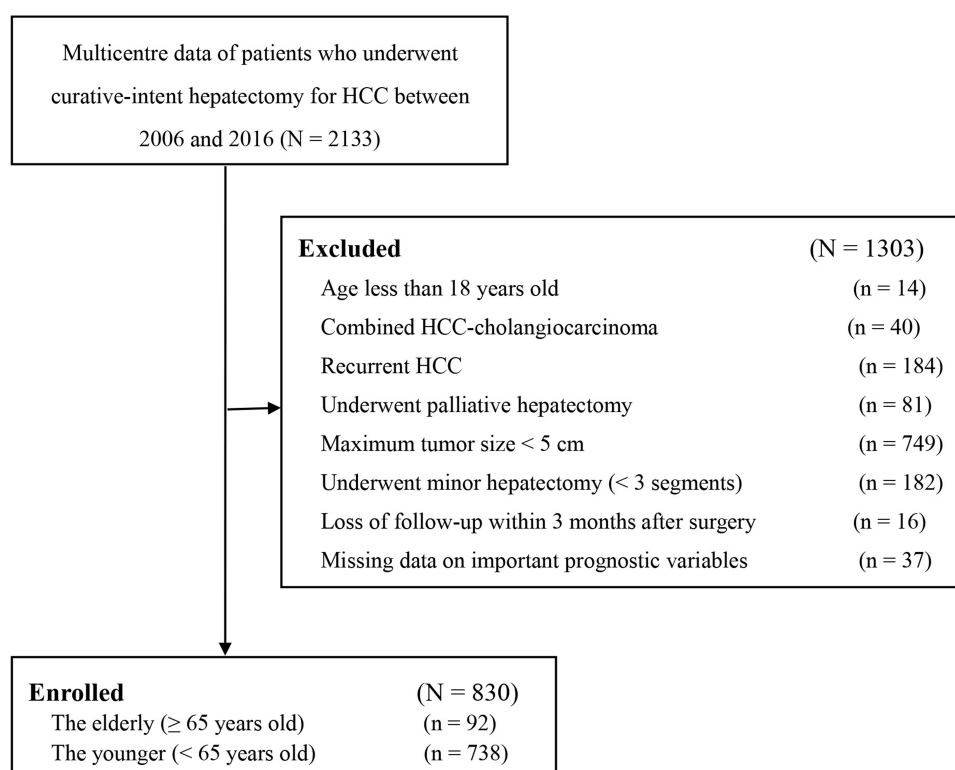


Figure 1 Flowchart of study population. HCC, hepatocellular carcinoma.

shown in [Table 3](#) and [Figure 2](#), the 1-, 3- and 5-year OS and RFS rates in the elderly group were 71.3%, 43.2% and 35.0%, and 41.4%, 27.3% and 20.0%, respectively, which were comparable to the younger group (68.9%, 42.0% and 33.2%, and 44.0%, 28.3% and 20.8%, respectively).

Analyses of Prognostic Factors for OS and RFS in the Entire Cohort

Independent risk factors associated with OS and RFS after major hepatectomy for large HCC were identified by univariable and multivariable Cox-regression analyses ([Tables 4 and 5](#)). Multivariable analyses demonstrated that old age was not independently associated with OS and RFS (both $P > 0.2$), but preoperative AFP level $>400 \mu\text{g/L}$ (hazard ratio [HR] 1.53, 95% confidence interval [CI] 1.29–1.82), satellite nodules (HR 1.75, 95% CI 1.48–2.08), macrovascular invasion (HR 2.48, 95% CI 2.06–2.99), microvascular invasion (HR 2.30, 95% CI 1.91–2.76), and intraoperative blood transfusion (HR 2.34, 95% CI 1.13–1.58) were independent risk factors of decreased OS, while preoperative AFP level $>400 \mu\text{g/L}$ (HR 1.54, 95% CI 1.31–1.81), satellite nodules (HR 1.51, 95% CI 1.28–1.78), macrovascular invasion (HR 2.14, 95% CI 1.76–2.46), microvascular invasion (HR 1.62, 95% CI 1.34–1.95), intraoperative blood

transfusion (HR 1.27, 95% CI 1.08–1.49), and resection margin $<1 \text{ cm}$ (HR 2.08, 95% CI 1.76–2.46) were independent risk factors of decreased RFS after major hepatectomy for large HCC.

Prognostic Analyses for OS and RFS in the Elderly Cohort

[Table 6](#) lists the risk factors identified by univariable and multivariable Cox-regression analyses which were associated with OS after major hepatectomy for HCC in the elderly cohort. Multivariable analyses demonstrated that preoperative AFP level $>400 \mu\text{g/L}$ (HR 1.84, 95% CI 1.04–3.26), multiple tumors (≥ 3 tumor nodules) (HR 2.07, 95% CI 1.18–3.62), and macrovascular invasion (HR 3.01, 95% CI 1.58–5.74) were independent risk factors of decreased OS after major hepatectomy for elderly patients with a large HCC.

[Table 7](#) lists the risk factors identified by univariable and multivariable Cox-regression analysis which were associated with RFS after major hepatectomy for HCC in the elderly cohort. Multivariable analyses identified preoperative AFP level $>400 \mu\text{g/L}$ (HR 1.82, 95% CI 1.03–3.22), multiple tumors (HR 2.47, 95% CI 1.37–4.44), macrovascular invasion (HR 2.71, 95% CI 1.54–4.77), and

Table I Comparisons of Clinicopathologic Characteristics, Operative Variables and Short-Term Outcomes Following Major Hepatectomy for Large Hepatocellular Carcinoma Between Elderly and Younger Patients in the Entire Cohort

N (%)	The Younger (N=738)	The Elderly (N=92)	P
Clinicopathologic characteristics			
Age, years*	47.6±9.2	69.0±4.0	< 0.001
Male sex	654 (88.6)	73 (79.3)	0.018
Co-morbidities	108 (14.6)	31 (33.7)	< 0.001
ASA score > 2	75 (10.2)	39 (42.4)	< 0.001
Etiology of liver diseases			
HBV	672 (91.0)	63 (68.5)	< 0.001
HCV	5 (0.7)	2 (2.2)	
HBV+HCV	4 (0.5)	2 (2.2)	
Others**	57 (7.7)	25 (27.2)	
Cirrhosis	534 (72.4)	59 (64.1)	0.111
Portal hypertension	124 (16.8)	14 (15.2)	0.768
Child–Pugh grade B	79 (10.7)	8 (8.7)	0.718
Preoperative AFP level > 400 ug/L	308 (41.7)	30 (32.6)	0.115
Maximum tumor size, cm*	10.8±3.3	10.5±3.8	0.474
Maximum tumor size ≥ 10 cm	430 (58.3)	49 (53.3)	0.372
Multiple tumors (≥ 3 tumor nodules)	145 (19.6)	14 (15.2)	0.399
Satellite nodules	290 (39.3)	25 (27.2)	0.030
Poor tumor differentiation	540 (73.2)	63 (68.5)	0.385
Macrovascular invasion	189 (25.6)	25 (27.2)	0.800
Microvascular invasion	475 (64.4)	52 (56.5)	0.168
Incomplete tumor encapsulation	525 (71.1)	60 (65.2)	0.275
Resection margin < 1 cm	260 (35.9)	33 (35.9)	1.000
Operative variables			
Intraoperative blood loss, mL*	500 (50–8000)	550 (100–4300)	0.235
Intraoperative blood transfusion	260 (35.2)	41 (44.6)	0.085
Short-term outcomes			
Postoperative hospital stay*	13.6±6.3	14.6±7.8	0.178
Postoperative 30-day mortality	19 (2.6)	5 (5.4)	0.173
Acute liver failure	10	2	
Abdominal hemorrhage	3	1	
Pulmonary infection	3	1	
Cardiovascular accident	1	1	
Upper gastrointestinal bleeding	1	0	
Pulmonary embolism	1	0	
Postoperative 30-day morbidity	283 (38.3)	40 (43.5)	0.365
Postoperative 30-day major morbidity	130 (17.6)	16 (17.4)	1.000
Postoperative 30-day minor morbidity	153 (20.7)	24 (26.1)	0.280

Notes: *Values are mean ± standard deviation or median with range. **Others include alcoholic liver disease, non-alcoholic fatty liver disease, schistosomiasis cirrhosis, and cryptogenic cirrhosis.

Abbreviations: ASA, American Society of Anesthesiologists; HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, alpha-fetoprotein.

microvascular invasion (HR 1.85, 95% CI 1.06–3.21) to be independent risk factors of decreased RFS after major hepatectomy for elderly patients with a large HCC.

According to the number of three independent risk factors which could be identified before surgery, ie preoperative AFP level >400 µg/L, the presence of macrovascular

invasion, and multiple tumor (≥3 nodules), the 87 elderly patients were divided into 3 subgroups: 1) without any risk (n = 43); 2) with any one of the three risks (n = 30); and 3) with ≥2 of the three risks (n = 14; 10 patients with any 2 of the three risks and 4 patients with all three risks). As shown in Figure 3, there were significant differences between OS

Table 2 Univariable and Multivariable Logistic Regression Analyses of Risk Factors of Postoperative 30-Day Morbidity After Major Hepatectomy for Large Hepatocellular Carcinoma in the Entire Cohort

Variables	OR Comparison	UV OR (95% CI)	UV P	MV OR (95% CI)	MV P*
Age	Elderly vs Younger	1.16 (0.74–1.83)	0.365	NA	0.596
Sex	Male vs Female	1.14 (0.74–1.75)	0.555		
Co-morbidities	Yes vs No	1.84 (0.95–3.57)	0.070	NA	0.148
ASA score	> 2 vs ≤ 2	1.73 (1.15–2.61)	0.009	NA	0.072
Etiology of liver diseases	HBV vs Non-HBV	1.16 (0.72–1.86)	0.548		
Cirrhosis	Yes vs No	2.13 (1.52–2.98)	<0.001	2.03 (1.44–2.88)	< 0.001
Portal hypertension	Yes vs No	1.60 (1.10–2.33)	0.015	NA	0.482
Child–Pugh grade	B vs A	2.20 (1.37–3.54)	0.001	1.74 (1.06–2.83)	0.027
Preoperative AFP level	> 400 vs ≤ 400 µg/L	1.20 (0.90–1.59)	0.221		
Maximum tumor size	≥ 10 vs 5.0–9.9 cm	1.26 (0.94–1.68)	0.121		
Multiple tumors (≥ 3 nodules)	Yes vs No	1.51 (1.03–2.20)	0.034	1.67 (1.13–2.48)	0.011
Satellite nodules	Yes vs No	0.95 (0.71–1.28)	0.747		
Poor tumor differentiation	Yes vs No	0.78 (0.57–1.07)	0.131		
Macrovascular invasion	Yes vs No	1.42 (1.08–1.97)	0.033	NA	0.086
Microvascular invasion	Yes vs No	1.41 (1.05–1.89)	0.024	NA	0.169
Incomplete tumor encapsulation	Yes vs No	1.28 (0.93–1.75)	0.131		
Intraoperative blood loss	> 600 vs ≤ 600 mL	1.96 (1.46–2.64)	<0.001	NA	0.256
Intraoperative blood transfusion	Yes vs No	2.10 (1.56–2.82)	<0.001	2.05 (1.51–2.78)	< 0.001
Resection margin	< 1 vs ≥ 1 cm	1.17 (0.84–1.64)	0.349		

Notes: *As the most important variable, age was forced into multivariable logistic regression model; apart from age, other variables with a *P* value <0.1 in univariable analysis were subjected to multivariable logistic regression model.

Abbreviations: ASA, American Society of Anesthesiologists; HBV, hepatitis B virus; AFP, alpha-fetoprotein; CI, confidence interval; OR, odds ratio; UV, univariable; MV, multivariable; NA, not available.

Table 3 Comparisons of Long-Term Outcomes Following Major Hepatectomy for Large Hepatocellular Carcinoma Between Elderly and Younger Patients in the Entire Cohort of the Remaining 806 Patients After Excluding 24 Patients Who Died Within 30 Days After Surgery

N (%)	The Younger (N=719)	The Elderly (N=87)	P
Recurrence during the follow-up	559 (77.7)	63 (72.4)	0.280
Intrahepatic recurrence	500 (89.4)	52 (82.5)	
Extrahepatic recurrence	17 (3.0)	3 (4.8)	
Intra- and extrahepatic recurrence	42 (7.5)	8 (12.7)	
Death during the follow-up	508 (70.7)	61 (70.1)	0.901
Median OS, 95% CI	25.6 (21.4–29.8)	30.6 (22.0–39.2)	0.739
1-year OS rate, %	68.9	71.3	
3-year OS rate, %	42.0	43.2	
5-year OS rate, %	33.2	35.0	
Median RFS, 95% CI	8.8 (7.2–10.4)	9.8 (6.3–13.3)	0.632
1-year RFS rate, %	44.0	41.4	
3-year RFS rate, %	28.3	27.3	
5-year RFS rate, %	20.8	20.0	

Abbreviations: OS, overall survival; RFS, recurrence-free survival; CI, confidence interval.

and RFS among these three subgroups (both *P* < 0.001). Of note, the 1-year OS and RFS rates of those 14 patients who had any 2 of the three risks were only 35.7% and 14.3%, respectively.

Discussion

With aging populations, prolonged life expectancy, and improvements in perioperative management, the number of elderly patients undergoing hepatectomy for HCC in

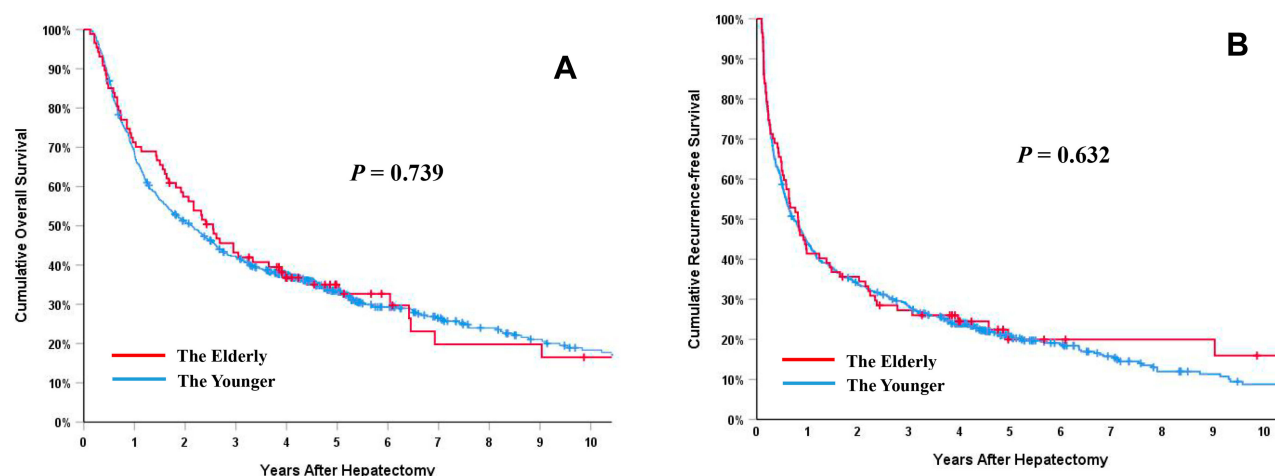


Figure 2 Cumulative incidence of overall survival (OS, **2A**) and recurrence-free survival (RFS, **2B**) curves comparisons between elderly and younger patients (calculated by Log-rank test).

centers around the world has significantly increased in the past three decades.^{5–7,10,18,19} However, the safety and effectiveness of major hepatectomy (≥ 3 segments) for large HCC (≥ 5 cm) among elderly patients have still not been well defined.^{20–22} There are several major areas of concern: 1) more comorbidities and compromised organ functional reserve in the elderly; 2) more complicated

surgical procedure resulting in higher perioperative risks in major hepatectomy; and 3) uncertain long-term survival outcomes for large HCC.

This large multicenter study of 830 patients with large HCC revealed that major hepatectomy can safely be performed in the elderly (≥ 65 years old), with postoperative morbidity and mortality rates similar to younger patients

Table 4 Univariable and Multivariable Cox-Regression Analyses of Risk Factors of Overall Survival After Major Hepatectomy for Large Hepatocellular Carcinoma in the Entire Cohort of the Remaining 806 Patients After Excluding 24 Patients Who Died Within 30 Days After Surgery

Variables	HR Comparison	UV HR (95% CI)	UV P	MV HR (95% CI)	MV P*
Age	Elderly vs Younger	0.96 (0.73–1.25)	0.739	NA	0.676
Sex	Male vs Female	0.99 (0.77–1.27)	0.918		
Co-morbidities	Yes vs No	1.21 (0.82–1.80)	0.340		
ASA score	> 2 vs ≤ 2	1.07 (0.84–1.36)	0.573		
Etiology of liver diseases	HBV vs Non-HBV	1.29 (0.97–1.71)	0.078	NA	0.414
Cirrhosis	Yes vs No	1.29 (1.07–1.56)	0.007	NA	0.436
Portal hypertension	Yes vs No	1.49 (1.21–1.83)	< 0.001	NA	0.207
Child–Pugh grade	B vs A	1.23 (0.94–1.61)	0.139		
Preoperative AFP level	> 400 vs ≤ 400 $\mu\text{g/L}$	1.79 (1.51–2.12)	< 0.001	1.53 (1.29–1.82)	< 0.001
Maximum tumor size	≥ 10 vs 5.0–9.9 cm	1.23 (1.04–1.46)	0.015	NA	0.673
Multiple tumors (≥ 3 nodules)	Yes vs No	1.93 (1.58–2.34)	< 0.001	NA	0.147
Satellite nodules	Yes vs No	2.09 (1.77–2.47)	< 0.001	1.75 (1.48–2.08)	< 0.001
Poor tumor differentiation	Yes vs No	0.96 (0.80–1.16)	0.686		
Macrovascular invasion	Yes vs No	2.97 (2.48–3.56)	< 0.001	2.48 (2.06–2.99)	< 0.001
Microvascular invasion	Yes vs No	1.68 (1.41–2.01)	< 0.001	2.30 (1.91–2.76)	< 0.001
Incomplete tumor encapsulation	Yes vs No	2.20 (1.81–2.69)	< 0.001	NA	0.214
Intraoperative blood loss	> 600 vs ≤ 600 mL	1.46 (1.24–1.73)	< 0.001	NA	0.725
Intraoperative blood transfusion	Yes vs No	1.47 (1.24–1.74)	< 0.001	2.34 (1.13–1.58)	0.001
Resection margin	< 1 vs ≥ 1 cm	2.30 (1.91–2.77)	< 0.001	NA	0.062

Notes: *As the most important variable, age was forced into multivariable Cox-regression model; apart from age, other variables with a P value < 0.1 in univariable analysis were subjected to multivariable Cox-regression model.

Abbreviations: ASA, American Society of Anesthesiologists; HBV, hepatitis B virus; AFP, alpha-fetoprotein; CI, confidence interval; HR, hazard ratio; UV, univariable; MV, multivariable; NA, not available.

Table 5 Univariable and Multivariable Cox-Regression Analyses of Risk Factors of Recurrence-Free Survival After Major Hepatectomy for Large Hepatocellular Carcinoma in the Entire Cohort of the Remaining 806 Patients After Excluding 24 Patients Who Died Within 30 Days After Surgery

Variables	HR Comparison	UV HR (95% CI)	UV P	MV HR (95% CI)	MV P*
Age	Elderly vs Younger	0.94 (0.73–1.21)	0.632	NA	0.266
Sex	Male vs Female	1.06 (0.84–1.33)	0.646		
Co-morbidities	Yes vs No	1.09 (0.75–1.57)	0.655		
ASA score	> 2 vs ≤ 2	0.98 (0.78–1.23)	0.851		
Etiology of liver diseases	HBV vs Non-HBV	1.45 (1.12–1.89)	0.006	NA	0.891
Cirrhosis	Yes vs No	1.23 (1.03–1.46)	0.019	NA	0.606
Portal hypertension	Yes vs No	1.36 (1.12–1.66)	0.002	NA	0.222
Child–Pugh grade	B vs A	1.42 (1.11–1.82)	0.005	NA	0.202
Preoperative AFP level	> 400 vs ≤ 400 µg/L	1.80 (1.54–2.11)	<0.001	1.54 (1.31–1.81)	< 0.001
Maximum tumor size	≥ 10 vs 5.0–9.9 cm	1.24 (1.06–1.45)	0.006	NA	0.806
Multiple tumors (≥ 3 nodules)	Yes vs No	1.79 (1.48–2.16)	<0.001	NA	0.276
Satellite nodules	Yes vs No	1.92 (1.64–2.24)	<0.001	1.51 (1.28–1.78)	< 0.001
Poor tumor differentiation	Yes vs No	1.16 (0.97–1.39)	0.098	NA	0.745
Macrovascular invasion	Yes vs No	2.82 (2.37–3.35)	<0.001	2.14 (1.76–2.46)	< 0.001
Microvascular invasion	Yes vs No	1.69 (1.43–1.99)	<0.001	1.62 (1.34–1.95)	< 0.001
Incomplete tumor encapsulation	Yes vs No	2.00 (1.68–2.39)	<0.001	NA	0.179
Intraoperative blood loss	> 600 vs ≤ 600 mL	1.46 (1.25–1.71)	<0.001	NA	0.706
Intraoperative blood transfusion	Yes vs No	1.42 (1.22–1.67)	<0.001	1.27 (1.08–1.49)	0.003
Resection margin	< 1 vs ≥ 1 cm	2.00 (1.69–2.36)	<0.001	2.08 (1.76–2.46)	< 0.001

Notes: *As the most important variable, age was forced into multivariable Cox-regression model; apart from age, other variables with a *P* value <0.1 in univariable analysis were subjected to multivariable Cox-regression model.

Abbreviations: ASA, American Society of Anesthesiologists; HBV, hepatitis B virus; AFP, alpha-fetoprotein; CI, confidence interval; HR, hazard ratio; UV, univariable; MV, multivariable; NA, not available.

of <65 years old; moreover, elderly patients can benefit from major hepatectomy for large HCC, with long-term OS and RFS outcomes similar to younger patients. This study supports the findings that age by itself is not a contraindication to major hepatectomy of large HCC, with oncological benefits and an acceptable safety profile. Major hepatectomy should be offered to selected elderly patients with large HCC. The present study on analyzing the prognostic factors of OS and RFS in the elderly cohort demonstrated that preoperative AFP level >400 µg/L, multiple tumors (≥3 tumor nodules) and macrovascular invasion were independently associated with decreased OS and RFS in elderly patients after major hepatectomy for large HCC. These data are helpful in the surgical decision-making in selecting patients for surgery and in assessing whether adjuvant therapy should be considered for elderly patients with large HCC. To our knowledge, this is the first study to evaluate specifically surgical safety and long-term survival outcomes in elderly patients who underwent major hepatectomy for large HCC. The results from this Multicenter cooperative study may lead to a more widely accepted consensus on the role of major hepatectomy in elderly patients with large HCC.

Malignancies are often considered to be a disease associated with aging.^{23,24} The probability of developing a malignant tumor in the elderly is higher than in younger populations. The risk of developing HCC is higher among patients over 60~70 years old, and most elderly patients with HCC should have a background of cirrhosis. However, in this study, the proportion of cirrhosis among the elderly in the entire cohort was lower than younger patients (64.1% vs 72.4%, *P* = 0.111). This is probably related to patient selection during surgical decision-making.

Some tumor-related factors, such as preoperative AFP level >400 µg/L, satellite nodules, macrovascular invasion, and microvascular invasion as identified in the entire cohort of this study were independently associated with decreased OS and RFS after major hepatectomy for large HCC. They have also been demonstrated by previously reported studies to be high-risk factors.^{25–27} In addition, the surgery-related variable of intraoperative blood transfusion was also identified in this study to be independent risk factors associated with OS and RFS. A possible explanation is that allogenic blood transfusion induces immunosuppression and decreases natural-killer cell and/or

Table 6 Univariable and Multivariable Cox-Regression Analyses of Risk Factors of Overall Survival After Major Hepatectomy for Large Hepatocellular Carcinoma in the 87elderly Patients

Variables	HR Comparison	UV HR (95% CI)	UV P	MV HR (95% CI)	MV P*
Age	≥ 75 vs 65–74 years	0.77 (0.31–1.93)	0.578	NA	0.556
Sex	Male vs Female	0.74 (0.36–1.50)	0.406		
Co-morbidities	Yes vs No	1.13 (0.56–2.30)	0.727		
ASA score	> 2 vs ≤ 2	1.12 (0.67–1.86)	0.660		
Etiology of liver diseases	HBV vs Non-HBV	2.21 (1.19–4.10)	0.012		
Cirrhosis	Yes vs No	1.16 (0.68–2.00)	0.586	1.84 (1.04–3.26)	0.037
Portal hypertension	Yes vs No	1.29 (0.67–2.49)	0.444		
Child–Pugh grade	B vs A	1.38 (0.55–3.47)	0.487		
Preoperative AFP level	> 400 vs ≤ 400 µg/L	2.20 (1.27–3.82)	0.005	2.07 (1.18–3.62)	0.001
Maximum tumor size	≥ 10 vs 5.0–9.9 cm	0.82 (0.49–1.36)	0.434		
Multiple tumors (≥3 nodules)	Yes vs No	2.43 (1.31–4.54)	0.005	NA	0.750
Satellite nodules	Yes vs No	2.30 (1.34–3.94)	0.003	3.01 (1.58–5.74)	0.011
Poor tumor differentiation	Yes vs No	1.25 (0.73–2.17)	0.417		
Macrovascular invasion	Yes vs No	2.68 (1.55–4.62)	<0.001		
Microvascular invasion	Yes vs No	1.76 (1.04–2.97)	0.036	NA	0.214
Incomplete tumor encapsulation	Yes vs No	3.75 (2.03–6.95)	<0.001	NA	0.245
Intraoperative blood loss	> 600 vs ≤ 600 mL	1.25 (0.75–2.08)	0.388	NA	0.341
Intraoperative blood transfusion	Yes vs No	1.14 (0.69–1.89)	0.609		
Resection margin	< 1 vs ≥ 1 cm	1.61 (0.938–2.77)	0.084		

Notes: *All variables with a P value <0.1 in univariable analysis were subjected to multivariable Cox-regression model.

Abbreviations: ASA, American Society of Anesthesiologists; HBV, hepatitis B virus; AFP, alpha-fetoprotein; CI, confidence interval; HR, Hazard ratio; UV, univariable; MV, multivariable; NA, not available.

Table 7 Univariable and Multivariable Cox-Regression Analyses of Risk Factors of Recurrence-Free Survival After Major Hepatectomy for Large Hepatocellular Carcinoma in the 87 Elderly Patients

Variables	HR Comparison	UV HR (95% CI)	UV P	MV HR (95% CI)	MV P*
Age	≥ 75 vs 65–74 years	0.68 (0.27–1.71)	0.415	NA	0.156
Sex	Male vs Female	0.69 (0.36–1.31)	0.257		
Co-morbidities	Yes vs No	0.94 (0.46–1.89)	0.855		
ASA score	> 2 vs ≤ 2	0.90 (0.56–1.47)	0.685		
Etiology of liver diseases	HBV vs Non-HBV	2.39 (1.35–4.23)	0.003		
Cirrhosis	Yes vs No	1.49 (0.89–2.48)	0.130	1.82 (1.03–3.22)	0.040
Portal hypertension	Yes vs No	1.85 (0.94–4.25)	0.142		
Child–Pugh grade	B vs A	1.76 (0.87–4.71)	0.201		
Preoperative AFP level	> 400 vs ≤ 400 µg/L	1.81 (1.08–3.03)	0.026	NA	0.096
Maximum tumor size	≥ 10 vs 5.0–9.9 cm	0.85 (0.53–1.37)	0.512	2.47 (1.37–4.44)	0.003
Multiple tumors (≥ 3 nodules)	Yes vs No	1.89 (1.02–3.53)	0.045		
Satellite nodules	Yes vs No	2.48 (1.46–4.22)	0.001	NA	0.851
Poor tumor differentiation	Yes vs No	1.68 (0.99–2.88)	0.056		
Macrovascular invasion	Yes vs No	3.57 (2.06–6.19)	< 0.001		
Microvascular invasion	Yes vs No	2.15 (1.31–3.55)	0.003	1.85 (1.06–3.21)	0.029
Incomplete tumor encapsulation	Yes vs No	3.21 (1.84–5.57)	< 0.001	NA	0.297
Intraoperative blood loss	> 600 vs ≤ 600 mL	1.41 (0.87–2.28)	0.164	NA	0.297
Intraoperative blood transfusion	Yes vs No	1.21 (0.75–1.96)	0.428		
Resection margin	< 1 vs ≥ 1 cm	1.41 (0.89–2.67)	0.167		

Notes: *All variables with a P value <0.1 in univariable analysis were subjected to multivariable Cox-regression model.

Abbreviations: ASA, American Society of Anesthesiologists; HBV, hepatitis B virus; AFP, alpha-fetoprotein; CI, confidence interval; HR, hazard ratio; UV, univariable; MV, multivariable; NA, not available.

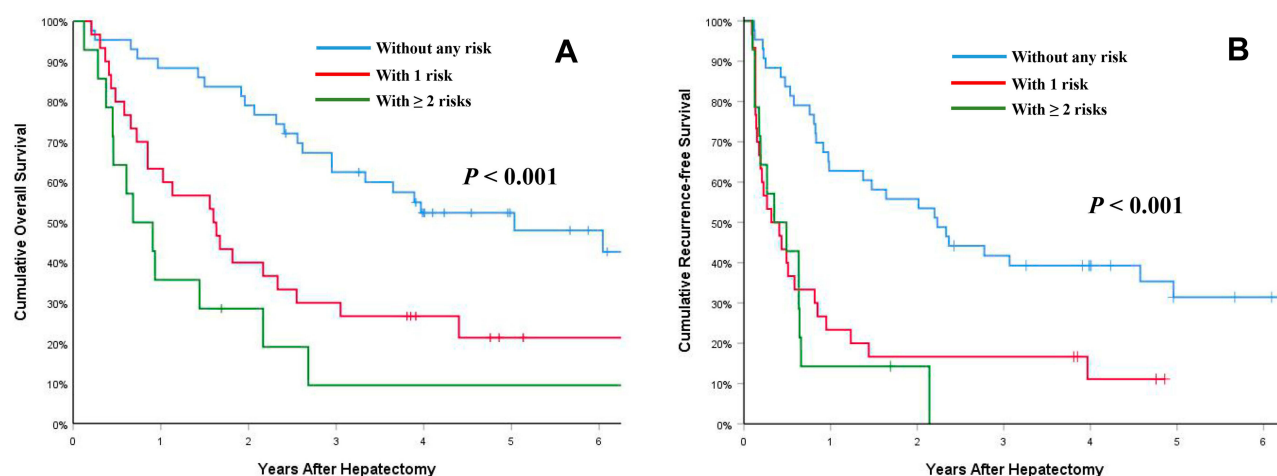


Figure 3 Cumulative incidence of overall survival (OS, **3A**) and recurrence-free survival (RFS, **3B**) curves comparisons among three subgroups of the elderly patients (calculated by Log-rank test).

helper T-cell activities.²⁸ In fact, the relationship between blood transfusion and long-term prognosis after curative resection of many malignancies, including HCC, remains controversial.^{16,29} Anyway, avoidance of unnecessary blood transfusions is of importance for other reasons like saving costs, avoiding transfusion reactions and transfusion-related acute lung injury, and reducing risks of blood-transmitting diseases.

In this study of 830 patients with large HCC, 25.6% had macrovascular invasion, 64.4% had microvascular invasion, 58.3% were huge (≥ 10 cm), and 19.6% were multiple tumors (≥ 3 tumor nodules). Therefore, it is understandable that the recurrence rate of this cohort was higher than those of previous studies of this kind. As the tumor size increases, the probability of having other advanced malignant pathological characteristics, including macrovascular and microvascular invasion, multiformity, satellite nodules, and incomplete tumor encapsulation, will increase. As shown in Tables 3 and 4, univariable analyses of the entire cohort revealed that there were significant differences of OS and RFS between patients with HCCs of 5.0–9.9 cm and HCCs ≥ 10 cm (HR: 1.23 and 1.24, $P = 0.015$ and 0.006, respectively). However, multivariable Cox-regression analyses did not reveal maximum tumor size (≥ 10 vs 5.0–9.9 cm) as an independent risk factor of OS and RFS, but macrovascular invasion, microvascular invasion and satellite nodules as independent risk factors associated with poorer OS and RFS. In one previous study, for solitary hepatocellular carcinoma without macroscopic vascular invasion, we demonstrated that tumor size did not independently affect long-term OS and RFS after curative

resection.³⁰ As we think, although tumor size is also an important prognostic factor of HCC resection, its effect on a cohort of patients with large HCC (≥ 5 cm) may be somewhat weaker compared with other tumor characteristics, such as macrovascular and microvascular invasion, and satellite nodules, etc.

A deeper understanding of the risk factors associated with long-term oncological survival outcomes in elderly patients subjected to major hepatectomy for HCC can help surgeons on management, decision-making and determine strategies whether to give adjuvant treatment. In the present study, univariable and multivariable Cox-regression analysis performed in the elderly cohort identified four independent risk factors associated with OS and DFS. With the exception of microvascular invasion, these risk factors of preoperative AFP level, tumor number and macrovascular invasion can be identified by preoperative laboratory and imaging examinations. Interestingly, the 14 (16.1%, 14 of 87) patients who had ≥ 2 of these 3 independent risk factors had 1-year OS and RFS rates of only 35.7% and 14.3%, respectively. Thus, for elderly patients with multiple risk factors, the benefit of major hepatectomy for large HCC is questionable. Future studies are required to better define how postoperative molecular-targeted and emerging immunotherapy drugs may be combined with hepatectomy to provide these patients with better survival outcomes.

This study has several limitations. First, this is a retrospective cohort study that had potential inherent biases. Second, patients in the present study were also treated exclusively in China and, therefore, the majority

of patients with HCC had a background of HBV-related cirrhosis. In the United States and Europe,^{31,32} HCV infection and excessive alcohol are the main etiological factors. As such, data from the present study need to be externally validated in Western patients to ensure whether the results are generalizable to other populations of patients.

List of Abbreviations

HCC, hepatocellular carcinoma; OS, overall survival; RFS, recurrence-free survival; ASA, American Society of Anesthesiologists; AFP, alpha-fetoprotein; CT, computed tomography; MRI, magnetic resonance imaging; HBV, hepatitis B virus; HR, hazard ratio; CI, confidence interval; HCV, hepatitis C virus; MV, multivariable; NA, not available; UV, univariable; OR, odds ratio.

Author Contributions

Conception: Zheng-Liang Chen, Cheng-Wu Zhang, Tian Yang, Ying-Jian Liang, Wan Yee Lau; Study design: Ying-Jian Liang, Zheng-Liang Chen, Cheng-Wu Zhang, Lei Liang, Feng Shen; Administrative support: Cheng-Wu Zhang, Meng-Chao Wu, Feng Shen, Ying-Jian Liang, Tian Yang; Data collection and acquisition: Zheng-Liang Chen, Lei Liang, Han Wu, Wan-Guang Zhang, Yong-Yi Zeng, Wei-Min Gu, Ting-Hao Chen, Jie Li, Yao-Ming Zhang, Hong Wang, Ya-Hao Zhou, Chao Li, Yong-Kang Diao; Data analysis: Ying-Jian Liang, Zheng-Liang Chen, Tian Yang, Yong-Kang Diao; Writing-original draft: Zheng-Liang Chen, Lei Liang, Han Wu, Wan-Guang Zhang, Yong-Yi Zeng, Wei-Min Gu, Ting-Hao Chen, Jie Li, Yao-Ming Zhang, Hong Wang, Ya-Hao Zhou, Chao Li, Yong-Kang Diao; Writing-review & editing: Wan Yee Lau, Feng Shen, Meng-Chao Wu, Ying-Jian Liang, Tian Yang; Final approval of manuscript: All authors. All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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