Research Paper

Management of hepatocellular carcinoma in patients who are 70 years or older ☆

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ABSTRACT

Background: Although liver transplantation has been done successfully in elderly patients with hepatocellular carcinoma, these are likely well-selected patients. This study uses a large database of patients with hepatocellular carcinoma to explore treatment and potential candidacy for liver transplantation in the elderly.
Methods: Retrospective review of 1,533 hepatocellular carcinoma cases identified 2 groups: 475 patients 70 years or older (70+) and 1,058 patients <70 years. Demographics, risk factors, tumor characteristics, treatments, and survival were compared. Three- and 5-year survival rates were determined, and logistic regression was used to identify factors predictive of 3-year survival.
Results: Patients 70+ were more likely to have metabolic factors and less likely to have viral hepatitis, cirrhosis, hepatocellular carcinoma found with surveillance (21.7% vs 28.4%, P = .005), and hepatocellular carcinoma within Milan criteria (37.3% vs 43.8%, P = .019). Model for End-stage Liver Disease score was similar, but patients 70+ had higher mean creatinine and lower mean bilirubin. Patients 70+ were equally likely to undergo liver resection but less likely to undergo liver transplantation (0.4% vs 10.2%, P < .001). Three- and 5-year survival rates were significantly worse in 70+, and predictors of 3-year survival included hepatocellular carcinoma found with surveillance, meeting Milan criteria, and normal alpha fetoprotein.
Discussion: Elderly patients with hepatocellular carcinoma were less likely to undergo liver transplantation potentially due to metabolic factors and advanced disease. Although there is no age cutoff for liver transplantation, elderly patients should be given realistic expectations of liver transplantation candidacy. Continued surveillance for hepatocellular carcinoma in elderly patients may allow for earlier diagnosis and improved liver transplantation candidacy.
Key Message: Hepatocellular carcinoma in patients who are 70 years or older can be managed with liver transplantation in select cases, but more patients will be managed with liver resection and nonoperative therapies.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer in men and ninth most common cancer in women worldwide and was responsible for more than 830,000 deaths in 2020 [1]. Among the available therapeutic options for HCC, liver resection and transplantation offer the best long-term survival, with transplantation having superior disease-free survival [2]. However, transplantation is limited by the

scarcity of available donor livers. In the United States, 8,906 liver transplantations (LTs) were performed in 2020, whereas more than 13,000 patients continue to wait for transplant. Approximately 17.1% of these patients have HCC. Of the waitlisted patients, 20.8% were 65 years or older in 2019 compared to 8.9% in 2009 [3]. The proportion of elderly patients with HCC listed for LT has also tripled from 2003 to 2017 [4].

With the limited number of available donor livers and LT being a high-risk procedure, transplant centers must carefully select recipients to maximize utilization of each liver. Although Organ Procurement and Transplantation Network data show that recipients older than 65 years have worse 5-year graft survival compared to all other age groups, several studies have shown comparable outcomes between elderly and younger LT recipients [3,5–7]. These studies utilized large databases from individual transplant centers or the Scientific Registry of Transplant Recipients, and they generally included patients who had been

referred to transplant centers or undergone LT. These are thus patients who are already well-selected and likely the "best" elderly patients. There are likely many more patients who were not acceptable candidates for referral and whose outcomes have not been explored.

With an aging global population, HCC in the elderly is expected to rise. Aging itself can also be a risk factor in HCC development. In a national study of 504,646 patients from 2002 to 2013, each 5-year age increment was associated with a 1.24-fold increased risk in HCC development [8]. HCC in the elderly is associated with different clinical characteristics when compared to HCC in younger populations. The elderly are more likely to have medical comorbidities and metabolic diseases, such as diabetes, obesity, and nonalcoholic fatty disease/nonalcoholic steatohepatitis (NASH). Based on existing nonalcoholic fatty disease/ NASH epidemiology data, modeling suggests that HCC related to NASH in the aging population will only continue to increase [9]. It is thus imperative that we develop an optimal management plan for the increasing elderly patients with HCC.

This study uses a detailed database of a large patient cohort with HCC from various referral sources to examine the proportion of elderly patients who would reasonably qualify for LT and to identify factors that may have affected their candidacy and outcome.

METHODS/MATERIALS

Patients. This was a retrospective study of 1,533 HCC cases referred over a 28-year period (1993–2021) to a group of physicians who were associated with the only LT and liver disease center in Hawaii. It was also the tertiary referral center for the American Territories of the Pacific Basin (including Samoa, Guam, Saipan, the Marshall Islands, and Federated States of Micronesia). These centers were initially affiliated with St Francis Medical Center before 2012 and then with the Queen's Medical Center after 2012. These comprised about 60%–70% of all the HCC cases in Hawaii. This study was approved by the Institutional Review Board of The University of Hawaii at Manoa. In compliance with ethical regulations, all data were deidentified prior to use and thus exempt from patient consent.

Most HCCs were diagnosed histologically by percutaneous biopsy or at surgery. In the first decade, consistent with the previous United Network for Organ Sharing policy regarding transplant for HCC, patients without histologic confirmation were included if they had a history of chronic liver disease, a mass of at least 2 cm seen on 2 imaging studies (ultrasound, computed tomographic [CT] scan, or magnetic resonance imaging [MRI]), and 1 of the following: (1) vascular blush evident on CT scan or MRI, (2) alpha fetoprotein (AFP) > 200 ng/mL, or (3) arteriogram confirming the tumor. More recently, the diagnosis of HCC was frequently made with imaging alone if a contrast-enhanced study (dynamic CT or MRI) showed typical arterial enhancement with "washout" in the venous phase, as described by the American Association for the Study of Liver Disease guidelines [10,11].

Data Collected. Information on demographics, medical history, laboratory data, tumor characteristics, treatment, and survival was collected from clinical records. Demographic data included age, sex, birthplace, and self-reported ethnicity. Ethnicity was then categorized as "White," "Asian," "Pacific Islander," "Hispanic," "Black," or "Other" (which included mixed ethnicity and Native Americans). Medical history included diabetes mellitus, hyperlipidemia, smoking, and risk factors for HCC: viral hepatitis, significant alcohol use (defined as 2 or more alcoholic beverages daily for at least 10 years), and other chronic liver diseases. We also recorded any known family history of HCC. Measured height and weight were used to determine body mass index (BMI). *Obesity* was defined as BMI ≥ 30.

Laboratory data were obtained within 2 weeks of the initial visit, which included bilirubin, albumin, prothrombin time with international normalized ratio (INR), creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), platelet count, and AFP. Hepatitis B

and C serologies were obtained if unknown. We also noted patients with hepatitis B core antibody positivity in the absence of hepatitis B surface antigen positivity. AFP was categorized as "normal" if the value was less than 20 ng/mL.

We collected information on the presences of ascites, encephalopathy, and/or tumor rupture at presentation. Childs–Turcotte–Pugh score and Model for End-stage Liver Disease (MELD) score were calculated. AST/platelet ratio (APRI) was used as a surrogate marker for liver fibrosis.

Although our Liver Center recommended HCC surveillance in patients with chronic viral hepatitis and/or cirrhosis using biannual AFP and liver ultrasound, there was no uniform screening protocol used in the cohort as referring physicians used a combination of AFP and/or imaging (ultrasound, CT scan, or MRI) at variable intervals. HCC was deemed to be found with "surveillance" if the patient had a previous negative imaging study from 3 to 12 months before the positive study. Patients without surveillance had symptomatic HCC (pain, abdominal mass, weight loss, jaundice) or incidental HCC diagnosed with imaging for unrelated reasons. We also noted if patients had chronic viral hepatitis or known cirrhosis, for which surveillance would be warranted.

Tumor characteristics were determined with contrast-enhanced imaging. We recorded the largest tumor size, number of tumors, and whether the patients' tumor met Milan criteria (single tumor <5 cm or 2–3 tumors all <3 cm). Liver cirrhosis was determined by either liver biopsy or imaging.

Treatments. Treatments included liver resection, transplantation, locoregional therapies (radiofrequency ablation, cryosurgery, percutaneous ethanol injection, transarterial chemoembolization [TACE], or yttrium-90 radioembolization), and systemic therapies. Liver resection was considered in patients with good underlying liver function and no evidence of portal hypertension. LT was considered in patients with unresectable HCC within Milan criteria. All liver resections and transplantations were performed by a single surgical group practice.

Statistical Analysis. Patients were divided into 2 groups; patients less than 70 years of age (age < 70) and those who were 70 years or older (age 70 +) All analyses were performed using Excel (Microsoft) and SPSS statistical software (IBM, version 27). Categorical variables were analyzed using χ^2 analysis, and post hoc testing was performed using the Bonferroni method as appropriate. Continuous variables were analyzed using Mann–Whitney *U* test. Odds ratios with 95% confidence intervals (CIs) were calculated using binary logistic regression. Overall survival was evaluated using Kaplan–Meier and Cox regression analyses.

Results

In the entire cohort of 1,533 patients, mean age was 63.7 years (SD 11.3 years). There were 1,145 men and 388 women. Ethnicity distribution was as follows: Asians, 869 (56.7%); White, 320 (20.9%); Pacific Islander, 241 (15.7%); Hispanic, 35 (2.3%); Black, 10 (0.7%); and Other, 58 (3.8%). Distribution of the Asian races was as follows: Japanese, 348; Filipino, 207; Chinese, 170; Korean, 70; Southeast, 65; and Mixed Asian, 9. In terms of birthplace, 61% were born in the United States, 28.4% were born in an Asian country, and 5.2% were born in a Pacific Island Nation/US Territory.

In terms of risk factors, 375 patients (24.5%) were hepatitis B surface antigen positive, and 166 (10.8%) were hepatitis B core antibody positive in the absence of hepatitis B surface antigen positivity. Hepatitis C positivity was noted in 615 patients (40.1%), and 212 patients had NASH (13.8%). Significant alcohol use was noted in 660 patients (43.1%), and smoking history was noted in 947 patients (61.8%). However, only 205 (13.4%) were currently smoking. A family relative with HCC was noted in 102 patients (6.6%).

Table 1

Patient demographics and risk factors

	Age < 70 (n = 1056)	Age 70 + (n = 477)	P value
Male, no. (%)	827 (78.3)	318 (66.7)	P < .001
Ethnicity			P < .001
Asian, no. (%)	527 (49.9)	342 (71.7)	
White, no. (%)	250 (23.7)	70 (14.7)	
Pacific Islander, no. (%)	194 (18.4)	47 (9.9)	
Hispanic, no. (%)	26 (2.5)	9 (1.9)	
Black, no. (%)	10 (0.9)	0 (0.0)	
Other, no. (%)	49 (4.6)	9 (1.9)	
Finished high school, no. (%)	637 (83.1)	271 (78.6)	P = .07
Hepatitis B surf Ag positive, no. (%)	299 (28.4)	76 (16.1)	P < .001
Hepatitis B core Ab positive, no. (%)	100 (9.5)	66 (14)	P = .01
Hepatitis C positive, no. (%)	509 (48.4)	106 (22.3)	P < .001
Alcohol, no. (%)	522 (49.6)	138 (29.1)	P < .001
NASH, no. (%)	90 (8.5)	122 (25.8)	P < .001
HCC found with surveillance, no. (%)	300 (28.4)	103 (21.6)	P = .005
Screenable disease, no. (%)	885 (83.8)	256 (53.8)	P < .001
Previous other cancer, no. (%)	109 (10.3)	93 (19.5)	P < .001
Smoking, no. (%)	688 (66.2)	259 (54.8)	P < .001
Diabetes mellitus, no. (%)	324 (30.7)	229 (48.1)	P < .001
Hyperlipidemia, no. (%)	215 (20.8)	212 (45.2)	P < .001
Hypertension, no. (%)	463 (51.4)	319 (77.8)	P < .001
Obesity (BMI > 30), no. (%)	257 (26.7)	74 (17.7)	P < .001
BMI, mean (SD), kg/m^2	27.6 (8.4)	26.1 (4.9)	P < .001

Table 1 compares demographics and risk factors between the 2 groups. Both groups had a male predominance. However, this predominance was less evident in the older patients. Ethnicity distribution was also different between the groups, notably with 71.7% of the age 70 + group being Asian. Hepatitis B surface antigen and hepatitis C were more likely to be positive in the age < 70 group, whereas there was a higher proportion of the age 70 + group who had hepatitis B core antibody positivity only. Older patients were more likely to have NASH, diabetes, hypertension, and hyperlipidemia, whereas younger patients were more likely to have obesity and higher mean BMI. Older patients were less likely to have a screenable disease (53.8% vs 83.8%, P < .001) and were less likely to have their HCC found with surveillance (21.6% vs 28.4%, P < .005).

Age 70 + patients had a larger mean tumor size and were more likely to have single tumors but less likely to have HCC that met Milan criteria. Older patients had a lower APRI score and were less likely to have cirrhosis (Table 2). Although MELD scores were similar in the groups, younger patients had higher bilirubin and prothrombin time and a lower creatinine.

Age 70 + patients were just as likely to undergo liver resection as those who were age < 70. Significantly more patients in the age

< 70 group underwent LT compared to those age 70 + (10.2% vs 0.4%, P < .001). One-year survival was similar for both groups but significantly worse for older patients at 3 and 5 years (Table 3). On Kaplan–Meier analysis, age 70 + has worse mean median survival time (1.65 years; 95% CI: 1.34–1.96) than age < 70 group (2.91 years; 95% CI: 2.39–3.43) (Fig 1). The significant positive predictors for 3- and 5-year survival were HCC within Milan criteria and HCC found on surveillance. Age 70 + was the strongest negative predictor of 3- and 5-year survival (Table 4).

DISCUSSION

Many studies have shown that elderly patients can tolerate liver resection, locoregional therapy, and systemic therapies for management of HCC. In a large Italian multicenter retrospective cohort study, 1,834 HCC cases from 1987 to 2004 were separated into the elderly (age ≥ 70, n = 614) and younger (<70, n = 1104) and were followed for a median of 15 months [12]. With propensity matching, the median survival was equivalent between the older and younger patients for each therapy: hepatic resection, percutaneous ablation, TACE, or other/palliation for treatment. They concluded that age over 70 did not affect life expectancy and the overall applicability of each therapy for HCC. Similar

Table 2

Tumor characteristics and laboratory values

	Age < 70 (n = 1056)	Age 70 + (n = 477)	P value
Tumor size, mean (SD), cm	5.6 (4.4)	6.2 (4.3)	P < .001
Bilateral, no. (%)	134 (14.7)	57 (13.3)	P = .51
Single tumor, no. (%)	690 (67.2)	350 (73.8)	P = .009
Met Milan criteria, no. (%)	462 (43.8)	178 (37.4)	P = .02
Normal AFP, no. (%)	414 (39.4)	212 (45.0)	P = .04
AFP, mean (SD), ng/mL	11,980 (54576)	9743 (60365)	P = .006
Cirrhosis, no. (%)	774 (74.4)	303 (64.6)	P < .001
Rupture, no. (%)	40 (3.8)	18 (3.8)	P = .99
APRI, mean (SD)	0.79 (0.84)	0.45 (0.64)	P < .001
MELD, mean (SD)	10.5 (4.5)	10.2 (4.09)	P = .56
Childs–Turcotte–Pugh Score, mean (SD)	6.5 (2.0)	5.9 (1.4)	P < .001
Bilirubin, mean (SD), mg/dL	1.7 (2.7)	1.2 (1.7)	P < .001
Albumin, mean (SD), g/dL	3.52 (0.74)	3.71 (0.63)	P < .001
Prothrombin time, mean (SD), s	14.6 (2.4)	14.1 (2.0)	P < .001
INR, mean (SD)	1.18 (0.27)	1.13 (0.23)	P < .001
Platelets, mean (SD), 10^3/μL	161.3 (95.8)	183.0 (92.5)	P < .001
Creatinine, mean (SD), mg/dL	0.98 (0.71)	1.18 (0.93)	P < .001
AST, mean (SD), IU/L	91.5 (84.8)	61.8 (54.2)	P < .001
ALT, mean (SD), IU/L	67.0 (60.5)	50.6 (45.2)	P < .001

Table 3
Patient treatment and outcome

	Age < 70 (n = 1056)	Age 70 + (n = 477)	P value
Transplantation, no. (%)	108 (10.2)	2 (0.4)	P < .001
Liver resection, no. (%)	211 (20.0)	84 (17.6)	P = .28
Nonsurgical therapy only, no. (%)	499 (47.3)	266 (55.8)	P = .002
No therapy, no. (%)	241 (22.8)	125 (26.5)	P = .15
1-y survival, no. (%)	667 (66.0)	282 (62.3)	P = .16
3-y survival, no. (%)	432 (45.8)	132 (31.5)	P < .001
5-y survival, no. (%)	321 (35.8)	66 (16.8)	P < .001

conclusions were made in separate single center studies performed in Taiwan and Korea, in which elderly patients had comparable survival outcomes to younger patients undergoing the same therapy, including surgical resection, ablation, or TACE [13,14].

Several studies have compared LT in older and younger patients. One of the earliest retrospective studies reported 1,446 LT recipients over a 13-year period. Overall, elderly patients (age ≥ 60, n = 241) had worse survival than younger patients (age < 60, n = 1205), with age over 60 being an independent risk factor for poor survival. Worse survival was noted in older patients with low albumin, marked prolonged INR, Childs–Turcotte–Pugh score > 10 points, severely malnourished, and hospitalized patients. However, older patients with bilirubin < 10 mg/dL had similar survival outcomes as younger patients [15]. Lipshutz et al compared LT outcomes in 62 patients aged 70 or older to 864 patients age 50–59 years. Although there was no difference in survival between the groups, death after the first year was generally due to chronic conditions, including cardiovascular disease, for which advanced age was a strong risk factor [16]. Sonny et al in a retrospective study of 223 older (age ≥ 60 years) LT recipients and 515 younger recipients found no difference in 1-year mortality or composite outcome. However, age > 65 years was an independent predictor for 1-year mortality. Coronary artery disease and arrhythmias were independent predictors for 1-year composite outcome. They suggested that carefully selected older recipients had comparable outcomes to younger recipients, but the elderly needed better pretransplant evaluation and cardiovascular disease optimization [17]. Finally, in a retrospective study of 1,529 HCC patients from 2002 to 2019, long-term outcomes were

analyzed for 538 LT patients and 162 patients who had liver resection, stratified by age. Patients older than 65 were less likely to be considered or listed for LT (27% vs 73%, P < .01). However, for patients who underwent LT, the overall survival, disease-specific survival, and disease-free survival were not significantly different between the groups. LT patients older than 65 years were more likely to be disease-free and alive at the end of the study period. They suggested that older candidates were less likely to be considered for transplant, but judicious selection can lead to comparable survival to younger patients [5].

In these studies on LT, the study population consisted of patients who were referred to transplant centers or had undergone LT. These are inherently highly selected patients that medical professionals had assessed and deemed fit enough to tolerate the stress of LT. Thus, it is not a great surprise that the elderly had comparable posttransplant outcomes to the younger patients. However, this is with the caveat that these were carefully selected patients. Our study offers the unique perspective of HCC treatment in a heterogeneous population using a database with a broad referral pattern of all-comers. Consistent with many studies, we also showed that elderly patients were more likely to have NASH and associated metabolic risk factors. Our elderly patients were also less likely to have underlying viral hepatitis or cirrhosis. The lower mean APRI and higher mean platelet count also agree with lower incidence of cirrhosis and portal hypertension previously described in the elderly with HCC. Although MELD scores were similar, elderly patients were more likely to have a higher creatinine and lower bilirubin, suggesting that the elevation in MELD score in the elderly is mainly from a renal, rather than hepatic, etiology.
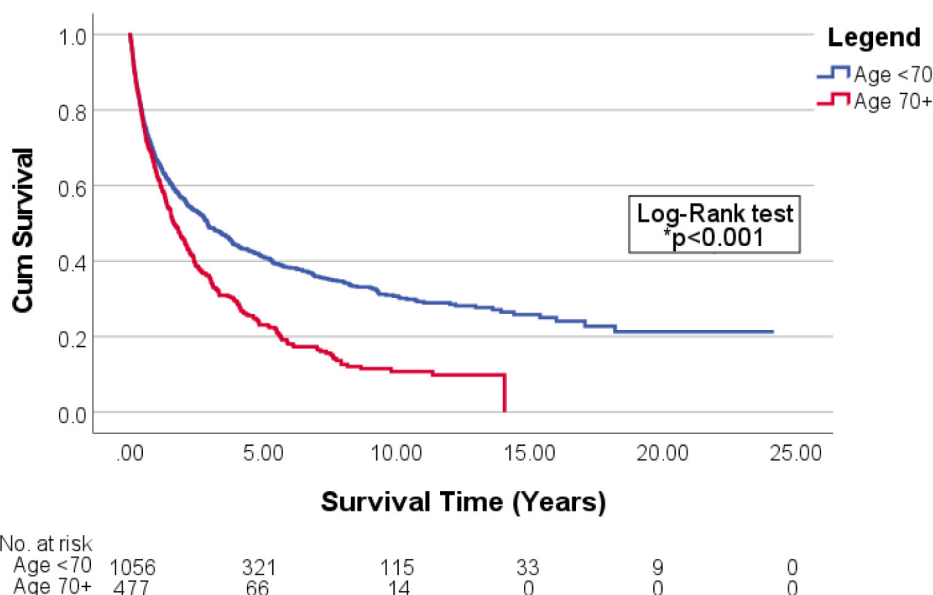

Fig 1. Overall patient survival by age group.

Table 4
Predictors of 3- and 5-year survival by binary logistic regression

Factors	3-y survival		5-y survival	
	OR (95% CI)	P value	OR (95% CI)	P value
Age 70 +	0.49 (0.35, 0.69)	P < .001	0.32 (0.22, 0.47)	P < .001
Male	1.01 (0.71, 1.42)	P = .975	1.18 (0.81, 1.72)	P = .39
Hepatitis B S Ag positive	1.24 (0.82, 1.88)	P = .315	1.09 (0.69, 1.71)	P = .714
Hepatitis C	1.03 (0.69, 1.53)	P = .889	0.87 (0.57, 1.35)	P = .54
Alcohol	0.83 (0.60, 1.14)	P = .248	0.62 (0.44, 0.88)	P = .008
NASH	0.71 (0.43, 1.17)	P = .174	0.59 (0.33, 1.06)	P = .08
Screened for HCC	1.51 (1.08, 2.10)	P = .015	1.45 (1.02, 2.06)	P = .04
Other cancer	0.94 (0.63, 1.39)	P = .739	1.02 (0.67, 1.57)	P = .91
Smoking	0.77 (0.57, 1.05)	P = .101	0.64 (0.46, 0.89)	P = .008
Diabetes	0.68 (0.49, 0.94)	P = .019	0.58 (0.41, 0.83)	P = .003
Hyperlipidemia	1.28 (0.90, 1.83)	P = .169	1.04 (0.70, 1.54)	P = .86
Hypertension	0.83 (0.61, 1.13)	P = .233	0.78 (0.56, 1.08)	P = .13
Normal AFP	1.88 (1.41, 2.51)	P < .001	1.56 (1.14, 2.13)	P = .005
Milan criteria	3.34 (2.47, 4.53)	P < .001	3.00 (2.15, 4.18)	P < .001
Cirrhosis	0.82 (0.58, 1.16)	P = .254	1.00 (0.68, 1.46)	P = .99
APRI[a]	0.74 (0.59, 0.92)	P = .008	0.82 (0.65, 1.03)	P = .09
MELD[b]	0.88 (0.84, 0.91)	P < .001	0.88 (0.84, 0.92)	P < .001

[a] APRI: AST to platelet ratio index.
[b] MELD: Model for end stage liver disease.

Despite less severe underlying liver disease, our elderly patients had more advanced HCC, as indicated by larger tumor size or being beyond Milan criteria. This is within the context of the elderly patients less likely to have HCC detected with surveillance. Within our study population, less than 1% of the elderly underwent LT compared to more than 10% of the younger patients. Elderly patients were more likely to have non-operative, locoregional therapy. Associated metabolic disease and more advanced HCC outside of Milan criteria likely contributed to decreased transplant candidacy. With logistic regression analysis, the only factors that contributed to survival included having HCC found with surveillance, normal AFP, and tumor within Milan criteria. Taken together, this suggested that surveillance and early detection of HCC in the elderly patients may have allowed for more treatment options, including LT, and better outcome.

Multiple retrospective studies have demonstrated the potential benefit of surveillance in enhancing early detection and ultimately improving survival [18–20]. The value of surveillance can be especially seen in countries like Japan, where LT is not as readily available. The Japan Society of Hepatology published clinical guidelines with recommendation of ultrasonographic and biomarker screening as frequently as every 3–4 months in high-risk patients [21]. With superior surveillance, Japanese centers have been able to find 63.5% of 19,536 HCCs in a 2-year period with a solitary nodule, with 56.6% being less than 3 cm [22]. In a study of 1,797 patients diagnosed with surveillance from two US and two Japanese centers, the Japanese patients were diagnosed with smaller tumor size and less advanced stage and were more likely to undergo curative treatment [23]. Median survival time was also longer in patients from Japan. After propensity matching analysis, there was better survival in Japanese patients who underwent resection. This study underlies the importance of a robust HCC surveillance program in improving overall patient outcome.

This study was limited as it was retrospectively designed and from a single institution with a high proportion of Asian patients. We likely had a higher influence of hepatitis B, as many patients emigrated from Asian or Pacific Island nations where hepatitis B was endemic. Furthermore, the specific reasons for a patient not undergoing LT were unclear. Insurance, financial, or psychosocial reasons may have contributed to noncandidacy. The exact cause of death was unknown, so it is unclear if death was specifically due to HCC.

Although this study may not completely reflect the population of all US centers, our study had granular data on risk factors and laboratory studies that are not typically collected in administrative databases. This study also provided information that would not be available from transplant centers that primarily evaluate early-stage HCC patients. LT is possible in well-selected elderly patients, but most elderly patients will not undergo LT. Although transplant centers may consider use of extended-criteria donors to increase the transplant rate in this population, it is unclear if this is the optimal solution. This study suggests that elderly patients are more likely to have metabolic comorbidities, NASH, and larger tumors. The elderly are less likely to have HCC that is found with surveillance or meets Milan criteria; however, it is possible that elderly patients have less advanced underlying liver disease that would warrant surveillance. Physicians should continue to refer appropriate elderly patients for LT, but patients should be given realistic expectations that many will not be candidates. Future studies will be needed to determine if better efforts at HCC surveillance in elderly patients will allow more elderly patients to undergo LT.

Author Contribution

The following are author contributions listed by author:
Wong: research design, performance of the research, writing of the paper.
Lee: data analysis, writing of the paper.
Karasaki: writing of the paper, research design.
Ogihara: writing of the paper, critical analysis.
Tran: writing of the paper, critical analysis.

Conflict of Interest

Dr Wong is on the speakers bureau for Eisai and Helsinn. All other authors have no conflicts to declare.

Funding Source

Ethics Approval

This study was approved by the Institutional Review Board of The University of Hawaii at Manoa. In compliance with ethical regulations, all data were deidentified prior to use and thus exempt from patient consent.

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