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

Jia-Le Pu, Zhong Chen, Lan-Qing Yao, Ji-Ye Feng, Yong-Kang Diao, Ming-Cheng Guan, Ju-Dong Li, Zheng-Liang Chen, Ya-Hao Zhou, Hong Wang, Wei-Min Gu, Jie Li, Chao Li, Ming-Da Wang, Hong Zhu, Ying-Jian Liang, Feng Shen, Timothy M. Pawlik, Wan Yee Lau, and Tian Yang

1Department of Hepatobiliary Surgery, The First Affiliated Hospital of Nantong University, Nantong, Jiangsu, China
2Department of Hepatobiliary Surgery, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University, Shanghai, China
3Department of Hepatobiliary & Pancreatic Surgery, The Affiliated People’s Hospital of Ningbo University, Ningbo, Zhejiang, China
4Department of Hepatobiliary Surgery, Pancreatic and Minimal Invasive Surgery, Zhejiang Provincial People’s Hospital, People’s Hospital of Hangzhou Medical College, Hangzhou, Zhejiang, China
5Department of Medical Oncology, The First Affiliated Hospital of Soochow University, Soochow, Jiangsu, China
6Department of Pancreatic-biliary Surgery, Changzheng Hospital, Second Military Medical University (Naval Medical University), Shanghai, China
7Department of Hepatobiliary Surgery, The First Affiliated Hospital of Harbin Medical University, Harbin, Heilongjiang, China
8Department of Hepatobiliary, Pancreatic and Minimal Invasive Surgery, Zhejiang Provincial People’s Hospital, People’s Hospital of Hangzhou Medical College, Hangzhou, Zhejiang, China
9Department of General Surgery, Liuyang People’s Hospital, Liuyang, Hunan, China
10The First Department of General Surgery, The Fourth Hospital of Harbin, Harbin, Heilongjiang, China
11Department of Hepatobiliary Surgery, Fuyang People’s Hospital, Fuyang, Anhui, China
12Department of Surgery, Ohio State University, Wexner Medical Center, Columbus, Ohio, USA
13Faculty of Medicine, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong SAR, China

*Correspondence to: Department of Hepatobiliary Surgery, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University (Navy Medical University), No. 225, Changhai Road, Shanghai 200438, China (e-mail: yangtiandfgd@hotmail.com)

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, \(P = 0.533\)) 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. HCC is also common, however, among young patients in areas endemic for hepatitis B virus (HBV) infection, including China and Korea. Partial hepatectomy remains the most commonly used primary treatment modality with curative intent for HCC in appropriately selected patients. 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.
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. Theuer and colleagues 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. 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. For example, Huang and colleagues 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, 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 or young versus non-young groups) with different cut-off values may have contributed to different findings. 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.

To balance differences in the baseline characteristics due to selection bias between the young and the elderly, the PSM method 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, Fu’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, 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. 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 was used.
as described by Rubin and Rosenbaum\textsuperscript{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\textsuperscript{37–39}.

Statistical analysis

Statistical analyses were carried out using SPSS\textsuperscript{9}, 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\textsuperscript{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 3 (2.1 versus 2.6 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$^*$          |
| Elderly§ (n = 140)                              | Elderly§ (n = 140)                              | P$^*$          |
| Age (years)*                                   |                                                |                |
| 30.1 (4.4)                                     | 75.0 (4.6)                                     | <0.001         |
| Female sex                                     |                                                |                |
| 162 (85.4)                                     | 223 (79.6)                                     | 0.098          |
| Co-morbidities                                 |                                                |                |
| 4 (2.1)                                        | 106 (31.3)                                     | <0.001         |
| ASA score >2                                   |                                                |                |
| 7 (3.6)                                        | 126 (37.2)                                     | <0.001         |
| HBV positive                                   |                                                |                |
| 182 (94.8)                                     | 234 (69.0)                                     | <0.001         |
| Cirrhosis                                      |                                                |                |
| 130 (67.7)                                     | 207 (61.1)                                     | 0.012          |
| Portal hypertension                            |                                                |                |
| 43 (22.4)                                      | 52 (15.3)                                      | 0.042          |
| Child-Pugh grade B                             |                                                |                |
| 14 (7.3)                                       | 13 (3.8)                                       | 0.081          |
| Preoperative ALT level >40 U/l                 |                                                |                |
| 76 (41.5)                                      | 41 (32.0)                                      | 0.099          |
| Preoperative AST level >40 U/l                 |                                                |                |
| 82 (44.8)                                      | 45 (35.2)                                      | 0.088          |
| Preoperative AFP level >400 µg/l               |                                                |                |
| 108 (56.3)                                     | 116 (34.2)                                     | <0.001         |
| Maximum tumour size >5 cm                      |                                                |                |
| 112 (58.3)                                     | 134 (43.7)                                     | 0.001          |
| Multiple tumours                               |                                                |                |
| 27 (14.1)                                      | 30 (8.8)                                       | 0.062          |
| Macrovascular invasion                         |                                                |                |
| 28 (14.6)                                      | 18 (5.3)                                       | 0.001          |
| Microvascular invasion                         |                                                |                |
| 82 (44.8)                                      | 103 (30.4)                                     | <0.001         |
| Satellite nodules                              |                                                |                |
| 51 (26.6)                                      | 52 (15.3)                                      | 0.002          |
| Poor tumour differentiation                    |                                                |                |
| 130 (67.7)                                     | 217 (64.0)                                     | 0.390          |
| Incomplete tumour envelope                     |                                                |                |
| 105 (54.7)                                     | 252 (74.3)                                     | <0.001         |
| TNM stage$^{34}$                               |                                                |                |
| I                                              |                                                |                |
| 89 (46.4)                                      | 204 (60.2)                                     | <0.001         |
| II                                             |                                                |                |
| 47 (24.5)                                      | 96 (28.3)                                      | 0.004          |
| III-IV                                        |                                                |                |
| 56 (29.2)                                      | 39 (11.5)                                      | 0.001          |
| BCLC stage$^{34}$                              |                                                |                |
| 0/A                                            |                                                |                |
| 101 (52.6)                                     | 221 (65.2)                                     | <0.001         |
| B/C                                           |                                                |                |
| 91 (47.4)                                      | 138 (34.8)                                     | 0.004          |
| Resection margin <1 cm                         |                                                |                |
| 88 (45.8)                                      | 183 (54.0)                                     | 0.071          |
| Intraoperative blood loss >400 ml              |                                                |                |
| 77 (42.1)                                      | 50 (39.1)                                      | 0.595          |
| Intraoperative blood transfusion               |                                                |                |
| 47 (24.5)                                      | 57 (16.8)                                      | 0.032          |
| Major hepectomy                               |                                                |                |
| 64 (33.3)                                      | 65 (19.2)                                      | <0.001         |

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 χ² 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$^*$          |
| Elderly§ (n = 140)                              | Elderly§ (n = 140)                              | P$^*$          |
| Period of follow-up (months)*                   |                                                |                |
| 51.2 (40.2)                                     | 53.7 (36.0)                                     | 0.471          |
| Recurrence during follow-up                    |                                                |                |
| 130 (67.7)                                     | 127 (37.5)                                     | <0.001         |
| Site of initial recurrence                     |                                                |                |
| Intrahepatic                                    |                                                |                |
| 88 (45.8)                                      | 111 (32.7)                                     | 0.003          |
| Extrahepatic                                    |                                                |                |
| 12 (6.3)                                       | 5 (1.5)                                        | 0.003          |
| Intrahepatic and extrahepatic                   |                                                |                |
| 30 (15.6)                                      | 11 (3.2)                                       | <0.001         |
| Death during follow-up                         |                                                |                |
| Cancer-specific death                           |                                                |                |
| 100 (52.1)                                     | 96 (28.3)                                      | <0.001         |
| Non-cancer-specific death                      |                                                |                |
| 11 (5.7)                                       | 93 (27.4)                                      | <0.001         |
| OS                                              |                                                |                |
| Median OS (months)†                             |                                                |                |
| 57.0 (47.3–66.7)                                | 65.8 (55.6–76.0)                                | 0.064          |
| 1-year OS rate (%)                             |                                                |                |
| 80.2                                            | 89.0                                           | 0.001          |
| 3-year OS rate (%)                             |                                                |                |
| 62.2                                           | 71.1                                           | 0.001          |
| 5-year OS rate (%)                             |                                                |                |
| 49.1                                           | 53.9                                           | 0.001          |
| CSS                                             |                                                |                |
| Median CSS (months)†                            |                                                |                |
| 63.2 (39.4–87.0)                                | 144.9 (110.9–178.9)                            | <0.001         |
| 1-year CSS rate (%)                            |                                                |                |
| 80.2                                           | 94.9                                           | 0.001          |
| 3-year CSS rate (%)                            |                                                |                |
| 62.7                                           | 83.3                                           | 0.001          |
| 5-year CSS rate (%)                            |                                                |                |
| 50.8                                           | 71.5                                           | 0.001          |
| TTR                                             |                                                |                |
| Median TTR (months)†                            |                                                |                |
| 23.2 (11.3–35.1)                                | 145.1 (46.5–243.7)                             | <0.001         |
| 1-year TTR rate (%)                            |                                                |                |
| 43.6                                           | 17.3                                           | 0.001          |
| 3-year TTR rate (%)                            |                                                |                |
| 56.9                                           | 34.7                                           | 0.001          |
| 5-year TTR rate (%)                            |                                                |                |
| 66.3                                           | 43.3                                           | 0.001          |

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 χ² test, as appropriate. PSM, propensity score matching; OS, overall survival; CSS, cancer-specific survival; TTR, time to recurrence.
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 CSS 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.
and the elderly groups (more than 150 patients for each group).

In independent correlation between age difference and oncological outcomes, multivariable Cox regression analysis was used to determine any associations.

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 χ² test, as appropriate. HBV, hepatitis B virus; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AFP, alpha-fetoprotein; NS, not significant.

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                              |                         | 0.98 (0.71, 1.35)    | 0.901                   | NS          | 0.126      |
| Sex                              |                         | 0.94 (0.62, 1.44)    | 0.775                   |             |            |
| Co-morbidities                   |                         | 0.98 (0.63, 1.52)    | 0.916                   |             |            |
| ASA score                        |                         | 1.19 (0.83, 1.72)    | 0.341                   |             |            |
| HBV positive                     |                         | 0.93 (0.53, 1.65)    | 0.807                   |             |            |
| Cirrhosis                        |                         | 1.27 (0.90, 1.80)    | 0.171                   |             |            |
| Portal hypertension              |                         | 1.02 (0.70, 1.48)    | 0.939                   |             |            |
| Child–Pugh grade                 |                         | 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                 |                         | 3.51 (2.31, 5.35)    | <0.001                  | 1.66 (1.07, 2.56) | 0.023 |
| Macrovascular invasion           |                         | 3.72 (2.50, 5.54)    | <0.001                  | 3.85 (2.24, 6.59) | <0.001 |
| Microvascular invasion           |                         | 2.51 (1.82, 3.46)    | <0.001                  | 1.28 (1.10, 2.56) | 0.428 |
| Satellite nodules                |                         | 4.20 (2.95, 5.99)    | <0.001                  | 1.95 (1.21, 3.14) | 0.006 |
| Poor tumour differentiation      |                         | 1.17 (0.84, 1.65)    | 0.354                   |             |            |
| Incomplete tumour envelope       |                         | 2.22 (1.56, 3.16)    | <0.001                  | 1.13 (0.71, 1.82) | 0.628 |
| Intraoperative blood loss        |                         | 1.73 (1.25, 2.37)    | 0.001                   | 1.13 (0.71, 1.82) | 0.628 |
| Intraoperative blood transfusion |                         | 2.34 (1.64, 3.34)    | <0.001                  | 1.13 (0.71, 1.82) | 0.628 |
| Extent of hepatectomy            |                         | 2.09 (1.48, 2.94)    | <0.001                  | 1.13 (0.71, 1.82) | 0.628 |

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 χ² 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                              |                         | 1.35 (0.94, 1.94)    | 0.108                   | 1.69 (1.08, 2.64) | 0.021 |
| Sex                              |                         | 1.01 (0.62, 1.65)    | 0.979                   |             |            |
| Co-morbidities                   |                         | 0.74 (0.42, 1.28)    | 0.280                   |             |            |
| ASA score                        |                         | 1.01 (0.66, 1.55)    | 0.978                   |             |            |
| HBV positive                     |                         | 0.99 (0.52, 1.90)    | 0.981                   |             |            |
| Cirrhosis                        |                         | 1.22 (0.82, 1.80)    | 0.324                   |             |            |
| Portal hypertension              |                         | 1.09 (0.72, 1.67)    | 0.678                   |             |            |
| Child–Pugh grade                 |                         | 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                 |                         | 3.69 (2.33, 5.84)    | <0.001                  | 1.56 (1.01, 2.41) | 0.048 |
| Microvascular invasion           |                         | 4.61 (3.01, 7.04)    | <0.001                  | 5.12 (2.93, 8.97) | <0.001 |
| Satellite nodules                |                         | 3.41 (2.34, 4.97)    | <0.001                  | 1.95 (1.21, 3.14) | 0.006 |
| Poor tumour differentiation      |                         | 4.92 (3.34, 7.24)    | <0.001                  | 2.04 (1.26, 3.33) | 0.004 |
| Incomplete tumour envelope       |                         | 1.32 (0.89, 1.96)    | 0.163                   |             |            |
| Resection margin                 | ≤1.0 versus >1.0 cm     | 2.38 (1.58, 3.57)    | <0.001                  | NS          | 0.071      |
| Intraoperative blood loss        | ≤400 versus ≤400 ml     | 2.09 (1.45, 3.02)    | <0.001                  | 1.74 (1.10, 2.74) | 0.017 |
| Intraoperative blood transfusion | ≤400 versus ≤400 ml     | 2.54 (1.71, 3.76)    | <0.001                  | NS          | 0.647      |
| Extent of hepatectomy            |                         | 2.52 (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 χ² 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)    | 0.029                   |                       |                      |
| Preoperative AST level            | >40 versus ≤40 U/l      | 1.51 (1.06, 2.13)    | 0.021                   |                       |                      |
| 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 χ² 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 undergoing 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 resection40,41. 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 sarcopenia42, frailty43 and cancer-related fatigue44, 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 indicator of the impact of that disease on society45. In the future, an in-depth study will be performed on this issue using the authors’ population-based data.
Acknowledgements
J.-L.P., Z.C., L.-Q.Y., J.-Y.F., Y.-K.D., M.-C.G., J.-D.L., and Z.-L.C. contributed equally to this work. Conception: J.-L.P., T.Y., Z.C., F.S.; study design: T.Y., J.-L.P., L.-Q.Y., J.-Y.F., Y.-K.D., M.-C.G., J.-D.L., Z.-L.C., C.L.; administrative support: Z.C., F.S.; data collection and acquisition: J.-L.P., L.-Q.Y., J.-Y.F., Y.-K.D., M.-C.G., J.-D.L., Z.-L.C., Y.-H.Z., H.W., W.-M.G., J.L., C.L., M.-D.W.; data analysis: J.-L.P., L.-Q.Y., T.Y.; manuscript preparation: J.-L.P., L.-Q.Y., C.L., T.Y., W.Y.L.; critical revision: Z.C., F.S., T.M.P., W.Y.L.; final approval of manuscript: all authors.

Funding
This study was supported by the National Natural Science Foundation of China (no. 81972726).

Disclosure. The authors declare no conflict of interest.

Supplementary material
Supplementary material is available at BJS Open online.

References
1. El-Serag HB, Rudolph KL. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. Gastroenterology 2007;132:2557–2576.
2. Lam CM, Chan AO, Ho P, Ng IO, Lo CM, Liu CL et al. Different presentation of hepatitis B-related hepatocellular carcinoma in a cohort of 1863 young and old patients – implications for screening. Aliment Pharmacol Ther 2004;19:771–777.
3. Ishikawa T. Clinical features of hepatitis B virus-related hepatocellular carcinoma. World J Gastroenterol 2010;16:2463–2467.
4. Zaydfudim VM, Vachharajani N, Klintmalm GB, Jarnagin WR, Hemming AW, Doyle MB et al. Liver resection and transplantation for patients with hepatocellular carcinoma beyond Milan criteria. Ann Surg 2016;264:650–658.
5. Sapisochin G, Castells L, Dopazo C, Bilbao I, Minguez B, Lázaro JL et al. Single HCC in cirrhotic patients: liver resection or liver transplantation? Long-term outcome according to an intention-to-treat basis. Ann Surg Oncol 2013;20:1194–1202.
6. Yu JJ, Shen F, Chen TH, Liang L, Han J, Xing H et al. Multicentre study of the prognostic impact of preoperative bodyweight on long-term prognostic of hepatocellular carcinoma. Br J Surg 2019;106:276–285.
7. Kath R, Fiehler J, Schneider CP, Höfken K. Gastric cancer in very young adults: apropos four patients and a review of the literature. J Cancer Res Clin Oncol 2000;126:233–237.
8. Wang J, Wang J, Li Q, Zhang P, Yuan P, Ma F et al. Young breast cancer patients who develop distant metastasis after surgery have better survival outcomes compared with elderly counterparts. Oncotarget 2017;8:44851–44859.
9. Fu J, Yang J, Tan Y, Jiang M, Wen F, Huang Y et al. Young patients (≤ 35 years old) with colorectal cancer have worse outcomes due to more advanced disease: a 30-year retrospective review. Medicine (Baltimore) 2014;93:e135.
10. Cheng L, Chen S, Wu W, Kuo ZC, Wei Z, Meng S et al. Gastric cancer in young patients: a separate entity with aggressive features and poor prognosis. J Cancer Res Clin Oncol 2020;146:2937–2947.
11. Theuer CP, Kurosaki T, Taylor TH, Anton-Culver H. Unique features of gastric carcinoma in the young: a population-based analysis. Cancer 1998;83:25–33.
12. Cho SJ, Yoon JH, Hwang SS, Lee HS. Do young hepatocellular carcinoma patients with relatively good liver function have poorer outcomes than elderly patients? J Gastroenterol Hepatob 2007;22:1226–1231.
13. Kim JH, Choi MS, Lee H, Kim DY, Lee JH, Koh KC et al. Clinical features and prognosis of hepatocellular carcinoma in young patients from a hepatitis B-endemic area. J Gastroenterol Hepatob 2006;21:588–594.
14. Chang PE, Ong WC, Lui HF, Tan CK. Is the prognosis of young patients with hepatocellular carcinoma poorer than the prognosis of older patients? A comparative analysis of clinical characteristics, prognostic features, and survival outcome. J Gastroenterol 2008;43:881–888.
15. Niederle IM, Wörns MA, Koch S, Nguyen-Tat M, Düber C, Otto G et al. Clinicopathologic features and prognosis of young patients with hepatocellular carcinoma in a large German cohort. J Clin Gastroenterol 2012;46:775–778.
16. Takeishi K, Shirabe K, Muto J, Toshima T, Taketomi A, Maehara Y. Clinicopathological features and outcomes of young patients with hepatocellular carcinoma after hepatectomy. World J Surg 2011;35:1063–1071.
17. Yamazaki Y, Kakizaki S, Sohara N, Sato K, Takagi H, Arai H et al. Hepatocellular carcinoma in young adults: the clinical characteristics, prognosis, and findings of a patient survival analysis. Dig Dis Sci 2007;52:1103–1107.
18. Ha SY, Sohn I, Hwang SH, Yang JW, Park CK. The prognosis of hepatocellular carcinoma after curative hepatectomy in young patients. OncoTarget 2015;6:18664–18673.
19. Ni YH, Chang MH, Hsu HY, Hsu HC, Chen CC, Chen WJ et al. Hepatocellular carcinoma in childhood. Clinical manifestations and prognosis. Cancer 1991;68:1737–1741.
20. Lee CL, Ko YC. Survival and distribution pattern of childhood liver cancer in Taiwan. Eur J Cancer 1998;34:2064–2067.
21. Zeng J, Lin K, Liu H, Huang Y, Guo P, Zeng Y et al. Prognostic factors of young patients undergoing curative resection for hepatitis B virus-related hepatocellular carcinoma: a multicenter study. Cancer Manag Res 2020;12:6597–6606.
22. Lee CR, Lim JH, Kim SH, Ahn SH, Park YN, Choi GH et al. A comparative analysis of hepatocellular carcinoma after hepatic resection in young versus elderly patients. J Gastrointest Surg 2012;16:1736–1743.
23. Shimada S, Kamiyama T, Yokoo H, Wakayama K, Tsuruga Y, Kakisaka T et al. Clinicopathological characteristics and prognostic factors in young patients after hepatectomy for hepatocellular carcinoma. World J Surg Oncol 2013;11:52.
24. Huang J, Li BK, Chen GH, Li JQ, Zhang YQ, Li GH et al. Long-term outcomes and prognostic factors of elderly patients with hepatocellular carcinoma undergoing hepatectomy. J Gastrointest Surg 2009;13:1627–1635.
25. Lui WY, Chau GY, Wu CW, King KL. Surgical resection of hepatocellular carcinoma in elderly cirrhotic patients. Hepatogastroenterology 1999;46:640–645.
26. Aldrighetti L, Arru M, Caterini R, Finazzi R, Comotti L, Torri G et al. Impact of advanced age on the outcome of liver resection. World J Surg 2003;27:1149–1154.
27. Poon RT, Fan ST, Lo CM, Liu CL, Ngan H, Ng IO et al. Hepatocellular carcinoma in the elderly: results of surgical and nonsurgical management. Am J Gastroenterol 1999;94:2460–2466.
28. Hanazaki K, Kajikawa S, Shimozawa N, Shimada K, Hiraguri M, Koide N et al. Hepatic resection for hepatocellular carcinoma in the elderly. J Am Coll Surg 2001;192:38–46.
29. Kishida N, Hibi T, Itano O, Okabayashi K, Shinoda M, Kitago M et al. Validation of hepatectomy for elderly patients
with hepatocellular carcinoma. Ann Surg Oncol 2015;22:3094–3101
30. Hirokawa F, Hayashi M, Miyamoto Y, Asakuma M, Shimizu T, Komeda K et al. Surgical outcomes and clinical characteristics of elderly patients undergoing curative hepatectomy for hepatocellular carcinoma. J Gastrointest Surg 2013;17:1929–1937
31. Sato S, Tanaka K, Nojiri K, Kumamoto T, Mori R, Taniguchi K et al. Hepatic resection for hepatocellular carcinoma in the elderly: selecting hepatectomy procedures based on patient age. Anticancer Res 2015;35:6855–6860
32. Liu XY, Xu JF. Liver resection for young patients with large hepatocellular carcinoma: a single center experience from China. World J Surg Oncol 2014;12:175
33. Farhi DC, Shikes RH, Murari PJ, Silverberg SG. Hepatocellular carcinoma in young people. Cancer 1983;52:1516–1525
34. Chun YS, Pawlik TM, Vauthey JN. 8th edition of the AJCC cancer staging manual: pancreas and hepatobiliary cancers. Ann Surg Oncol 2018;25:845–847
35. Rubin DB, Thomas N. Matching using estimated propensity scores: relating theory to practice. Biometrics 1996;52:249–264
36. Rosenbaum PR, Rubin DB. Constructing a control group using multivariate matched sampling methods that incorporate the propensity score. Am Stat 1985;39:33–38
37. Yang T, Lu JH, Lau WY, Zhang TY, Zhang H, Shen YN et al. Perioperative blood transfusion does not influence recurrence-free and overall survivals after curative resection for hepatocellular carcinoma: a propensity score matching analysis. J Hepatol 2016;64:583–593
38. Yang T, Tabrizian P, Zhang H, Lau WY, Han J, Li ZL et al. Comparison of patterns and outcomes of liver resection for hepatocellular carcinoma: east vs west. Clin Gastroenterol Hepatol 2017;15:1972–1974
39. Yang T, Hu LY, Li ZL, Liu K, Wu H, Xing H et al. Liver resection for hepatocellular carcinoma in non-alcoholic fatty liver disease: a multicenter propensity matching analysis with HBV-HCC. J Gastrointest Surg 2020;24:320–329
40. Yang T, Liu K, Liu CF, Zhong Q, Zhang J, Yu JJ et al. Impact of postoperative infective complications on long-term survival after liver resection for hepatocellular carcinoma. Br J Surg 2019;106:1228–1236
41. Li LQ, Liang L, Sun LY, Li C, Wu H, Zhang YM et al. Postoperative morbidity adversely impacts long-term oncologic prognosis following hepatectomy for hepatocellular carcinoma: a multicenter observational study. Eur J Surg Oncol 2021;47:2551–2560
42. Williams GR, Dunne RF, Giri S, Shachar SS, Caan BJ. Sarcopenia in the older adult with cancer. J Clin Oncol 2021;39:2068–2078
43. Yamada S, Shimada M, Morine Y, Imura S, Ikemoto T, Arakawa Y et al. Significance of frailty in prognosis after hepatectomy for elderly patients with hepatocellular carcinoma. Ann Surg Oncol 2021;28:439–446
44. Soones T, Ombres R, Escalante C. An update on cancer-related fatigue in older adults: a narrative review. J Geriatr Oncol 2021; DOI:10.1016/j.jgo.2021.07.006; PMID: 34353750
45. Famularo S, Di Sandro S, Giani A, Angrisani M, Lauterio A, Romano F et al. The impact of age and ageing on hepatocarcinoma surgery: short- and long-term outcomes in a multicentre propensity-matched cohort. Liver Int 2019;39:894–904