ORIGINAL ARTICLE

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# The Effect of Age on the Long-term Prognosis of Patients With Hepatocellular Carcinoma After Resection Surgery

## *A Propensity Score Matching Analysis*

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**Objective:** The effect of age on the clinicopathologic manifestations of hepatocellular carcinoma (HCC) and on the survival rate in patients with HCC after resection surgery remains controversial. We aim to compare the clinicopathological features and prognoses between younger and older patients with HCC undergoing resection.

**Design:** Retrospective review.

**Setting:** A tertiary medical center.

**Patients:** We enrolled 1074 consecutive patients with HCC who were undergoing a partial hepatectomy. Patients who were 55 years of age or younger were defined as the younger group (n=374), and patients who were older than 55 years of age were defined as the older group (n=700).

**Main Outcome Measures:** The postoperative prognoses of the younger and older groups using multivariate analysis and propensity score matching analysis.

**Results:** The younger patients had better liver functional reserve but more aggressive tumor factors than did the older patients. After a median follow-up of 41.0 months, 543 patients died. The cumulative 10-year survival rates were 41.3% in younger patients and 28.8% in the older patients ($P=.02$). However, using both multivariate analysis and propensity score matching analysis, we failed to demonstrate that age was an independent risk factor associated with overall survival. Besides, there were 643 patients with tumor recurrence after surgery. Using both multivariate analysis and propensity score matching analysis, we found that the incidence of tumor recurrence in younger patients was comparable to that in the older patients.

**Conclusions:** Age is not a risk factor to determine the prognosis of patients with HCC who underwent resection. Older patients with HCC who have good liver functional reserve are encouraged to receive resection surgery.

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HEPATOCELLULAR CARCINOMA (HCC) is the third most common cause of cancer mortality worldwide.[1,2] Surgical resection remains a mainstay of treatment for patients whose liver function is well preserved.[3] However, recurrence of HCC is common and occurs within 2 years after surgery in most cases.[4-7] In addition, this recurrence is the main cause of mortality for patients with HCC who undergo surgical resection. Several factors (including tumor size, number of tumors, presence of vascular invasion, performance status, and degree of liver functional reserve) reportedly contribute to tumor recurrence and the long-term prognosis of HCC in such patients.[1,6,8-13]

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Whether age plays an important role in the prognosis of HCC remains debatable.[14-19] Several studies[14,18] demonstrate that younger and older patients with HCC exhibit a similar prognosis. Some researchers declare that younger patients have better long-term outcomes,[16,17,19] whereas other studies disclose that younger patients tend to present with advanced-stage tumors at the time of diagnosis, thereby indicating a poorer prognosis.[14] The discrepancy between these studies may be due to the diverse demographic characteristics, clinicopathologic features, and treatment modalities of the enrolled patients. In recent years, propensity score matching analysis has been used to overcome potential selection biases and

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minimize confounding factors in nonrandomized retrospective studies.[19-21] Consequently, our study performed both multivariate analysis and propensity score matching analysis to evaluate the true effect of age on the long-term prognosis of patients with HCC who underwent resection surgery.

## METHODS

### PATIENTS AND FOLLOW-UP

A total of 1074 consecutive patients with HCC who underwent a hepatectomy at the Taipei Veterans General Hospital in Taiwan during the period from 1991 to 2006 were retrospectively enrolled in our study. The criteria for liver resection and the operative procedures were previously described elswhere.[4,22-24] Major surgery included an extended lobectomy, a lobectomy, and an indicated resection of 3 or more Couinaud segments, whereas a segmentectomy, a subsegmentectomy, and a wedge resection were considered minor surgery. After surgery, the macroscopic features of the tumor or tumors (including the size, number, and presence of a tumor or tumors in the hepatic or portal vein [ie, vascular invasion]) were recorded. Histologically, the presence of microscopic vascular invasion, as well as satellite lesions, was carefully examined by routine light microscopic examination. Consequently, the number of tumors and the presence of macroscopic venous invasion were determined by the surgeon at the time of resection; the presence of satellite lesions and microscopic vascular invasion was diagnosed by the pathologist. The differentiation of cancer cells was determined by the Edmondson and Steiner grading system.[25]

Of the 1074 patients in our study, 19 (1.8%) died in the hospital after surgery. The remaining 1055 patients were followed up every 3 months after hospital discharge with tests to determine serum liver biochemistries and α-fetoprotein (AFP) levels and with ultrasonographic examinations until January 31, 2010. All patients were followed up until their last visit in our hospital or death.

Tumor recurrences were suspected if there was elevation of serum AFP levels (>20 ng/mL; to convert to micrograms per liter, multiply by 1.0) or if new lesions were detected by use of surveillance ultrasonography. These recurrences were further confirmed and diagnosed with the use of dynamic computed tomographic or magnetic resonance imaging scans showing contrast enhancement during the arterial phase and washout during the venous phase. Our study complied with the standards of the Declaration of Helsinki.

### BIOCHEMICAL AND SEROLOGIC MARKERS

Seropositivity for hepatitis B surface antigen was tested using a radioimmunoassay (Abbott Laboratories, North Chicago, Illinois), whereas antibody to hepatitis C virus (HCV) was measured using a second-generation enzyme immunoassay (Abbott Laboratories). Serum biochemistries were measured using a systemic multi-autoanalyzer (Technicon SMAC; Technicon Instruments Corp, Tarrytown, New York). The serum AFP level was measured using a radioimmunoassay (Serono Diagnostic SA, Coinsin/VD, Switzerland).

### STATISTICAL ANALYSIS

The baseline characteristics to be evaluated with outcomes were selected according to the 2001 European Association for the Study of the Liver guidelines.[26] The parameters assessed for overall survival were based on all of the 1074 patients, whereas the cohort for the analysis of recurrence was limited to the 1055 patients successfully discharged from the hospital after surgery.

Because the median age of patients with HCC who underwent resection surgery was 56 years in our previous research,[11] the present study defined patients 55 years of age or younger as the younger group and patients older than 55 years of age as the older group. After comparing the demographic data between these 2 groups, we performed propensity analysis using logistic regression to create a propensity score for younger and older patients. Subsequently, a one-to-one match between these 2 groups was done using the nearest-neighbor matching method.[19-21]

Pearson $\chi^2$ analysis or the Fisher exact test was used to compare categorical variables, whereas the Mann-Whitney *U* test was used to compare continuous variables. Cumulative recurrence rates or overall survival rates were estimated using the Kaplan-Meier method and were compared using the log-rank test or the Cox proportional hazards model. Variables with statistical significance ($P<.05$) or approximate statistical significance ($P<.1$) in univariate analysis were subjected to multivariate analysis using a Cox forward stepwise logistic regression model. A 2-tailed *P* value of less than .05 was considered to be statistically significant. All statistical analyses were performed using SPSS version 17.0 for Windows (SPSS Inc, Chicago, Illinois).

## RESULTS

### CLINICAL DEMOGRAPHICS AND BIOCHEMICAL, SURGICAL, AND PATHOLOGICAL DATA

As shown in **Table 1**, younger patients had a higher incidence of a family history of HCC and a higher rate of seropositivity for hepatitis B surface antigen. Regarding liver functional reserve, younger patients had higher serum albumin levels, higher platelet counts, and lower indocyanine green dye retention rates at 15 minutes than did older patents. Nevertheless, in considering tumor factors, younger patients had larger tumor sizes, higher serum AFP levels, higher rates of macroscopic vascular invasion, higher Cancer of the Liver Italian Program scores, and more advanced Barcelona Clinic Liver Cancer stages. In addition, a larger proportion of younger patients underwent major surgery.

### COMPARISON OF OVERALL SURVIVAL BETWEEN YOUNGER AND OLDER PATIENTS WITH HCC STRATIFIED BY AGE AND STAGING

After a median follow-up of 41.0 months (25th-to-75th percentile range, 19.0-75.0 months), 543 patients died, and 531 patients were still alive for their last visit. The overall cumulative survival rates at 1, 2, 3, 5, and 10 years were 85.2%, 75.3%, 66.7%, 54.0%, and 33.0%, respectively. To stratify the analysis by age, the overall cumulative survival rates at 1, 2, 3, 5, and 10 years were 82.4%, 73.5%, 67.3%, 58.9%, and 41.3%, respectively, in younger patients with HCC and 86.7%, 76.3%, 66.4%, 51.4%, and 28.8%, respectively, in the older patients with HCC. The overall survival rates were higher in younger patients with HCC than in the older patients with HCC (**Figure**, A). Furthermore, the analysis disclosed that a higher proportion of younger patients than older patients died of HCC ($P=.001$) (Table 1).

Our univariate and multivariate analyses for determining the risk factors associated with overall survival



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**Table 1. Comparison of Demographic Data and Outcomes Between Younger (≤55 Years of Age) and Older (>55 Years of Age) Patients With Hepatocellular Carcinoma**

| Parameter | Total (n = 1074) | Younger Patients (n = 374) | Elder Patients (n = 700) | *P* Value |
|---|---|---|---|---|
| Patient demographics | | | | |
| Age, median (25th-75th percentile range), y | 62.0 (50.75-71.0) | 46.5 (41.0-51.0) | 69.0 (63.0-73.0) | <.001 |
| Male, No. (%) | 886 (82.5) | 310 (82.9) | 576 (82.3) | .87 |
| Family history of HCC, No. (%) | 169 (15.7) | 91 (24.3) | 78 (11.1) | <.001 |
| Serum biochemistry and liver function test results, median level[a] (25th-75th percentile range) | | | | |
| Albumin, g/dL | 4.1 (3.8-4.3) | 4.1 (3.8-4.3) | 4.0 (3.8-4.3) | .012 |
| Total bilirubin, mg/dL | 0.9 (0.6-1.1) | 0.8 (0.6-1.1) | 0.9 (0.7-1.1) | .45 |
| ALT, U/L | 45 (28-73) | 46 (30-73) | 42 (27-74) | .28 |
| ICG-15R, % | 11 (7-16) | 8 (5-13) | 12 (8-18) | <.001 |
| Platelet count, $mm^3$ | 1 620 00 (1 160 00-2 170 00) | 1 810 00 (1 390 00-2 330 00) | 1 500 00 (1 100 00-2 040 00) | <.001 |
| Viral factors,[a] No. (%) | | | | |
| HBsAg | | | | |
| Positive | 664 (63.4) | 319 (86.4) | 345 (50.9) | <.001 |
| Negative | 383 (36.6) | 50 (13.6) | 333 (49.1) | |
| Anti-HCV | | | | |
| Positive | 262 (25.6) | 47 (13.1) | 215 (32.3) | <.001 |
| Negative | 763 (74.4) | 313 (86.9) | 450 (67.7) | |
| Macroscopic tumor factors | | | | |
| Major surgery, No. (%) | 323 (30.1) | 148 (39.6) | 175 (25.0) | <.001 |
| Tumor size, median (25th-75th percentile range), cm | 4.0 (2.5-6.7) | 4.5 (2.4-8.5) | 3.8 (2.6-6.1) | <.001 |
| AFP,[a] median, (25th-75th percentile range), ng/mL | 33.8 (7.5-470.5) | 81.2 (9.1-1041.0) | 21.7 (6.7-274.0) | <.001 |
| Macroscopic single tumor, No. (%) | 628 (58.5) | 212 (56.7) | 416 (59.4) | .43 |
| Macroscopic vascular invasion,[a] No. (%) | | | | |
| Yes | 160 (15.0) | 68 (18.3) | 92 (13.2) | .03 |
| No | 908 (85.0) | 304 (81.7) | 604 (86.8) | |
| Microscopic tumor factors,[a] No. (%) | | | | |
| Edmondson and Steiner grading system | | | | |
| Grade I | 63 | 20 | 43 | .93 |
| Grade II | 651 | 231 | 420 | |
| Grade III | 309 | 109 | 200 | |
| Grade IV | 18 | 7 | 11 | |
| Microscopic satellite lesion | | | | |
| Yes | 383 (56.9) | 132 (53.9) | 251 (58.6) | .26 |
| No | 290 (43.1) | 113 (46.1) | 177 (41.4) | |
| Microscopic vascular invasion | | | | |
| Yes | 685 (63.8) | 242 (64.7) | 443 (63.4) | .72 |
| No | 388 (36.2) | 132 (35.3) | 256 (36.6) | |
| Cirrhosis on nontumor part | | | | |
| Yes | 436 (41.8) | 155 (42.3) | 281 (41.4) | .83 |
| No | 608 (58.2) | 211 (57.7) | 397 (58.6) | |
| Tumor stages, No. (%) | | | | |
| CLIP score | | | | |
| 0 | 475 (44.2) | 149 (39.8) | 326 (46.6) | .04 |
| ≥1 | 599 (55.8) | 225 (60.2) | 374 (53.4) | |
| BCLC stage | | | | |
| A/B | 914 (85.1) | 306 (81.8) | 608 (86.9) | .03 |
| C | 160 (14.9) | 68 (18.2) | 92 (13.1) | |
| Outcomes, No. (%) | | | | |
| Extrahepatic recurrence | 196 (30.5) | 83 (37.2) | 113 (26.9) | .009 |
| Intrahepatic recurrence only | 447 (69.5) | 140 (62.8) | 307 (73.1) | |
| Mortality due to HCC | 282 (51.9) | 104 (62.7) | 178 (47.2) | .001 |

Abbreviations: AFP, α-fetoprotein; ALT, alanine aminotransferase; BCLC, Barcelona Clinic Liver Cancer; CLIP, Cancer of the Liver Italian Program; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ICG-15R, indocyanine green dye retention rate at 15 minutes.

SI conversion factors: To convert albumin to grams per liter, multiply by 10.0; to convert total bilirubin to micromoles per liter, multiply 17.104; to convert ALT to microkatals per liter, multiply by 0.0167; and to convert AFP to micrograms per liter, multiply by 1.0.

[a] Missing data at the time of resection surgery for this parameter.



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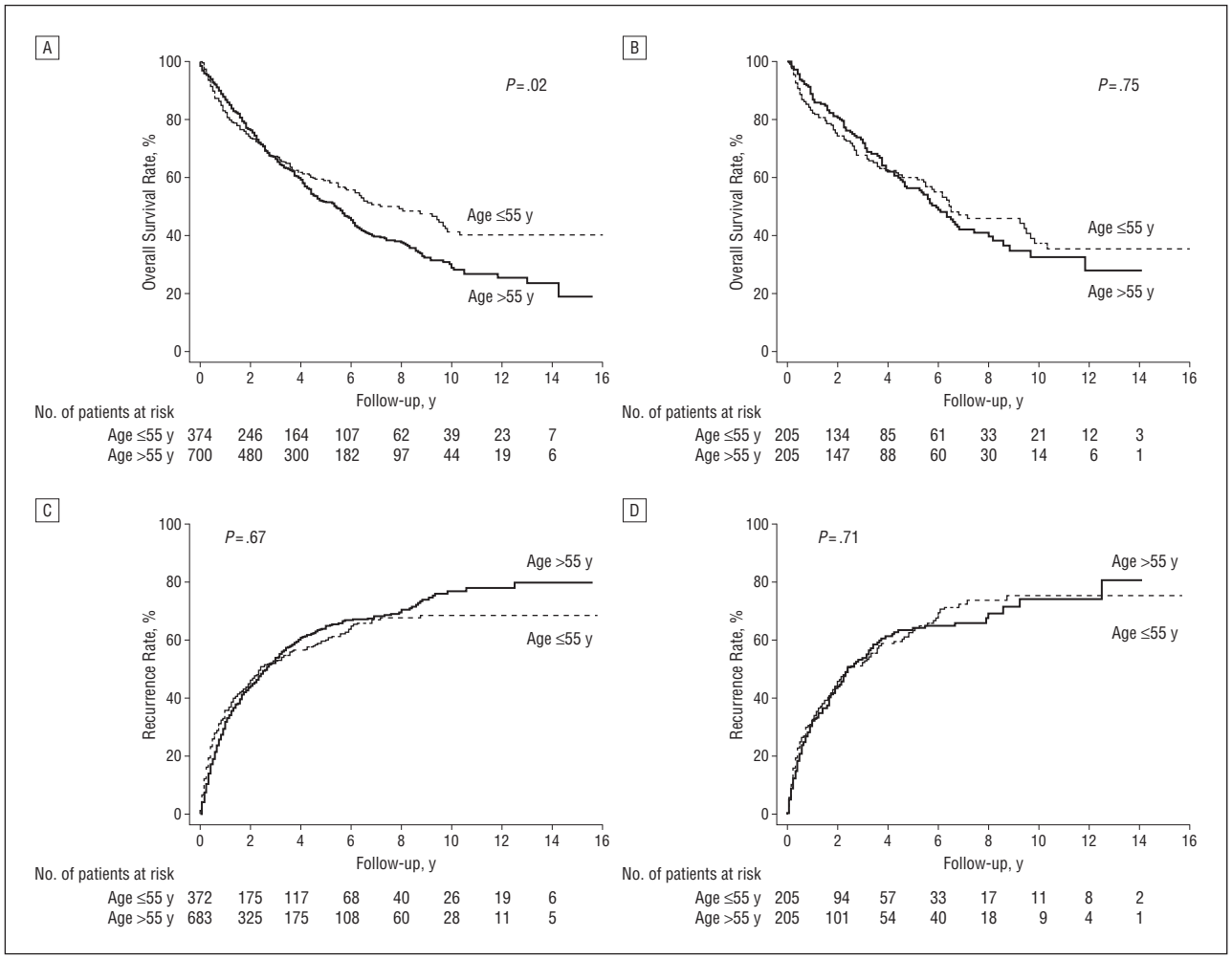


**Figure.** A, Cumulative overall survival in patients with hepatocellular carcinoma stratified by age. Patients who were 55 years of age or younger had a better overall survival rate than did patients who were older than 55 years of age (*P*=.02). B, Cumulative overall survival in patients with hepatocellular carcinoma by propensity score matching analysis. The overall survival rates were similar between younger patients and older patients after matching with the propensity analysis (*P*=.75). C and D, Cumulative rates of recurrence after resection surgery stratified by age. Younger patients with hepatocellular carcinoma had similar incidences of recurrence before (C) and after (D) matching with the propensity analysis.

are shown in eTable 1 (http://www.archsurg.com) and **Table 2**, respectively. These analyses disclosed that male sex, a serum albumin level of 4 g/dL or less (to convert to grams per liter, multiply by 10.0), a platelet count of $\times 10^5/mm^3$ or less, an indocyanine green dye retention rate at 15 minutes of greater than 10%, the occurrence of multinodularity, a tumor size of greater than 5 cm, and the presence of macroscopic and microscopic vascular invasion were the independent risk factors for predicting poor overall survival by multivariate analysis. Although the younger patients with HCC had a higher overall survival rate in the univariate analysis, age failed to predict overall survival by multivariate analysis.

## COMPARISON OF OVERALL SURVIVAL BETWEEN YOUNGER AND OLDER PATIENTS WITH HCC AFTER PROPENSITY SCORE CORRECTION WITH ONE-TO-ONE NEAREST-NEIGHBOR MATCHING METHOD

Because the demographic data were diverse between younger and older patients, we subsequently matched 205 pairs of cases by propensity score matching analysis to reduce the bias of comparison (eTable 2). After matching by sex, serum albumin level, aspartate aminotransferase level, indocyanine green dye retention rate at 15 minutes, platelet count, rate of seropositivity for hepatitis B surface antigen and anti-HCV antibody, tumor size and number, serum AFP levels, presence of macroscopic and microscopic vascular invasion, and type of surgery, the overall survival rates were also comparable between younger patients and older patients (Figure, B). Consequently, age was not apparent in predicting overall survival by both multivariate analysis and propensity score matching analysis.

## FACTORS ASSOCIATED WITH OVERALL SURVIVAL STRATIFIED BY AGE

**Table 3** shows the risk factors associated with overall survival for younger and older patients, respectively. For younger patients, a serum albumin level of 4 g/dL or less, an aspartate aminotransferase level of greater than 60 U/L (to convert to microkatals per liter, multi-



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**Table 2. Multivariate Analysis of Factors Associated With Overall Survival and Tumor Recurrence After Resection Surgery**

| Variable | HR (95% CI) | *P* Value |
|---|---|---|
| Survival | | |
| Male vs female | 1.550 (1.027-2.342) | .04 |
| Albumin level, ≤4 g/dL vs >4 g/dL | 1.488 (1.111-1.996) | .008 |
| Platelet count, ≤$10^5$/mm$^3$ vs >$10^5$/mm$^3$ | 1.517 (1.080-2.128) | .02 |
| ICG-15R, >10% vs ≤10% | 1.399 (1.041-1.880) | .03 |
| Multiple tumor, yes vs no | 1.603 (1.186-2.166) | .002 |
| Tumor size, >5 cm vs ≤5 cm | 1.356 (1.000-1.839) | .050 |
| Macroscopic vascular invasion, yes vs no | 1.591 (1.010-2.506) | .045 |
| Microscopic vascular invasion, yes vs no | 1.458 (1.079-1.971) | .014 |
| Recurrence | | |
| Albumin level, ≤4 g/dL vs >4 g/dL | 1.289 (1.000-1.661) | .050 |
| AST level, >60 U/L vs ≤60 U/L | 1.433 (1.105-1.859) | .007 |
| Multiple tumor, yes vs no | 1.403 (1.082-1.819) | .011 |
| Microscopic vascular invasion, yes vs no | 1.440 (1.107-1.874) | .007 |

Abbreviations: AST, aspartate aminotransferase; HR, hazard ratio; ICG-15R, indocyanine green dye retention rate at 15 minutes.

SI conversion factors: To convert albumin to grams per liter, multiply by 10.0; and to convert AST to microkatals per liter, multiply by 0.0167.

ply by 0.0167), an indocyanine green dye retention rate at 15 minutes of greater than 10%, the occurrence of multinodularity, an AFP level of greater than 20 ng/mL, and the presence of macroscopic vascular invasion were the independent risk factors associated with mortality by multivariate analysis.

For older patients, a serum albumin level of 4 g/dL or less, a platelet count of $10^5$/mm$^3$ or less, the occurrence of multinodularity, a tumor size of greater than 5 cm, and the presence of macroscopic and microscopic vascular invasion were associated with a poor prognosis. Both younger and older patients shared similar risk factors in overall survival, and both tumor factors and liver functional reserve were crucial in determining a prognosis irrespective of age.

## FACTORS ASSOCIATED WITH RECURRENCE AFTER SURGERY

After surgery, 643 patients had tumor recurrence, with a median time of development of 12.0 months (range, 1-150 months). The cumulative rates of recurrence at 1, 2, 3, 5, and 10 years were 33.1%, 44.8%, 53.4%, 63.0%, and 73.6%, respectively. The overall recurrence rates between younger and older patients were both comparable before and after matching with the propensity (Figure, C and D). However, younger patients with HCC had a higher rate of developing extrahepatic metastasis than did older patients with HCC (Table 1).

Our univariate and multivariate analyses for determining the risk factors associated with recurrence are shown in eTable 3 and Table 2, respectively. Multivariate analysis showed that a serum albumin level of 4 g/dL or less, an aspartate aminotransferase level of greater than 60 U/L, the occurrence of multinodularity, and the presence of microscopic vascular invasion were associated with higher incidence of developing recurrence after surgery.

The risk factors associated with recurrence in younger and older patients were demonstrated in **Table 4**. Multivariate analysis revealed that a serum albumin level of 4 g/dL or less, the occurrence of multinodularity, an AFP level of greater than 20 ng/mL, a cut margin of 1 cm or less, and the presence of macroscopic vascular invasion were independent risk factors associated with tumor recurrence in younger patients with HCC. For older patients with HCC, a serum albumin level of 4 g/dL or less,

**Table 3. Multivariate Analysis of Factors Associated With Poor Overall Survival After Resection Surgery Stratified by Age**

| Variable | Cases, No. | HR (95% CI) | *P* Value |
|---|---|---|---|
| Younger patients (n=374) | | | |
| Albumin level | | | |
| ≤4 g/dL | 171 | 1.701 (1.147-2.525) | .008 |
| >4 g/dL | 199 | | |
| AST level | | | |
| >60 U/L | 129 | 1.801 (1.223-2.654) | .003 |
| ≤60 U/L | 242 | | |
| ICG-15R | | | |
| >10% | 132 | 1.505 (1.010-2.244) | .045 |
| ≤10% | 232 | | |
| Multiple tumor | | | |
| Yes | 160 | 2.047 (1.358-3.085) | .001 |
| No | 212 | | |
| AFP level | | | |
| >20 ng/mL | 237 | 1.743 (1.133-2.681) | .012 |
| ≤20 ng/mL | 129 | | |
| Macroscopic vascular invasion yes/no | | | |
| Yes | 68 | 1.743 (1.133-2.681) | .012 |
| No | 304 | | |
| Older patients (n=700) | | | |
| Albumin level | | | |
| ≤4 g/dL | 355 | 1.580 (1.263-1.976) | <.001 |
| >4 g/dL | 333 | | |
| Platelet count | | | |
| ≤$10^5$/mm$^3$ | 130 | 1.661 (1.284-2.151) | <.001 |
| >$10^5$/mm$^3$ | 524 | | |
| Multiple tumor | | | |
| Yes | 281 | 1.416 (1.116-1.798) | .004 |
| No | 416 | | |
| Tumor size | | | |
| >5 cm | 235 | 1.358 (1.061-1.737) | .02 |
| ≤5 cm | 463 | | |
| Macroscopic vascular invasion | | | |
| Yes | 92 | 2.075 (1.493-2.882) | <.001 |
| No | 604 | | |
| Microscopic vascular invasion | | | |
| Yes | 443 | 1.310 (1.021-1.681) | .03 |
| No | 256 | | |

Abbreviations: AFP, α-fetoprotein; AST, aspartate aminotransferase; HR, hazard ratio; ICG-15R, indocyanine green dye retention rate at 15 minutes.

SI conversion factors: To convert albumin to grams per liter, multiply by 10.0; to convert AST to microkatals per liter, multiply by 0.0167; and to convert AFP to micrograms per liter, multiply by 1.0.



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**Table 4. Multivariate Analysis of Factors Associated With Recurrence After Resection Surgery Stratified by Age**

| Variable | Cases, No. | HR (95% CI) | *P* Value |
|---|---|---|---|
| Younger patients (n=372) | | | |
| Albumin level | | | |
| ≤4 g/dL | 170 | 1.536 (1.167-2.024) | .002 |
| >4 g/dL | 198 | | |
| Multiple tumor | | | |
| Yes | 158 | 1.626 (1.204-2.196) | .002 |
| No | 212 | | |
| AFP level | | | |
| >20 ng/mL | 236 | 1.542 (1.140-2.085) | .005 |
| ≤20 ng/mL | 128 | | |
| Cut margin | | | |
| ≤1 cm | 240 | 1.427 (1.048-1.942) | .02 |
| >1 cm | 130 | | |
| Macroscopic vascular invasion | | | |
| Yes | 66 | 1.650 (1.146-2.375) | .007 |
| No | 304 | | |
| Older patients (n=683) | | | |
| Albumin level | | | |
| ≤4 g/dL | 343 | 1.353 (1.099-1.667) | .004 |
| >4 g/dL | 328 | | |
| AST level | | | |
| >60 U/L | 232 | 1.303 (1.057-1.608) | .013 |
| ≤60 U/L | 445 | | |
| Multiple tumor | | | |
| Yes | 270 | 1.506 (1.221-1.857) | <.001 |
| No | 410 | | |
| Tumor size | | | |
| >5 cm | 228 | 1.274 (1.031-1.573) | .03 |
| ≤5 cm | 453 | | |
| AFP level | | | |
| >20 ng/mL | 336 | 1.239 (1.009-1.522) | .04 |
| ≤20 ng/mL | 331 | | |
| Cut margin | | | |
| ≤1 cm | 475 | 1.353 (1.079-1.701) | .009 |
| >1 cm | 204 | | |
| Microscopic vascular invasion | | | |
| Yes | 431 | 1.474 (1.181-1.840) | .001 |
| No | 251 | | |

Abbreviations: AFP, α-fetoprotein; AST, aspartate aminotransferase; HR, hazard ratio.

SI conversion factors: To convert albumin to grams per liter, multiply by 10.0; to convert AFP to micrograms per liter, multiply by 1.0; and to convert AST to microkatals per liter, multiply by 0.0167.

an aspartate aminotransferase level of greater than 60 U/L, the occurrence of multinodularity, a tumor size of greater than 5 cm, an AFP level of greater than 20 ng/mL, a cut margin of 1 cm or less, and the presence of microscopic vascular invasion were correlated with tumor recurrence after resection.

## COMMENT

Consistent with previous studies,[15,20,27] the results herein indicate that, based on 2 lines of evidence, younger patients with HCC have more advanced tumor factors than do older patients with HCC. First, younger patients have larger tumor sizes, higher serum AFP levels, higher incidences of macroscopic vascular invasion, more advanced Barcelona Clinic Liver Cancer stages and higher Cancer of the Liver Italian Program scores at presentation, and higher rates of major surgery. Second, they have a higher incidence of developing extrahepatic recurrence during follow-up. There are 3 possible mechanisms involved: the process of hepatocarcinogenesis may be different between these 2 groups; the younger patients have a delayed diagnosis; or the stringent selection criteria for resection surgery preclude older patients with advanced tumor stages from being candidates for the surgery.

In the present study, the risk factors associated with overall survival and recurrence are similar between the 2 groups, which implies that they may share a similar process of hepatocarcinogenesis and that younger patients may have a delayed diagnosis due to unawareness and lack of surveillance. In the 2 recent studies from Hong Kong[18] and Italy,[20] younger patients diagnosed with HCC more often had symptomatic presentations and were less likely to be identified by surveillance. If tumors could be detected at the early stage by surveillance and if curative therapy is instituted early, long-term cancer-free survival can be expected in the younger patients owing to better liver functional reserve.

Both tumor factors and liver functional reserve are crucial to predicting the postoperative prognosis in patients with HCC.[11,14] The novelty of the present study is that we provide a comprehensive analysis of age-related clinicopathologic features and prognoses from a large patient cohort with an adequate follow-up period at a single medical center. In our cohort, the younger patients with HCC had more advanced tumor factors but better liver functional reserve than did the older patients with HCC. We performed multivariate analysis and propensity score matching analysis to compensate for the confounding factors between the younger and older patients with HCC. These analyses helped better clarify the true effect of age on the postoperative prognosis of HCC. After using the one-to-one nearest-neighbor matching method, we reanalyzed the patients for comparable clinicopathologic characteristics. Although the overall survival rate was higher in the younger patients before matching, the effect of age on prognosis was not obvious by multivariate analysis or by propensity score matching analysis, which suggests that the better prognosis of younger patients might be attributed to their better liver function reserve, not to age per se. Also, it implies that older patients with HCC still have a good long-term prognosis after resection if they exhibit better liver functional reserve. They should be encouraged to undergo aggressive curative resection surgery.

In the present study, the occurrence of multinodularity is an important independent risk factor for predicting overall survival and recurrence in both younger and older patients with HCC. Nevertheless, larger tumor size (>5 cm) is only associated with the prognosis of older patients. It is not an independent risk factor correlated with overall survival and recurrence in the younger patients. In our cohort, a higher proportion of younger patients than older patients received major surgery (39.8% vs 25.2%; $P<.001$), which implies that the older patients might have a higher incidence of undergoing lim-



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ited resection owing to relatively poor liver functional reserve because of large tumors. Consequently, the incidence of recurrence would be increasing owing to the presence of potential undetectable viable tumors. However, younger patients were more likely to receive a more aggressive resection with the advantage of complete excision of tumor tissue and hepatic parenchyma around the tumor, which might have undetectably micrometastasized to the hepatic vein. Therefore, the effect of tumor size on prognosis is not so obvious if the patients could receive complete curative resection owing to well-preserved liver function.

Our study also demonstrates that the majority of younger patients with HCC have hepatitis B virus (HBV) infection, whereas HCV plays a more important role in the hepatocarcinogenesis of older patients. The mechanism may be attributed to several factors. First, HBV infection is endemic in Taiwan, and most patients are infected during the perinatal period or in early childhood; HCV exposure most often occurs in adulthood. Because hepatocarcinogenesis is a complex process, it needs time to accumulate sufficient mutations.[1,2] It is not surprising to find that most younger patients have HCC that is caused by HBV infection rather than HCV infection owing to the longer time of HBV infection and incubation. Second, HBV can integrate into the host genome, which may lead to direct hepatocarcinogenesis in the absence of background fibrosis or cirrhosis. Moreover, the HBV X protein has been shown to be an important oncogenic stimulus for the development of HCC.[28] It plays a crucial role in modulating the process of gene transcription, protein degradation, apoptosis, and signaling pathways.[28] A previous study[29] showed that childhood HCC in Taiwan is almost always attributed to HBV infection and that the nationwide universal vaccination program has reduced the incidence of childhood HCC, suggesting a close relationship between childhood HCC and HBV.

However, viral factors are not the independent risk factors associated with overall survival or recurrence by multivariate analysis. Moreover, we also performed propensity score matching analysis to minimize the effect of confounding factors and to evaluate the true effect of age on the long-term prognosis for patients with HCC undergoing resection surgery. After matching, we found that the younger and older patients with HCC had comparable demographic and tumor characteristics, including viral status (eTable 2). And they still had comparable overall survival rates and recurrence rates, consistent with the results of multivariate analysis.

In conclusion, we found that age is not a risk factor to determine the prognosis of patients with HCC who underwent resection. Older patients with HCC who have good liver functional reserve are encouraged to receive resection surgery.

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