

Hepatocellular Carcinoma Survival by Etiology: A SEER-Medicare Database Analysis

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In the United States, hepatocellular carcinoma (HCC) survival varies with tumor characteristics, patient comorbidities, and treatment. The effect of HCC etiology on survival is less clearly defined. The relationship between HCC etiology and mortality was examined using Surveillance, Epidemiology, and End Results–Medicare data. In a cohort of 11,522 HCC cases diagnosed from 2000 through 2014, etiologies were identified from Medicare data, including metabolic disorders (32.9%), hepatitis C virus (8.2%), alcohol (4.7%), hepatitis B virus (HBV, 2.1%), rare etiologies (0.9%), multiple etiologies (26.7%), and unknown etiology (24.4%). After adjusting for demographics, tumor characteristics, comorbidities and treatment, hazard ratios (HRs) and survival curves by HCC etiology were estimated using Cox proportional hazard models. Compared with HBV-related HCC cases, higher mortality was observed for those with alcohol-related HCC (HR 1.49; 95% confidence interval [95% CI] 1.25–1.77), metabolic disorder–related HCC (HR 1.25; 95% CI 1.07–1.47), and multiple etiology-related HCC (HR 1.25; 95% CI 1.07–1.46), but was not statistically significant for hepatitis C virus–related, rare disorder–related, and HCC of unknown etiology. For all HCC etiologies, there was short median survival ranging from 6.1 months for alcohol to 10.3 months for HBV. *Conclusion:* More favorable survival was seen with HBV-related HCC. To the extent that HCC screening is more common among persons with HBV infection compared to those with other etiologic risk factors, population-based HCC screening, applied evenly to persons across all HCC etiology categories, could shift HCC diagnosis to earlier stages, when cases with good clinical status are more amenable to curative therapy. (*Hepatology Communications* 2020;4:1541–1551).

Hepatocellular carcinoma (HCC) is the sixth most commonly occurring cancer worldwide and is approximately tied with gastric cancer as the third leading cause of cancer mortality.⁽¹⁾ In the United States in 2018, there were 42,220 new diagnoses and 30,200 deaths due to liver cancer.⁽²⁾ The 5-year survival rate of persons with HCC is less than 20%⁽²⁾; however, survival varies by stage at diagnosis

and treatment.⁽³⁾ In general, patients with few comorbidities and preserved liver function who have small, isolated HCCs confined to the liver have the most favorable survival rate,⁽⁴⁾ and are most able to benefit from potentially curative therapies including ablation, resection, and transplantation.^(5,6)

HCC survival by etiology varies across studies. This reflects regional variation in HCC etiology⁽⁷⁾

Abbreviations: AASLD, American Association for the Study of Liver Diseases; CI, confidence interval; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; mCCI, modified Charlson Comorbidity Index; NAFLD, nonalcoholic fatty liver disease; SEER, Surveillance, Epidemiology, and End Results.

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in Asia,⁽⁸⁻¹²⁾ Europe,^(13,14) North America,^(15,16) and South America.⁽¹⁷⁾ Furthermore, the source of data on the relationship between HCC etiology and survival varies by site, including clinics,^(8,9,11,14,17) multicenter studies,^(10,18) cancer registries,^(13,15,16) and meta-analyses.^(16,19) Changes in clinical practice over time also affect HCC survival. While HCC had an almost universally poor prognosis as recently as the 1980s,^(8,20) uptake of HCC screening in some etiologic risk groups (e.g., people with hepatitis B virus [HBV] infection) increased the proportion of patients with HCC with early-stage diagnoses. HCC survival began to improve in the 1990s,^(11,12,16,18,19) and increased in the 2000s^(9,10,13-15,17) as more patients were diagnosed with early-stage HCC in the absence of severe comorbidities, making them candidates for curative ablation, resection, or transplantation. Studies of HCC survival by etiology have varied aims, from understanding the role of surveillance^(10,14) to the impact of surgery^(11,17,19) and other treatments.^(15,16) Some studies compared differences in survival only for selected etiologies such as HBV and hepatitis C virus (HCV) infections,^(8,9,11,12,19) or nonalcoholic fatty liver disease (NAFLD),⁽¹³⁾ diabetes,^(17,20) and alcohol.⁽¹⁵⁾ The present population-based study examines HCC survival by etiology based on Medicare claims data linked to Surveillance, Epidemiology, and End Results (SEER) cancer registry data from an area covering approximately one third of the U.S. population.⁽²¹⁾

In this SEER-Medicare study of 11,522 patients diagnosed with HCC from 2000 through 2014, relationships among mortality risk, survival, and HCC etiology (i.e., HCV, HBV, alcohol, metabolic disorders, rare disorders, multiple etiologies, and unknown

etiologies) were examined with adjustment for patient comorbidities, tumor characteristics, and therapy in addition to patient demographic characteristics.

Patients and Methods

The SEER-Medicare database is a linkage of SEER cancer registry data with Medicare claims data.⁽²²⁾ The SEER registries included in the current project include 18 cancer registries in 16 states and two metropolitan areas, covering approximately 34.6% of the U.S. population.⁽²³⁾ All registries, except the Alaska Native Registry, contributed data to the current analysis. The present study included HCC cases diagnosed between 2000 and 2014, with follow-up through December 31, 2015. Cases were identified using the International Classification of Diseases (ICD) for Oncology, Third Revision topography codes (C22) and morphology codes (8170-8175).⁽²⁴⁾ Of the 11,522 cases in the study cohort, 11 were coded to C22.1, whereas the rest were coded to C22.0. Analysis was restricted to the first HCC diagnosed per person.

Of the 41,019 HCC cases diagnosed, 11,522 were included in the current analysis. The remaining 29,497 were excluded for the following reasons: unknown month of diagnosis ($n = 454$), diagnosed before age 68 years old (allowing 3 years of burn-in after 65 years, the age requirement for Medicare eligibility), or diagnosed at age 101 years or older ($n = 18,021$), diagnosis based on autopsy or death certificate only ($n = 366$), death within 1 month of diagnosis ($n = 2,088$), or no tumor mass was found ($n = 19$). Persons not enrolled in Medicare Parts A and B continuously during the study period

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($n = 2,437$) and persons enrolled in a health maintenance organization (HMO) at any time during the study period ($n = 6,112$) were also excluded, as individual treatment data from HMOs were not available. A minimum participant age of 68 years was chosen to allow sufficient time after Medicare enrollment for risk factor identification.

The patient demographic variables of interest included gender, age at diagnosis, race, and ethnicity. A modified Charlson Comorbidity Index (mCCI)⁽²⁵⁾ that excluded diabetes and liver disease, risk factors for HCC, was included in the analysis to assess the overall extent of poor health. The mCCI was defined by scores from 0 to 6, with a higher score indicating a greater number of comorbidities.

Tumor characteristics included in the analysis were based on the following SEER variables: extent of disease (defined as a single nodule confined to the liver, multiple nodules confined to the liver, extension beyond the liver, and number of nodules not otherwise specified) and size of tumor (defined as greater or less than 5 cm or unknown). Tumor stage was categorized into localized, regional, distant, or unknown stage. Treatment was obtained from SEER data and classified as resection, transplantation, ablation (including radiofrequency ablation, cryoablation, percutaneous alcohol injection, or microwave ablation), external beam radiotherapy, and arterial directed therapy (including transarterial embolization, transcatheter arterial chemoembolization [TACE], drug-eluting beads TACE, and β -emitting yttrium-90).

International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes for classification of etiology are provided in Supporting Table S1.⁽²⁶⁾ The ICD-9-CM coding system is used to define diagnoses and procedures of hospital use in the United States. HCC etiology risk groups for analysis were HCV, HBV, alcohol-related disorders, metabolic disorders, rare disorders, multiple etiologies, and no etiology recorded. Trade-offs exist in the use of administrative codes to assign etiology. A case could be made to limit alcohol etiology codes to codes for alcohol dependence; however, we included alcohol-related liver damage to improve sensitivity. Code 5712 ("Alcoholic cirrhosis of liver") was the second-leading alcohol etiology-defining diagnosis in the study population. Two more alcohol-related liver codes were also included: 5713 ("Alcoholic liver damage, unspecified") and 5710 ("Alcoholic fatty liver"). These three

codes combined accounted for 350,383 of 1,496,645 (23.5%) cases with a reported etiology of alcohol.

In the classification system used, metabolic disorders included diabetes mellitus, obesity, NAFLD, impaired fasting glucose, and metabolic syndrome. Rare disorders known to be associated with HCC included hemochromatosis, Wilson disease, porphyrias, alpha-1 antitrypsin deficiency, and glycogen storage disorders. Multiple etiologies clustered into major groups were driven by the occurrence of metabolic disorders (87%), HCV (56%), and alcohol (49%), followed by HBV (21%) and rare etiologies (11%).

STATISTICAL ANALYSIS

Covariate adjusted survival analyses of all-cause mortality were conducted using multivariable Cox proportional hazard models to estimate adjusted hazard ratios and 95% confidence intervals (CIs).⁽²⁷⁾ HBV-related HCC was chosen as the referent group for analysis based on existing recommendations to screen HBV-infected individuals, which may confer favorable survival in comparison to other HCC-related etiologies.⁽⁴⁾ The time metric used was time on study. Patients with HCC diagnosed between the ages of 68 and 100 were followed from date of diagnosis of HCC until mortality or end of follow-up (December 31, 2015), whichever came first. The Cox proportional hazard regression models adjusted for age, and age-squared at diagnosis, gender, race/ethnicity, tumor extension and size, mCCI, and HCC therapies. In addition, results from the Cox regression modeling were used to plot the covariate adjusted survival curves for each etiology, from which the median survival time by etiology was obtained.⁽²⁸⁾ All analyses were conducted using SAS v9.2 (SAS Institute, Cary, NC).

Results

The demographic characteristics of the cases are given in Table 1. Among the 11,522 cases included in analysis, most were male (66.3%) and non-Hispanic white (64.3%). The most common age group at diagnosis was 68-75 years (46.5%), followed by 76-80 years (26.6%) and 81+ years (26.9%).

Forty-nine percent of the cases were assigned a single etiology, 26.7% had multiple etiologies, and 24.4%

TABLE 1. DEMOGRAPHIC CHARACTERISTICS OF HCC BY ETIOLOGY, SEER-MEDICARE, 2000-2014

	All HCC		Etiology						
			Metabolic*	HCV	Alcohol	HBV	Rare [†]	Multiple	Unknown
	11,522		3,801	944	543	240	109	3,075	2,810
	100.0%		33.0%	8.2%	4.7%	2.1%	0.9%	26.7%	24.4%
	n		%	%	%	%	%	%	%
Sex									
Male	7,639	66.3	65.7	50.1	86.4	72.5	47.7	69.3	65.6
Female	3,883	33.7	34.3	49.9	13.6	27.5	52.3	30.7	34.4
Race/Ethnicity									
NH white	7,405	64.3	70.9	54.3	73.7	23.3	84.4	55.4	69.2
NH black	823	7.1	4.3	11.2	—	—	—	10.1	6.8
NH Asian/PI	1,846	16.0	10.7	24.8	—	69.2	—	18.7	15.4
Hispanic	1,336	11.6	12.9	—	12.5	—	—	14.8	7.8
Other/unknown	112	1.0	1.2	—	—	—	—	1.0	0.8
Age at dx (years)									
68-75	5,353	46.5	39.6	52.0	53.8	55.4	47.7	58.8	38.2
76-80	3,070	26.6	29.4	25.4	28.0	22.1	29.4	25.2	24.9
81+	3,099	26.9	31.0	22.6	18.2	22.5	22.9	16.0	36.9

*Metabolic disorders include diabetes mellitus, obesity, NAFLD, impaired fasting glucose, and metabolic syndrome.

[†]Rare genetic disorders include hemochromatosis, Wilson disease, porphyrias, alpha-1 antitrypsin deficiency, and glycogen storage disorders.

Abbreviations: dx, diagnosis; NH, non-Hispanic; PI, Pacific Islanders.

had unknown etiology. The most common etiologic group was metabolic conditions (33.0%), followed by multiple etiologies (26.7%). The least common etiology was rare disorders (0.9%), which was diagnosed primarily among non-Hispanic white persons (84.4%). There was a higher proportion of males than females among patients with metabolic, alcohol, or HBV-related HCC, and a higher proportion of females than males among patients with HCC related to rare disorders. There was a higher proportion of Asian/Pacific Islanders than other race/ethnic groups among patients with HBV-related HCC. There was a higher proportion of patients aged 68-75 years among the three age groups across all of the etiology types.

Clinical characteristics of the cases are provided in Table 2. Most cases (83.6%) had an mCCI score of 0. Based on the mCCI score, 90.8% of persons with HBV-related HCC had no comorbidities, followed in descending order by cases with unknown etiology (89.9%), HCV (89.3%), alcohol (86.7%), rare diseases (86.2%), metabolic disorders (80.3%), and multiple etiologies (79.1%). Among all patients with HCC, less than one-third (32.7%) of the tumors were confined to

a single nodule in the liver, whereas over 40.0% were either multinodular or had extension beyond the liver. Approximately one-third (33.8%) of the tumors were 5 cm or less in size, whereas 39.8% were greater than 5 cm. Approximately half of the tumors were localized, 25.0% had regional extension, and 14.4% had distant extension. Patients with HBV-related HCC had the highest proportion of localized disease (single nodule 40.4%) and small tumors (43.8% \leq 5 cm). Cases with unknown etiology and rare disorder-associated HCC had the highest proportion of extension beyond the liver (16.3% and 15.6%, respectively). Cases with unknown etiology and with metabolic disorder-related HCC had the greatest proportion of large tumors (46.1% and 45.9% \geq 5 cm, respectively), whereas those with HCC related to HCV and multiple etiologies had the greatest proportion of small tumors (48.6% and 47.5%, respectively). Distant-stage diagnoses were seen most often with unknown etiology and metabolic disorders (16.8% and 16.5%, respectively), while localized stage disease was most often diagnosed among cases with HBV (57.1%), HCV (55.8%), and multiple etiologies (54.4%).

TABLE 2. CHARACTERISTICS OF HCC CASES, SEER-MEDICARE, 2000-2014

	All HCC		Etiology of HCC						
			Metabolic*	HCV	Alcohol	HBV	Rare [†]	Multiple	Unknown
	11,522		3,801	944	543	240	109	3,075	2,810
mCCI									
0	9,637	83.6	80.3	89.3	86.7	90.8	86.2	79.1	89.9
1	839	7.3	7.9	5.9	5.3	—	—	8.9	5.4
2+	1,046	9.1	11.7	4.7	8.0	—	—	12.0	4.7
Extension									
1 nodule in liver	3,766	32.7	31.9	35.6	27.1	40.4	31.2	34.7	31.0
>1 nodule in liver	3,293	28.6	26.0	31.3	35.0	34.2	25.7	31.7	26.1
Extension beyond liver	1,559	13.5	14.3	11.7	14.4	10.0	15.6	10.7	16.3
Number of nodules NOS	2,904	25.2	27.8	21.5	23.6	15.4	27.5	22.8	26.6
Tumor Size									
≤5.0 cm	3,897	33.8	26.6	48.6	33.0	43.8	37.6	47.5	22.8
≥5.1 cm	4,581	39.8	45.9	29.0	36.5	37.1	31.2	30.7	46.1
Unknown	3,044	26.4	27.5	22.4	30.6	19.2	31.2	21.8	31.1
Stage									
Localized	5,661	49.1	47.2	55.8	43.1	57.1	45.0	54.4	44.4
Regional	2,875	25.0	24.4	22.5	30.4	25.8	26.6	24.9	25.4
Distant	1,657	14.4	16.5	11.3	14.9	10.0	12.8	10.7	16.8
Unknown	1,329	11.5	11.9	10.4	11.6	7.1	15.6	10.0	13.3

*Metabolic disorders include diabetes mellitus, obesity, NAFLD, impaired fasting glucose, and metabolic syndrome.

[†]Rare genetic disorders include hemochromatosis, Wilson disease, porphyrias, alpha-1 antitrypsin deficiency, and glycogen storage disorders.

Abbreviation: NOS, not otherwise specified.

As indicated in Table 3, 72.3% of cases received no treatment; those patients most likely to receive no treatment had alcohol-related (81.4%) and metabolic disorder-related (73.1%) HCC, whereas 14.5% were treated with arterial directed therapy, 9.0% with resection, 3.0% with ablation, 2.8% with radiation, and 1.2% with transplantation (some patients had more than one type of treatment). Those with HBV, HCV, and rare disorder-related HCC were more likely to undergo treatment than those with other etiologies. Persons with HBV-related HCC had the highest rates of both resection and transplantation. Ablation was used most frequently for cases with HBV, HCV, and multiple etiologies. Arterial directed therapy was more frequently used for cases with HCV, HBV, and multiple etiologies.

Adjusted hazard ratios (HRs) for the associations between risk of mortality and demographic characteristics are provided in Table 4. In unadjusted models, continuous age at diagnosis was associated with earlier HCC death (HR = 1.03, 95% CI: 1.02-1.03);

however, the association was no longer significant after adjustment for demographic characteristics, modified comorbidity index, etiology, tumor characteristics, and treatment. Male sex was significantly associated with risk of HCC death in the univariate analysis (HR = 1.05, 95% CI: 1.00-1.09) but not in the multivariable model (HR = 0.98, 95% CI: 0.94-1.02). With the exception of three etiologies (HCV, rare disorders, and unknown), statistical significance was the same in the univariate and multivariable models. Thus, multivariable results are discussed subsequently.

In comparison to non-Hispanic whites, mortality was significantly lower among Asians/Pacific Islanders (HR = 0.78, 95% CI: 0.73-0.82), but no differences were seen with the other racial/ethnic groups. Compared with HBV-related HCC, significantly higher risk of mortality was estimated for alcohol-related (HR = 1.49, 95% CI: 1.25-1.77), metabolic disorder-related (HR = 1.25, 95% CI: 1.07-1.47), and multiple etiology-related (HR = 1.25, 95% CI: 1.07-1.46) HCC. Although mortality risk was

TABLE 3. TREATMENT OF HCC CASES, SEER-MEDICARE, 2000-2014

	All HCC		Etiology of HCC						
			Metabolic*	HCV	Alcohol	HBV	Rare [†]	Multiple	Unknown
	11,522		3,801	944	543	240	109	3,075	2,810
Any treatment									
Yes	3,192	27.7	26.9	32.8	18.6	39.6	32.1	29.2	25.9
No	8,330	72.3	73.1	67.2	81.4	60.4	67.9	70.8	74.1
Resection									
Yes	1,034	9.0	10.4	8.2	2.2	18.8	11.0	6.6	10.4
No	10,488	91.0	89.6	91.8	97.8	81.3	89.0	93.4	89.6
Transplantation									
Yes	142	1.2	0.8	—	—	—	—	2.1	0.4
No	11,380	98.8	99.2	>90.0	>90.0	>90.0	—	97.9	99.6
Radiation									
Yes	325	2.8	3.1	3.3	2.6	—	—	2.5	2.8
No	11,197	97.2	96.9	96.7	97.4	>90.0	—	97.5	97.2
Ablation									
Yes	346	3.0	2.6	4.9	—	—	—	4.5	1.6
No	11,176	97.0	97.4	95.1	>90.0	>90.0	—	95.5	98.4
Arterial directed									
Yes	1,670	14.5	12.8	18.9	11.8	17.5	13.8	16.7	13.2
No	9,852	85.5	87.2	81.1	88.2	82.5	86.2	83.3	86.8

*Metabolic disorders include diabetes mellitus, obesity, NAFLD, impaired fasting glucose, and metabolic syndrome.

[†]Rare genetic disorders include hemochromatosis, Wilson disease, porphyrias, alpha-1 antitrypsin deficiency, and glycogen storage disorders.

higher for patients with rare disorder–related (HR = 1.21, 95% CI: 0.94-1.56), HCV-related (HR = 1.17, 95% CI: 0.99-1.37), and unknown etiology (HR = 1.16, 95% CI: 0.99-1.35) HCC, these results were not statistically significant. Compared to cases with one nodule confined to the liver, those with extension beyond the liver had a significantly higher risk of mortality (HR = 1.99, 95% CI: 1.87-2.12). Compared to cases with tumor size ≤ 5 cm, those with tumor size >5 cm had higher risk of mortality (HR = 1.53, 95% CI: 1.46-1.61). Compared to persons who did not receive liver transplantation, liver transplantation was associated with lower risk of mortality (HR = 0.24, 95% CI: 0.19-0.31), as was resection versus no resection (HR = 0.36, 95% CI: 0.34-0.39) and ablation versus no ablation (HR = 0.61, 95% CI: 0.54-0.69). There was no significant difference between no radiation and any radiation therapy (HR = 0.95, 95% CI: 0.85-1.07).

Adjusted survival curves and median survival times by etiology are shown in Fig. 1. Cases with alcohol-related HCC had the shortest estimated median survival (6.1 months), whereas those with HBV-related

HCC had the longest estimated median survival (10.3 months).

Discussion

In this study of 11,522 persons with incident HCC, differences in HCC risk of mortality were seen by underlying etiology after controlling for tumor characteristics, comorbidities, and treatment. Compared to persons with HBV-related HCC, risk of mortality was significantly higher among persons with alcohol, metabolic, and multiple etiology–related HCC. Persons with HCV-related, rare disorder–related, and unknown etiology HCC also had higher risk of mortality, but differences from HBV-related HCC were not statistically significant. The large sample size provided robust insight into differences in HCC mortality risk and survival by etiology in the United States. Because of international and temporal variation in etiology, information comparing different etiologies is needed to optimize HCC prevention, surveillance, and therapeutic strategies.⁽⁷⁾ Gaps continue to exist

TABLE 4. ASSOCIATIONS AMONG CASE DEMOGRAPHICS, TUMOR CHARACTERISTICS, ETIOLOGY, TREATMENT, AND SURVIVAL, SEER MEDICARE, 2000-2014

	Unadjusted HR	95% CI	Adjusted HR	95% CI
Age at diagnosis	1.03	1.02-1.03	0.96	0.89-1.03
Age squared	1.00	1.00-1.00	1.00	1.00-1.01
Sex				
Female	1.00	referent	1.00	referent
Male	1.05	1.00-1.09	0.98	0.94-1.02
Race and ethnicity				
NH white	1.00	referent	1.00	referent
NH black	1.04	0.97-1.12	0.97	0.90-1.05
NH Asian/PI	0.68	0.65-0.72	0.78	0.73-0.82
Hispanic	0.96	0.90-1.01	0.96	0.91-1.03
Other, unknown	0.93	0.76-1.13	0.93	0.76-1.14
mCCI				
0	1.00	referent	1.00	referent
1	1.22	1.14-1.31	1.20	1.11-1.29
2+	1.53	1.43-1.63	1.42	1.33-1.52
Etiology				
HBV	1.00	referent	1.00	referent
Metabolic disorders	1.94	1.67-2.26	1.25	1.07-1.47
HCV	1.51	1.28-1.78	1.17	0.99-1.37
Alcohol	2.41	2.03-2.86	1.49	1.25-1.77
Rare disorders*	1.74	1.36-2.23	1.21	0.94-1.56
Multiple	1.64	1.41-1.913	1.25	1.07-1.46
Unknown	1.85	1.59-2.15	1.16	0.99-1.35
Tumor characteristics extension				
1 nodule in liver	1.00	referent	1.00	referent
>1 nodule in liver	1.628	1.55-1.71	1.42	1.35-1.50
Extension beyond liver	2.531	2.38-2.69	1.99	1.87-2.12
Number of nodules NOS	1.822	1.73-1.92	1.29	1.22-1.36
Tumor size				
≤5.0 cm	1.00	referent	1.00	referent
≥5.1 cm	1.648	1.57-1.73	1.53	1.46-1.61
Unknown	2.458	2.34-2.59	1.89	1.78-1.99
Treatment				
None	1.00	referent	1.00	referent
Resection	0.355	0.33-0.38	0.36	0.34-0.39
Transplantation	0.221	0.17-0.28	0.24	0.19-0.31
Radiation	1.073	0.96-1.20	0.95	0.85-1.07
Ablation	0.497	0.44-0.56	0.61	0.54-0.69
Arterial directed therapy	0.755	0.72-0.80	0.72	0.68-0.76

*Hemochromatosis, Wilson disease, porphyrias, alpha-1 antitrypsin deficiency, and glycogen storage disorders. Abbreviations: NOS, not otherwise specified; PI, Pacific Islanders.

in understanding the contributions of tumor biology, patient comorbidities including the extent of underlying liver cirrhosis, screening, and treatment in HCC survival by etiology. Screening across all groups with HCC risk factors may increase the proportion of HCC cases who are diagnosed with early-stage

disease and identify potential candidates for curative therapies.

In the current study, HBV-related HCC cases had the most favorable comorbidity scores, tumor size and extension profiles, and received treatment more often than cases with any other etiology. The

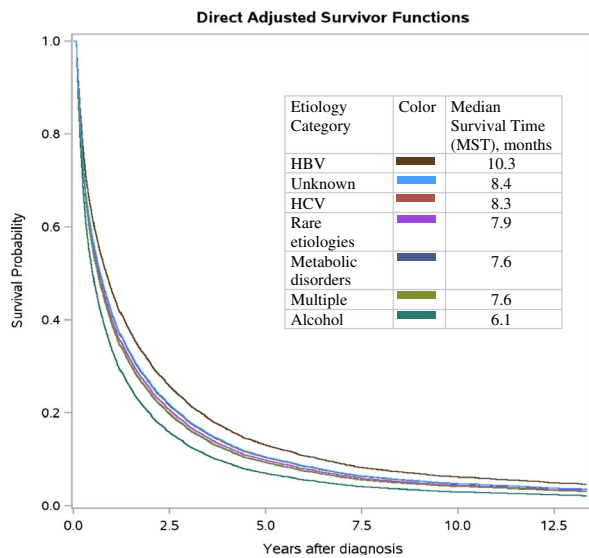


FIG. 1. The probability of survival compared by etiology in patients with HCC adjusted for other variables.

favorable survival of HBV-related HCC is consistent with a Taiwanese study,⁽⁸⁾ but dissimilar from findings of other studies.^(9,11,12,18,19) Most of these studies included cases diagnosed before 2000,^(8,11,12,18,19) and two studies focused on outcomes after resection.^(11,19) The earlier stage at diagnosis of HBV-related HCC in the present report may be partially explained by greater use of screening to detect HCC among persons living with chronic HBV infection.^(10,14,29) Although the favorable survival among cases with HBV-related HCC is encouraging, only a small proportion of the cases (2.1%) in the current study were attributable to HBV, emphasizing the great need to improve survival for HCC of all etiologies.

Consistent with a previous SEER Medicare study,⁽¹⁵⁾ in the current study cases with alcohol-related HCC had the shortest median survival in comparison to HBV-related cases. In the present study, alcohol-related HCC accounted for 4.7% of all cases. A prospective study in France also found that patients with alcohol-related HCC had a shorter median overall survival time (5.7 months) than those with non-alcohol-related HCC (9.7 months, $P = 0.09$).⁽³⁰⁾ In the present study, cases with alcohol-related HCC had the highest percentage of late-stage diagnoses and the highest percentage of multiple nodules. This may reflect the relative lack of alcohol-related HCC screening, aggressive tumor biology, or both.⁽³¹⁾

However, the American Association for the Study of Liver Diseases (AASLD) guidelines recommend active surveillance of persons with alcohol-related disorders and cirrhosis.⁽³²⁾ Nevertheless, a Swedish study found that persons with alcoholic liver disease were screened less frequently than persons with other HCC etiologies, which resulted in less favorable survival.⁽¹⁴⁾ Cases with alcohol-related HCC in the current study were the least likely to receive curative therapy. HCC treatment options may be limited in the presence of alcohol-induced liver fibrosis due to poor performance status or liver function⁽³⁰⁾ or due to the negative effects of alcohol-related disease on secondary prevention and cancer presentation.⁽¹³⁾ While the current study found lower modified comorbidity scores in persons with alcohol-related HCC, liver fibrosis was excluded from the comorbidity index because of its ubiquity and role in HCC pathogenesis. These results suggest that a need exists to understand the contribution of deficient screening, tumor biology, and therapy to the poor survival of alcohol-related HCC.

Metabolic disorders were the leading HCC etiology in the current study, accounting for 33.0% of cases. These cases were older than other cases with known etiologies and had significantly higher mortality risk compared with HBV-related cases. Similarly, a meta-analysis of nearly 10,000 HCC cases from Asia and Italy found significantly higher risk of mortality among cases with diabetes mellitus compared with other cases,⁽²⁰⁾ as did a study of cases undergoing resection in Brazil.⁽¹⁷⁾ The higher risk may be a consequence of less HCC screening, as was found in a Swedish study that reported persons with NAFLD were less likely to undergo HCC screening than persons with other etiologies.⁽¹⁴⁾ While the role of tumor biology cannot be dismissed, a paucity of HCC screening among cases with metabolic disease-associated HCCs could partially explain the high proportion (45.9%) of HCCs that were large (defined by tumor size greater than or equal to 5.1 cm in diameter). Current AASLD guidelines do not address surveillance for persons with NAFLD in the absence of cirrhosis.⁽³²⁾ Studies of outcomes among cases receiving curative therapy (i.e., resection, transplantation, ablation) for NAFLD-related HCC suggest that recurrence and survival rates are similar to those of other etiologies,⁽³³⁻³⁷⁾ including a study of SEER-Medicare patients diagnosed from 1991 to 2011.⁽¹⁶⁾ Other findings suggest a more limited contribution for tumor

biology in the greater percentage of large-diameter metabolic disease-associated HCCs. Specifically, although metabolic disorders are more prevalent with advanced age, elderly patients experience similar success, if not better, with curative treatments compared with younger patients and should be considered for all treatments after assessment of their clinical status.⁽³⁸⁾ In this report, metabolic disease-associated HCC cases had a greater number of comorbidities than most cases with other etiologies. The high prevalence of cardiovascular disease and other comorbidities in persons with metabolic disease could limit the use of potentially curative therapies compared to HCCs with other etiologies (i.e., more resection with HBV infection, more transplantation for multiple etiologies, and more ablation for HCV infection and multiple etiologies). Thus, evidence suggests that enhanced HCC screening and treatment of metabolic disorder-related HCC at the population level may have merit.

In the present report, HCV-related risk of mortality was insignificantly higher than HBV-related risk of mortality. Because 8.2% of HCC cases in this study were attributed to HCV alone, optimized management of HCV-related cases could improve overall HCC outcomes. HCV-related cases had higher comorbidity scores, larger tumors, and more advanced disease compared with HBV-related cases and were less likely to receive tumor-directed treatment. Several studies predating the current report, primarily from Asia, reported that cases with viral etiology had worse prognoses than those with nonviral etiology.^(9,11,19) There is equivocal evidence on differences in survival among persons with HBV-related HCC versus HCV-related HCC, however. A Thai study found no difference in survival between HBV-related and HCV-related HCC,⁽¹²⁾ whereas a study from Taiwan reported significantly better survival among HCV-related cases than among HBV-related cases.⁽⁸⁾ HCV-related HCC survival in the United States may improve following implementation of Centers for Disease Control guidelines to screen persons born between 1945 and 1965,⁽³⁹⁾ if direct-acting antiviral therapy is used to treat HCV infection and surveillance recommendations for HCV-related HCC are followed.⁽³²⁾ Current AASLD guidelines recommend persons with HCV-related cirrhosis should receive periodic HCC screening, even if they achieve a sustained virological response with antiviral treatment, as the risk of HCC does not return to the background pre-HCV infection risk.⁽⁴⁰⁾

Rare disease etiology was associated with an HR of 1.21, an elevation in mortality risk that did not attain statistical significance (95% CI: 0.94-1.56). Although among the cases with known etiology, cases with rare disease-related HCC had both the highest percent of extension beyond the liver (15.6%) and unknown stage at diagnosis, they had an intermediate level of comorbidity and the highest percentage of liver transplantation among etiologic groups. Because a high proportion of people with rare HCC etiologies had tumor extension beyond the liver, heightened HCC screening of people with these rare etiologies could shift the stage distribution toward more localized diagnoses. Cases with unknown etiology accounted for 24.4% of all cases in the current study. Although this etiology group was similar to the other cases with regard to gender and race/ethnicity, they were dissimilar with regard to age, as they were disproportionately over 80 years of age. While their comorbidity scores were relatively low, they tended to be diagnosed with larger or unknown size tumors. Despite these less favorable tumor characteristics, cases with unknown etiology had the second highest median survival. The reasons for these findings are not clear, but it is possible that some individuals with unknown etiology were diagnosed incidentally and had more indolent disease. In addition, research to assess whether some tumors of unknown etiology appear histologically malignant but exhibit indolent biological behavior may be informative.

Tumors of multiple etiologies accounted for 26.7% of cases in this study. As a group, cases with multiple etiologies had poor survival. The multiple etiology cases were disproportionally in the youngest age group in this study (68-75 years of age), and non-whites were overrepresented, as were cases with high comorbidity scores. Tumor extension, size, and stage were not notably different from the overall case distribution, however. Consideration of appropriate prevention, screening, and treatment measures is recommended to improve survival among the large and heterogeneous subgroup of people diagnosed with HCC who have multiple etiologic risk factors.

The current study had both strengths and limitations. A major strength was the population-based design, with coverage of approximately 34.6% of the U.S. population.⁽²³⁾ In addition, all HCC diagnoses were verified by high-quality, population-based cancer registries. Limitations include the use of

Medicare insurance claims to categorize HCC etiology, as this could have introduced misclassification bias. In addition, it was necessary to restrict the study population to persons who were at least 68 years of age, to allow a sufficient burn-in period. Despite these limitations, this large study provides useful insight into HCC survival across major etiologic categories in the United States. Survival differences may be partially explained by differential screening and related treatment practices across patient groups with various HCC etiologies. The impact on survival of unique tumor biology associated with etiology should be investigated further. With implementation of current screening recommendations for people with chronic HBV and HCV infection, the opportunity to detect localized stage tumors when they are potentially curable is increasingly attainable.⁽⁴⁰⁾ Heightened screening of persons at risk for HCC due to etiologies including alcohol, metabolic disorders, and multiple etiologies could have merit as a conduit to treat people who are eligible for curative therapy based on suitable clinical status.⁽³²⁾ Further investigation is recommended into the contributions of tumor biology, comorbidities, screening, and treatment for differences in HCC survival across etiologies.

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