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Original Article

Long-term oncological prognosis after curative-intent liver resection for hepatocellular carcinoma in the young *versus* the elderly: multicentre propensity score-matching study

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Abstract

Background: Hepatocellular carcinoma (HCC) is the most common malignancy in the elderly worldwide, but it is also common among younger individuals in areas with endemic hepatitis B virus infection. The differences in long-term oncological prognosis of young *versus* elderly patients after R0 liver resection for HCC were explored in this study.

Methods: Using a Chinese multicentre database, consecutive patients who underwent R0 liver resection for HCC between 2007 and 2019 were analysed retrospectively. After excluding middle-aged (36–69 years old) patients, overall survival (OS), cancer-specific survival (CSS), and recurrence were compared between young (35 years or younger) and elderly (70 years or older) patients using propensity score matching (PSM).

Results: Among 531 enrolled patients, there were 192 (36.2 per cent) and 339 (63.8 per cent) patients categorized as young and elderly respectively. PSM created 140 pairs of matched patients. In the PSM cohort, 5-year OS was comparable for young *versus* elderly patients (51.7 *versus* 52.3 per cent, $P = 0.533$). Young patients, however, had a higher 5-year cumulative recurrence rate (62.1 *versus* 51.6 per cent, $P = 0.011$) and a worse 5-year CSS rate (54.0 *versus* 64.3 per cent, $P = 0.034$) than elderly patients. On multivariable Cox regression analyses, young patient age remained independently associated with an increased recurrence rate (hazard ratio 1.62, $P = 0.016$) and a decreased CSS rate (hazard ratio 1.69, $P = 0.021$) compared with older age.

Conclusion: Following R0 liver resection for HCC, younger patients were at a higher risk of recurrence, and elderly patients had a better CSS rate. Thus, enhanced surveillance for HCC recurrence should be implemented for young patients.

Introduction

Among solid malignancies in the elderly, hepatocellular carcinoma (HCC) is most common worldwide: the highest age-specific incidence of HCC is observed in persons aged over 70 years in developed countries[1]. HCC is also common, however, among young patients in areas endemic for hepatitis B virus (HBV) infection, including China and Korea[2,3]. Partial hepatectomy remains the most commonly used primary treatment modality with curative intent for HCC in appropriately selected patients[4,5]. Long-term prognosis after R0 liver resection for HCC remains unsatisfactory due to the high risk of postoperative recurrence: less than half of patients are alive more than 5 years after surgery. Efforts to identify risk factors associated with oncological prognosis are critical to improve long-term survival for patients who elect to undergo partial hepatectomy for HCC[6].

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Previous studies have identified age difference at disease presentation to be associated with postoperative long-term prognosis for some malignancies including gastric cancer, breast cancer and colorectal cancer[7–11]. Theuer and colleagues[11] reported that young patients (35 years and younger) with gastric cancer had more aggressive tumour characteristics and worse overall survival (OS) after radical resection than elderly patients (65 years and older). Similar results were identified between young (40 years and younger) and older (more than 40 years) patients with breast cancer[8]. The few studies on HCC that have investigated the impact of age on long-term postoperative prognosis after R0 liver resection have demonstrated varying results[12–32]. For example, Huang and colleagues[24] compared long-term survival after R0 liver resection for HCC among the elderly (67 patients) *versus* non-elderly (268 patients), using 70 years as a cut-off, and concluded that long-term survival of the elderly was more favourable than that of the non-elderly (5-year OS rate: 43.2 *versus* 31.4 per cent, $P = 0.017$). In contrast, in a study by Takeishi and co-workers[16] young (40 years and younger, 13 patients) and older (more than 40 years, 246 patients) patients had a comparable long-term oncological prognosis (5-year disease-free survival rate: 38.1 *versus* 36.9 per cent, $P = 0.762$) after HCC resection. The reason for these disparate results is likely to be multifactorial. The analysis of age as a binary variable (dividing groups into either elderly *versus* non-elderly[24–31] or young *versus* non-young groups[14–18,21,23,32]) with different cut-off values may have contributed to different findings[12–32]. In addition, a higher proportion of non-cancer-specific death occurs in the elderly than in the young; as such, analysis of only OS to determine oncological prognosis may be inadequate[12–17,19–25,27–32]. Furthermore, previous studies failed to exclude early postoperative deaths (up to 90 days after surgery) in the survival analyses, which can introduce bias[12–32]. To date, the overwhelming number of studies were also single-centre studies[12,14–16,18,19,22,24–32] with relatively small sample sizes (less than 100 patients either in the young or elderly groups)[12–20,22–26,29,31,32].

The objective of this multicentre study was to compare differences in long-term OS, cancer-specific survival (CSS), and recurrence after R0 liver resection of HCC among young (35 years and younger) *versus* elderly (70 years and older) patients. Propensity score matching (PSM) was used to balance the baseline characteristics between the two groups.

Methods

Study population

Patients who underwent partial hepatectomy with curative intent for HCC between 2007 and 2019 at 11 hospitals in China (the First Affiliated Hospital of Nantong University, Eastern Hepatobiliary Surgery Hospital, the Affiliated People's Hospital of Ningbo University, Zhejiang Provincial People's Hospital, the First Affiliated Hospital of Soochow University, Changzheng Hospital, the First Affiliated Hospital of Harbin Medical University, Pu'er People's Hospital, Liuyang People's Hospital, the Fourth Hospital of Harbin and Fuyang People's Hospital) were enrolled. Curative partial hepatectomy was defined as R0 liver resection, with complete resection of all microscopic and macroscopic tumours. Based on previous studies,[22,24,25,33] patients younger than 35 years old were defined as young, while individuals older than 70 years at the time of diagnosis were categorized as elderly.

Exclusion criteria included: age less than 13 years old; age between 36 and 69 years old (middle-aged); recurrent HCC; palliative liver resection (R1 or R2 resection); combined HCC–cholangiocarcinoma; early postoperative deaths (up to 90 days after surgery); loss to follow-up within 6 months after surgery; and missing data on important prognostic variables. The study was conducted in accordance with the Declaration of Helsinki and the Ethical Guidelines for Clinical Studies and was approved by the Institutional Review Boards at the participating hospitals.

Clinical characteristics and operative variables

Patient clinical characteristics included age, sex, co-morbidities, ASA score, HBV infection status, cirrhosis, portal hypertension, Child–Pugh grading, preoperative alanine aminotransferase (ALT), aspartate transaminase (AST) and alpha-fetoprotein (AFP) levels, maximum tumour size, tumour number, macrovascular and microvascular invasion, satellite nodules, tumour differentiation, tumour encapsulation, and tumour staging as determined by the 8th tumour node metastasis (TNM) staging system[34]. Operative variables included intraoperative blood loss, intraoperative blood transfusion, extent of hepatectomy (minor or major) and resection margin status. Co-morbidities included hypertension, diabetes mellitus, chronic obstructive pulmonary disease, renal dysfunction and cardiovascular diseases. Portal hypertension was defined as presence of splenomegaly with a decreased platelet count (less than or equal to 100×10^9/l) and/or oesophageal varices. Major hepatectomy was defined as partial hepatectomy of three or more Couinaud's liver segments, and minor hepatectomy as fewer than three segments.

Follow-up

Patients were regularly followed-up at each participating hospital. Surveillance strategies for postoperative recurrence consisted of serum AFP level, ultrasonography, or contrast-enhanced MRI or CT at 2- or 3-monthly intervals for the first 6 months, 3-monthly intervals for the next 18 months, and then 3- to 6-monthly thereafter. When HCC recurrence was suspected, contrast-enhanced MRI or CT scan, pulmonary CT scan, bone scintigraphy or PET were performed as indicated clinically. HCC recurrences were defined as new appearances of intrahepatic or extrahepatic tumour nodule(s), with typical imaging characteristics consistent with HCC on contrast-enhanced MRI or CT, with or without a rise in AFP level. The dates of initial recurrence, last follow-up, death, initial recurrence sites (intrahepatic and/or extrahepatic) and causes of death (cancer-specific or non-cancer-specific) were recorded. The causes of non-cancer-specific death included hepatic failure or upper gastrointestinal haemorrhage in patients with liver cirrhosis, cardiovascular or cerebrovascular accidents, and natural death due to aging without any specific reasons.

Study endpoints and propensity score matching

The primary endpoints of this study relating to long-term oncological prognosis after partial hepatectomy for HCC included OS, CSS and recurrence. OS was calculated from the date of partial hepatectomy to the date of death from any cause and patients were censored at the date of last follow-up if alive. CSS was calculated from the date of partial hepatectomy to either the date of cancer-specific death, and censored at the date of last follow-up if alive or death for non-cancer-specific death. Cumulative recurrence rate, that is time to recurrence, was calculated from the date of partial hepatectomy to the date of detection of initial recurrence of HCC, and censored at the date of last follow-up or death from any cause without a recurrence.

To balance differences in the baseline characteristics due to selection bias between the young and the elderly, the PSM method

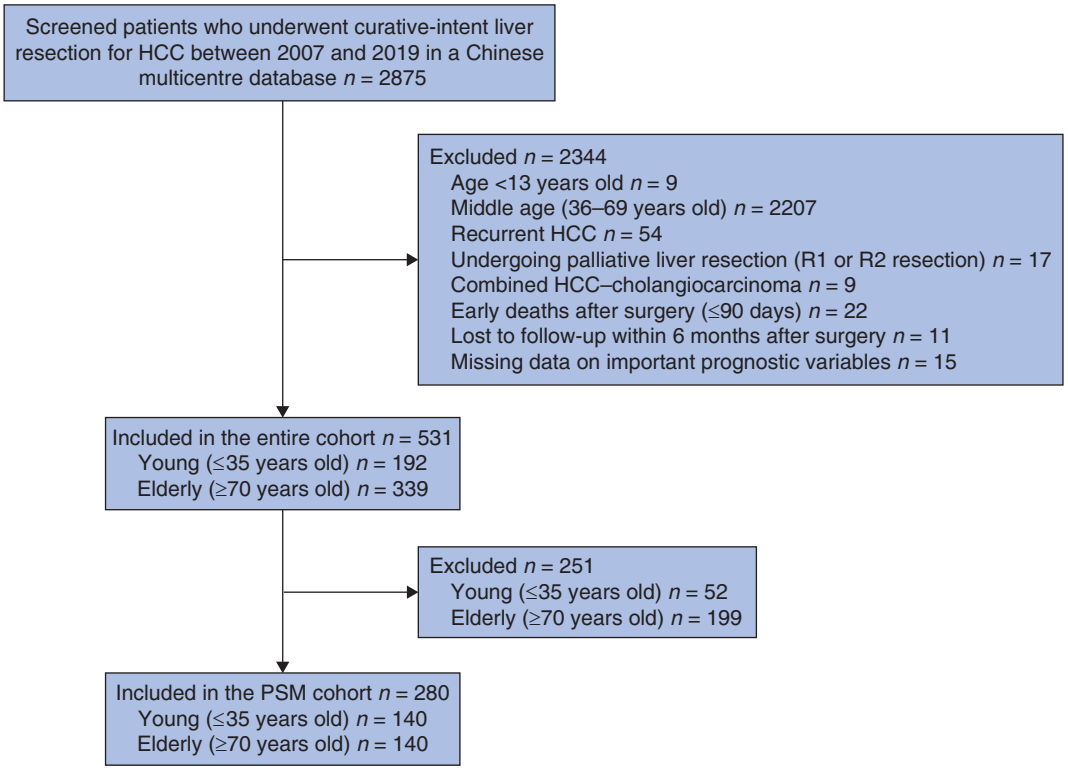

Fig. 1 Selection of the study population

HCC, hepatocellular carcinoma; PSM, propensity score-matching.

as described by Rubin and Rosenbaum[35,36] was used. The PSM model provided one-to-one matching between the two groups on liver- and tumour-related characteristics. Co-variables in this model included sex, liver-related variables (HBV infection, cirrhosis, portal hypertension, Child–Pugh grading, and preoperative ALT and AST levels), and tumour-related variables (preoperative AFP level, maximum tumour size, tumour number, macrovascular and microvascular invasion, satellite nodules, tumour differentiation and tumour encapsulation). As ASA score and co-morbidities are intrinsic variables that are known to be related to age, these variables were not matched in the PSM model in this study. The matching process has been described in the authors' previous studies[37–39].

Statistical analysis

Statistical analyses were carried out using SPSS®, version 25.0 (IBM, Armonk, New York, USA). Categorical variables were expressed as number or proportion, while continuous variables were expressed as mean(s.d.) or median (range). Continuous variables were compared using student's *t* test and categorical variables were compared using the Fisher's exact test or the χ^2 test, as appropriate. The OS, CSS and cumulative recurrence rates before and after PSM were compared between the young and the elderly groups using Kaplan–Meier curves generated by the log rank or Breslow tests. Univariable and multivariable Cox proportional hazard regression analyses were used with a forward stepwise variable selection. Variables with $P < 0.100$ on univariable analysis were included in multivariable analysis. As age was the topic of this study, this variable was forced into the multivariable model. $P < 0.050$ was considered statistically significant.

Results

Using the inclusion and exclusion criteria, 531 patients who underwent R0 liver resection for HCC during the study period were identified (*Fig. 1*). There were 192 young patients (36.2 per cent) and 339 elderly patients (63.8 per cent) with median ages of 31 (range: 14–35) years, and 74 (range: 70–93) years respectively. PSM created 140 pairs of young and elderly patients.

Comparisons of baseline characteristics

Comparisons of patient clinical characteristics and operative variables in the two groups before and after PSM are shown in *Table 1*. In the PSM cohort, there were no significant differences between young and elderly patients in all the liver- and tumour-related variables (all $P > 0.2$), apart from an ASA score greater than 2 (4.3 *versus* 42.9 per cent, $P < 0.001$) and presence of co-morbidities (2.1 *versus* 28.6 per cent, $P < 0.001$).

Comparisons of long-term oncological prognosis

Comparisons of long-term oncological outcomes between the young and the elderly groups before and after PSM are shown in *Table 2*. The overall incidences of recurrence in the young group were significantly higher than in the elderly group, both before (67.7 *versus* 37.5 per cent, $P < 0.001$) and after PSM (64.3 *versus* 45.7 per cent, $P = 0.002$). During follow-up, the overall mortality rates were comparable between the young and the elderly groups both before (57.8 *versus* 55.8 per cent, $P = 0.645$) and after PSM (55.7 *versus* 54.3 per cent, $P = 0.810$). However, the cancer-specific mortality rates in the young group were higher than in the elderly group both before and after PSM (52.1 *versus* 28.3 per cent before PSM, and 49.3 *versus* 35.7 per cent after PSM, both $P < 0.05$). In

Table 1 Comparisons of patients' clinical characteristics and operative variables between the young and the elderly before and after propensity score matching

	Entire cohort			PSM cohort		
	Young† ($n = 192$)	Elderly‡ ($n = 339$)	P§	Young† ($n = 140$)	Elderly‡ ($n = 140$)	P§
Age (years)*	30.1 (4.4)	75.0 (4.6)	<0.001	29.9 (4.4)	72.9 (3.8)	<0.001
Male sex	164 (85.4)	270 (79.6)	0.098	120 (85.7)	113 (80.7)	0.337
Co-morbidities	4 (2.1)	106 (31.3)	<0.001	3 (2.1)	40 (28.6)	<0.001
ASA score >2	7 (3.6)	126 (37.2)	<0.001	6 (4.3)	60 (42.9)	<0.001
HBV positive	182 (94.8)	234 (69.0)	<0.001	130 (92.9)	124 (88.6)	0.303
Cirrhosis	130 (67.7)	207 (61.1)	<0.126	97 (69.3)	91 (65.0)	0.525
Portal hypertension	43 (22.4)	52 (15.3)	0.042	33 (23.6)	27 (19.3)	0.467
Child–Pugh grade B	14 (7.3)	13 (3.8)	0.081	9 (6.4)	8 (5.7)	1.000
Preoperative ALT level >40 U/l	76 (41.5)	41 (32.0)	0.089	47 (35.6)	33 (40.7)	0.469
Preoperative AST level >40 U/l	82 (44.8)	45 (35.2)	0.088	58 (43.9)	33 (40.7)	0.671
Preoperative AFP level >400 μg/l	108 (56.3)	116 (34.2)	<0.001	63 (45.0)	62 (44.3)	1.000
Maximum tumour size >5 cm	112 (58.3)	148 (43.7)	0.001	67 (47.9)	77 (55.0)	0.232
Multiple tumours	27 (14.1)	30 (8.8)	0.062	18 (12.9)	14 (10.0)	0.574
Macrovascular invasion	28 (14.6)	18 (5.3)	<0.001	19 (13.6)	14 (10.0)	0.459
Microvascular invasion	92 (47.9)	103 (30.4)	<0.001	60 (42.9)	62 (44.3)	0.904
Satellite nodules	51 (26.6)	52 (15.3)	0.002	31 (22.1)	26 (18.6)	0.553
Poor tumour differentiation	130 (67.7)	217 (64.0)	0.390	91 (65.0)	89 (63.6)	0.901
Incomplete tumour envelope	105 (54.7)	252 (74.3)	<0.001	80 (57.1)	88 (62.9)	0.393
TNM stage[34]						
I	89 (46.4)	204 (60.2)	<0.001	70 (50.0)	72 (51.4)	0.295
II	47 (24.5)	96 (28.3)		34 (24.3)	44 (31.4)	
III–IV	56 (29.2)	39 (11.5)		36 (25.7)	24 (17.1)	
BCLC stage						
0/A	101 (52.6)	221 (65.2)	0.004	79 (56.4)	87 (62.1)	0.330
B/C	91 (47.4)	118 (34.8)		61 (43.6)	53 (37.9)	
Resection margin <1 cm	88 (45.8)	183 (54.0)	0.071	60 (42.9)	71 (50.7)	0.231
Intraoperative blood loss >400 ml	77 (42.1)	50 (39.1)	0.595	50 (37.9)	38 (46.9)	0.201
Intraoperative blood transfusion	47 (24.5)	57 (16.8)	0.032	28 (20.0)	29 (20.7)	1.000
Major hepatectomy	64 (33.3)	65 (19.2)	<0.001	41 (29.3)	33 (23.6)	0.343

Values in parentheses are percentages unless stated otherwise; *values are mean(s.d.). †35 years or younger; ‡70 years or older. §Continuous variables were compared using the student's *t* test and categorical variables were compared using the Fisher's exact test or the $\chi 2$ test, as appropriate. PSM, propensity score matching; HBV, hepatitis B virus; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AFP, alpha-fetoprotein; TNM, tumour node metastasis; BCLC, Barcelona Clinic Liver Cancer.

Table 2 Comparisons of long-term oncological outcomes between the young and the elderly before and after propensity score matching

	Entire cohort			PSM cohort		
	Young‡ ($n = 192$)	Elderly§ ($n = 339$)	P**	Young‡ ($n = 140$)	Elderly§ ($n = 140$)	P**
Period of follow-up (months)*	51.2 (40.2)	53.7 (36.0)	0.471	53.3 (41.2)	51.6 (35.8)	0.711
Recurrence during follow-up	130 (67.7)	127 (37.5)	<0.001	90 (64.3)	64 (45.7)	0.002
Site of initial recurrence						
Intrahepatic	88 (45.8)	111 (32.7)	0.003	59 (42.1)	56 (40.7)	0.808
Extrahepatic	12 (6.3)	5 (1.5)	0.003	9 (6.4)	1 (0.7)	0.010
Intrahepatic and extrahepatic	30 (15.6)	11 (3.2)	<0.001	22 (15.7)	6 (4.3)	0.001
Death during follow-up	111 (57.8)	189 (55.8)	0.645	78 (55.7)	76 (54.3)	0.810
Cancer-specific death	100 (52.1)	96 (28.3)	<0.001	69 (49.3)	50 (35.7)	0.022
Non-cancer-specific death	11 (5.7)	93 (27.4)	<0.001	9 (6.4)	26 (18.6)	0.002
OS						
Median OS (months)†	57.0 (47.3–66.7)	65.8 (55.6–76.0)	0.064	63.2 (49.3–77.1)	72.5 (55.4–89.6)	0.533
1-year OS rate (%)	80.2	89.0		81.4	87.3	
3-year OS rate (%)	62.2	71.1		65.4	69.9	
5-year OS rate (%)	49.1	53.9		51.7	52.3	
CSS						
Median CSS (months)†	63.2 (39.4–87.0)	144.9 (110.9–178.9)	<0.001	67.0 (29.1–104.9)	119.3 (71.3–167.3)	0.034
1-year CSS rate (%)	80.2	94.9		81.4	91.4	
3-year CSS rate (%)	62.7	83.3		66.1	77.3	
5-year CSS rate (%)	50.8	71.5		54.0	64.3	
TTR						
Median TTR (months)†	23.2 (11.3–35.1)	145.1 (46.5–243.7)	<0.001	34.6 (17.4–51.8)	59.5 (16.4–102.6)	0.011
1-year TTR rate (%)	43.6	17.3		38.4	27.2	
3-year TTR rate (%)	56.9	34.7		51.5	43.1	
5-year TTR rate (%)	66.3	43.3		62.1	51.6	

Values in parentheses are percentages unless stated otherwise; *values are mean(s.d.), †values are median (95 per cent confidence intervals). ‡35 years or younger; §70 years or older. **Continuous variables were compared using the student's *t* test and categorical variables were compared using the Fisher's exact test or the $\chi 2$ test, as appropriate. PSM, propensity score matching; OS, overall survival; CSS, cancer-specific survival; TTR, time to recurrence.

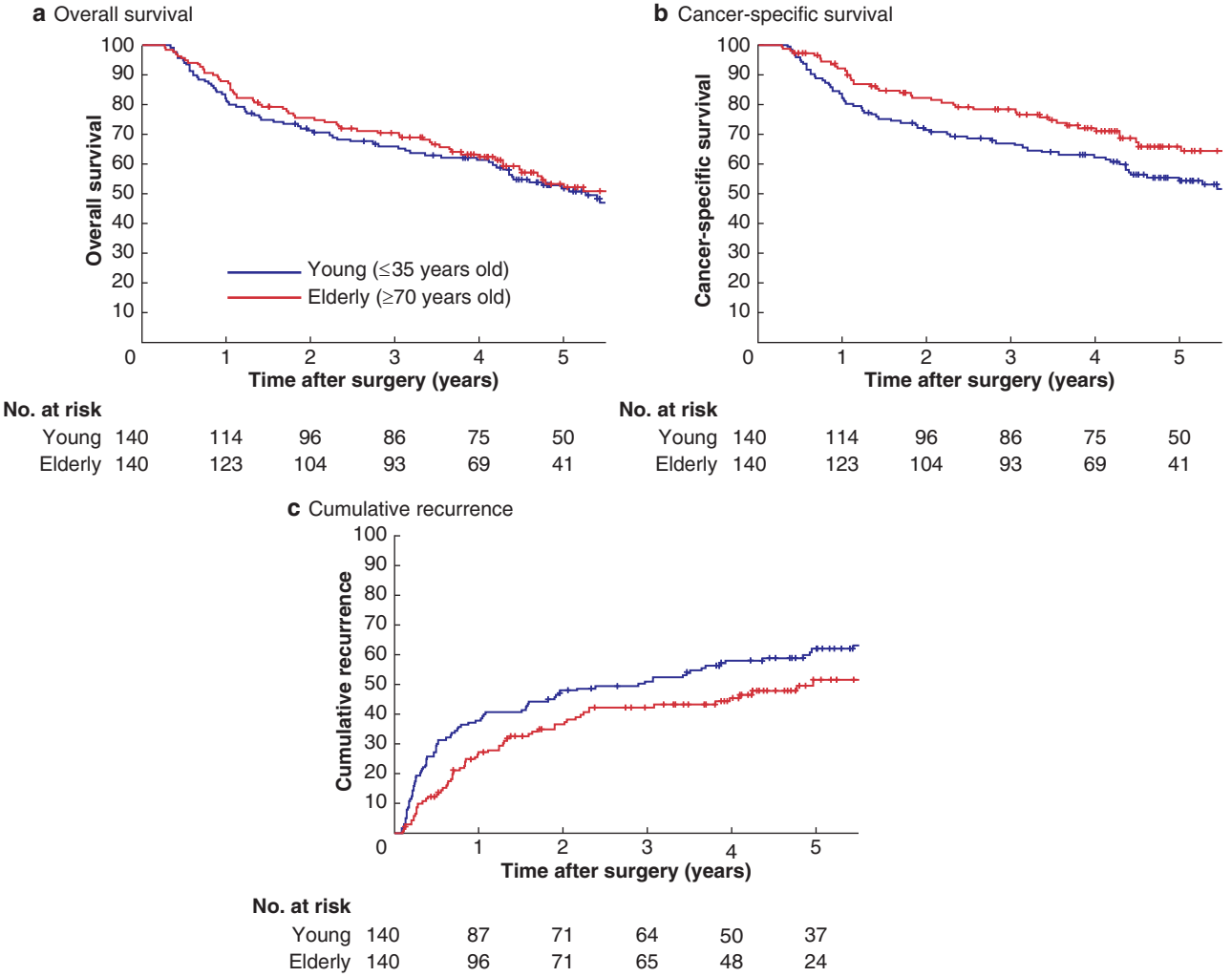

Fig. 2 Kaplan–Meier curves comparing the young and the elderly in the propensity score-matched cohort
a Cumulative incidence of overall survival ($P = 0.533$). **b** Cancer-specific survival ($P = 0.034$). **c** Cumulative recurrence ($P = 0.011$).

contrast, the non-cancer-specific mortality rate in the young group was lower than in the elderly group both before and after PSM (5.7 *versus* 27.4 per cent before PSM, and 6.4 *versus* 18.6 per cent after PSM, both $P < 0.01$).

Comparisons of the OS, CSS and cumulative recurrence rates between the young and the elderly groups before PSM are shown in *Figure S1*, and those after PSM are shown in *Fig. 2*. The 5-year OS rates were comparable between the young and the elderly groups both before and after PSM (49.1 *versus* 53.9 per cent before PSM, and 51.7 *versus* 52.3 per cent after PSM, both $P > 0.05$), yet the CCS rates in the young group were worse than in the elderly group (50.8 *versus* 71.5 per cent before PSM, and 54.0 *versus* 64.3 per cent after PSM, both $P < 0.05$). The 5-year cumulative recurrence rates in the young group were higher than in the elderly group both before and after PSM (66.3 *versus* 43.3 per cent before PSM, $P < 0.001$, and 62.1 *versus* 51.6 per cent after PSM, $P = 0.011$).

Univariable and multivariable analyses for OS, CSS and recurrence

Univariable and multivariable Cox regression analyses for predicting OS, CSS, and cumulative recurrence rate in the PSM cohort are shown in *Tables 3–5* respectively. Multivariable analyses revealed that when compared with elderly patients, younger patients remained independently and significantly associated with increased recurrence rate (hazard ratio 1.62, 95 per cent c.i. 1.09 to 2.39, $P = 0.016$), as well as decreased CSS (hazard ratio 1.69, 95 per cent c.i. 1.08 to 2.64, $P = 0.021$), yet there were similar OS rates ($P = 0.126$) after R0 liver resection for HCC.

Discussion

Using a large multicentre database from China, the clinicopathological features and long-term oncological prognosis after R0 liver resection for HCC between the young (35 years and younger) and elderly (at least 70 years old) were characterized and compared. Based on PSM and multivariable Cox regression analyses, young patients had a higher recurrence rate and a worse CSS rate than elderly patients, while the OS rates in the young were comparable to those in the elderly for both the entire and the PSM cohorts. Such differences in survival outcomes on postoperative follow-up can be explained by the significantly higher proportion of non-cancer-specific death in the elderly, while the proportion of cancer-specific deaths is significantly lower than in young patients. Consequently, CSS may be a more meaningful endpoint than OS when considering long-term oncological prognosis in the elderly population. The present study was novel in several ways: middle-aged (36–69 years old) patients and postoperative early deaths (up to 90 days after surgery) were excluded from

Table 3 Univariable and multivariable Cox regression analyses predicting overall survival after partial hepatectomy for hepatocellular carcinoma

Variables	Hazard ratio comparison	Univariable analysis		Multivariable analysis*	
		Hazard ratio	P†	Hazard ratio	P†
Age	Young *versus* elderly	0.98 (0.71, 1.35)	0.901	NS	0.126
Sex	Male *versus* female	0.94 (0.62, 1.44)	0.775		
Co-morbidities	Yes *versus* no	0.98 (0.63, 1.52)	0.916		
ASA score	>2 *versus* ≤2	1.19 (0.83, 1.72)	0.341		
HBV positive	Yes *versus* no	0.93 (0.53, 1.65)	0.807		
Cirrhosis	Yes *versus* no	1.27 (0.90, 1.80)	0.171		
Portal hypertension	Yes *versus* no	1.02 (0.70, 1.48)	0.939		
Child–Pugh grade	B *versus* A	1.75 (1.01, 3.04)	0.047	NS	0.576
Preoperative ALT level	>40 *versus* ≤40 U/l	1.29 (0.89, 1.87)	0.180		
Preoperative AST level	>40 *versus* ≤40 U/l	1.24 (0.86, 1.79)	0.247		
Preoperative AFP level	>400 *versus* ≤400 μg/l	2.29 (1.66, 3.16)	<0.001	2.62 (1.72, 4.01)	<0.001
Maximum tumour size	>5.0 versus ≤5.0 cm	1.94 (1.40, 2.69)	<0.001	1.58 (1.01, 2.48)	0.048
Multiple tumours	Yes *versus* no	3.51 (2.31, 5.35)	<0.001	1.66 (1.07, 2.56)	0.023
Macrovascular invasion	Yes *versus* no	3.72 (2.50, 5.54)	<0.001	3.85 (2.24, 6.59)	<0.001
Microvascular invasion	Yes *versus* no	2.51 (1.82, 3.46)	<0.001	NS	0.586
Satellite nodules	Yes *versus* no	4.20 (2.95, 5.99)	<0.001	1.95 (1.21, 3.14)	0.006
Poor tumour differentiation	Yes *versus* no	1.17 (0.84, 1.65)	0.354		
Incomplete tumour envelope	Yes *versus* no	2.22 (1.56, 3.16)	<0.001	NS	0.249
Resection margin	<1.0 *versus* ≥1.0 cm	1.73 (1.25, 2.37)	0.001	NS	0.245
Intraoperative blood loss	>400 *versus* ≤400 ml	2.38 (1.64, 3.44)	<0.001	1.68 (1.09, 2.61)	0.020
Intraoperative blood transfusion	Yes *versus* no	2.34 (1.64, 3.34)	<0.001	NS	0.794
Extent of hepatectomy	Major *versus* minor	2.09 (1.48, 2.94)	<0.001	NS	0.563

Values in parentheses are 95 per cent confidence intervals. *The variable of age and those variables found significant at $P < 0.100$ in univariable analyses were entered into multivariable Cox regression models. †Continuous variables were compared using the student's *t* test and categorical variables were compared using the Fisher's exact test or the $\chi 2$ test, as appropriate. HBV, hepatitis B virus; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AFP, alpha-fetoprotein; NS, not significant.

Table 4 Univariable and multivariable Cox regression analyses predicting cancer-specific survival after partial hepatectomy for hepatocellular carcinoma

Variables	Hazard ratio comparison	Univariable analysis		Multivariable analysis*	
		Hazard ratio	P†	Hazard ratio	P†
Age	Young *versus* elderly	1.35 (0.94, 1.94)	0.108	1.69 (1.08, 2.64)	0.021
Sex	Male *versus* female	1.01 (0.62, 1.65)	0.979		
Co-morbidities	Yes *versus* no	0.74 (0.42, 1.28)	0.280		
ASA score	>2 *versus* ≤2	1.01 (0.66, 1.55)	0.978		
HBV positive	Yes *versus* no	0.99 (0.52, 1.90)	0.981		
Cirrhosis	Yes *versus* no	1.22 (0.82, 1.80)	0.324		
Portal hypertension	Yes *versus* no	1.09 (0.72, 1.67)	0.678		
Child-Pugh grade	B *versus* A	1.73 (0.93, 3.23)	0.083	NS	0.644
Preoperative ALT level	>40 *versus* ≤40 U/l	1.37 (0.92, 2.03)	0.121		
Preoperative AST level	>40 *versus* ≤40 U/l	1.34 (0.91, 1.98)	0.140		
Preoperative AFP level	>400 *versus* ≤400 μg/l	2.53 (1.75, 3.66)	<0.001	2.84 (1.80, 4.48)	<0.001
Maximum tumour size	>5.0 versus ≤5.0 cm	2.51 (1.71, 3.68)	<0.001	2.21 (1.36, 3.61)	0.001
Multiple tumours	Yes *versus* no	3.69 (2.33, 5.84)	<0.001	1.56 (1.01, 2.41)	0.048
Macrovascular invasion	Yes *versus* no	4.61 (3.01, 7.04)	<0.001	5.12 (2.93, 8.97)	<0.001
Microvascular invasion	Yes *versus* no	3.41 (2.34, 4.97)	<0.001	NS	0.088
Satellite nodules	Yes *versus* no	4.92 (3.34, 7.24)	<0.001	2.04 (1.26, 3.33)	0.004
Poor tumour differentiation	Yes *versus* no	1.32 (0.89, 1.96)	0.163		
Incomplete tumour envelope	Yes *versus* no	2.38 (1.58, 3.57)	<0.001	NS	0.071
Resection margin	<1.0 *versus* ≥1.0 cm	2.09 (1.45, 3.02)	<0.001	NS	0.063
Intraoperative blood loss	>400 *versus* ≤400 ml	2.72 (1.83, 4.04)	<0.001	1.74 (1.10, 2.74)	0.017
Intraoperative blood transfusion	Yes *versus* no	2.54 (1.71, 3.76)	<0.001	NS	0.647
Extent of hepatectomy	Major *versus* minor	2.32 (1.59, 3.39)	<0.001	NS	0.976

Values in parentheses are 95 per cent confidence intervals. *The variable of age and those variables found significant at $P < 0.100$ in univariable analyses were entered into multivariable Cox regression models. †Continuous variables were compared using the student's *t* test and categorical variables were compared using the Fisher's exact test or the $\chi 2$ test, as appropriate. HBV, hepatitis B virus; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AFP, alpha-fetoprotein; NS, not significant.

the analysis; differences in the baseline characteristics between the two groups were balanced by PSM before prognostic analyses; multivariable Cox regression analysis was used to determine any independent correlation between age difference and oncological prognosis; and large sample sizes were used in both the young and the elderly groups (more than 150 patients for each group). These strengthening attributes are a marked improvement over previous reports on this topic, thus providing more robust and credible conclusions to be drawn.

Given the retrospective nature of the study, the major potential bias of the present study is the impossibility of retracing patient-selection criteria *a posteriori*. It is highly plausible that

Table 5 Univariable and multivariable Cox regression analyses predicting time-to-recurrence after hepatectomy for hepatocellular carcinoma

Variables	Hazard ratio comparison	Univariable analysis		Multivariable analysis*	
		Hazard ratio	P†	Hazard ratio	P†
Age	Young *versus* elderly	1.46 (1.06, 2.02)	0.021	1.62 (1.09, 2.39)	0.016
Sex	Male *versus* female	0.79 (0.52, 1.19)	0.250		
Co-morbidities	Yes *versus* no	0.69 (0.41, 1.14)	0.142		
ASA score	>2 *versus* ≤2	0.86 (0.58, 1.27)	0.442		
HBV positive	Yes *versus* no	0.89 (0.52, 1.52)	0.668		
Cirrhosis	Yes *versus* no	1.03 (0.74, 1.45)	0.856		
Portal hypertension	Yes *versus* no	1.08 (0.74, 1.57)	0.696		
Child–Pugh grade	B *versus* A	1.58 (0.87, 2.85)	0.130		
Preoperative ALT level	>40 *versus* ≤40 U/l	1.50 (1.05, 2.13)	0.025	NS	0.426
Preoperative AST level	>40 *versus* ≤40 U/l	1.51 (1.06, 2.13)	0.021	1.45 (1.01, 2.10)	0.048
Preoperative AFP level	>400 *versus* ≤400 μg/l	2.11 (1.53, 2.91)	<0.001	2.23 (1.52, 3.27)	<0.001
Maximum tumour size	>5.0 versus ≤5.0 cm	2.23 (1.61, 3.09)	<0.001	1.91 (1.29, 2.82)	0.001
Multiple tumours	Yes *versus* no	2.66 (1.73, 4.09)	<0.001	1.90 (1.24, 2.89)	0.003
Macrovascular invasion	Yes *versus* no	3.97 (2.65, 5.95)	<0.001	2.99 (1.85, 4.83)	<0.001
Microvascular invasion	Yes *versus* no	3.12 (2.25, 4.32)	<0.001	1.69 (1.12, 2.54)	0.012
Satellite nodules	Yes *versus* no	3.51 (2.47, 4.99)	<0.001	NS	0.467
Poor tumour differentiation	Yes *versus* no	1.54 (1.08, 2.18)	0.016	NS	0.264
Incomplete tumour envelope	Yes *versus* no	2.36 (1.67, 3.34)	<0.001	NS	0.153
Resection margin	<1.0 *versus* ≥1.0 cm	1.93 (1.40, 2.65)	<0.001	NS	0.084
Intraoperative blood loss	>400 *versus* ≤400 ml	1.97 (1.39, 2.79)	<0.001	NS	0.242
Intraoperative blood transfusion	Yes *versus* no	2.01 (1.39, 2.89)	<0.001	NS	0.664
Extent of hepatectomy	Major *versus* minor	1.91 (1.36, 2.68)	<0.001	NS	0.861

Values in parentheses are 95 per cent confidence intervals. *The variable of age and those variables found significant at $P < 0.100$ in univariable analyses were entered into multivariable Cox regression models. †Continuous variables were compared using the student's t test and categorical variables were compared using the Fisher's exact test or the $\chi 2$ test, as appropriate. HBV, hepatitis B virus; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AFP, alpha-fetoprotein; NS, not significant.

only the fit elderly patients were selected to be treated surgically. In the present study, before PSM, many tumour characteristics in young patients who underwent R0 liver resection for HCC were more aggressive than those in elderly patients. As a consequence, the proportion of TNM stage III–IV in the young in the entire cohort was significantly higher than that in the elderly (29.2 *versus* 11.5 per cent, $P < 0.001$). A possible explanation is that young patients with HCC tend to accept a more aggressive approach to undergo partial hepatectomy for a relatively more advanced stage of HCC than elderly patients. Furthermore, surgeons are more inclined to advise only elderly patients with relatively early stages of HCC to undergo surgery. Elderly patients with HCC also tend to have more severe co-morbidities, worse general physical condition, and more liver-related conditions, such as cirrhosis, portal hypertension and poor liver functional status, that preclude them from undergoing partial hepatectomy to treat HCC. It is also possible that the younger but sicker patients are offered surgery but not the elderly patients. Thus, selection biases exist in choosing elderly and young patients for partial hepatectomy for HCC in real-world clinical practice.

Like all other solid malignant tumours, the incidence of HCC increases with advancing age of patients. HCC developing in young patients has a higher tendency to evade the immune surveillance system of the patients, resulting in higher tumour invasiveness and metastatic ability than HCC in elderly patients. In the present study, the young had higher recurrence rates on follow-up than the elderly both before and after PSM. Furthermore, the proportions of patients with intra- and extrahepatic recurrences for the initial recurrence in the young were also significantly higher than in the elderly. The results of this study suggested that future surveillance and management algorithms of HCC for the young should be adjusted differently from those for elderly patients with HCC. Enhanced HCC screening and surveillance at shorter time intervals should be used for young patients who are at a high risk of developing HCC, especially in patients with chronic HBV infection.

The present study has several limitations. First, this was a retrospective study with its inherent biases. As such, PSM was performed in the present study to decrease the potential biases of a retrospective data analysis, although this statistical methodology does not completely eliminate them. Second, as all the enrolled patients came from China, and most patients had a background of HBV-related HCC, the results of this study require external validation in Western cohorts with other HCC aetiological factors, such as hepatitis C virus infection or alcoholic liver to ensure the findings are generalizable to other populations. Third, some previous studies have shown that postoperative overall/major morbidity or postoperative infective complications impacted on long-term survival outcomes after HCC resection[40,41]. The present study focused on the long-term prognosis after HCC resection between the young and the elderly, and patients who died within 90 days after surgery were excluded from the overall cohort before analysis. Early death in most of these patients was caused by major postoperative morbidity. Thus, the multivariable analyses of this study did not include the variable of postoperative major/minor morbidity, similar to previous studies on postoperative prognosis of HCC. Fourth, this study did not include some variables that are related to both old age and oncological prognosis. These variables, including sarcopenia[42], frailty[43] and cancer-related fatigue[44], have been of great research interest in recent years. The authors' future studies on HCC will explore these variables in geriatric oncology using their prospectively collected multicentre database. Last, the potential years of life lost is a popular and interesting concept representing a population-based indicator of the impact of that disease on society[45]. In the future, an in-depth study will be performed on this issue using the authors' population-based data.

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Supplementary material

Supplementary material is available at *BJS Open* online.

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