Factors Associated With Detection and Survival of T1 Hepatocellular Carcinoma in the United States: National Cancer Database Analysis

Ju Dong Yang, MD, MS^{1,2,3}; Michael Luu, MPH⁴; Amit G. Singal, MD⁵; Mazen Nouredin, MD^{1,2}; Alexander Kuo, MD^{1,2}; Walid S. Ayoub, MD^{1,2}; Vinay Sundaram, MD^{1,2}; Honore Kotler, ACNP²; Irene K. Kim, MD²; Tsuyoshi Todo, MD²; Georgios Voidonikolas, MD²; Todd V. Brennan, MD²; Kambiz Kosari, MD²; Andrew S. Klein, MD²; Andrew Hendifar, MD³; Shelly C. Lu, MD^{1,3}; Nicholas N. Nissen, MD^{2,3}; and Jun Gong, MD³

ABSTRACT

Background: It remains unknown to what extent hepatocellular carcinomas (HCCs) are detected very early (T1 stage; ie, unifocal <2 cm) in the United States. The aim of this study was to investigate the trends and factors associated with very early detection of HCC and resultant outcomes. **Methods:** Patients with HCC diagnosed from 2004 through 2014 were identified from the National Cancer Database. Logistic regression was used to identify factors associated with T1 HCC detection, and Cox proportional hazard analyses identified factors associated with overall survival among patients with T1 HCC. **Results:** Of 110,182 eligible patients, the proportion with T1 HCC increased from 2.6% in 2004 to 6.8% in 2014 ($P<.01$). The strongest correlate of T1 HCC detection was receipt of care at an academic institution (odds ratio, 3.51; 95% CI, 2.31–5.34). Older age, lack of insurance, high Model for End-Stage Liver Disease (MELD) score, high alpha-fetoprotein, increased Charlson-Deyo comorbidity score, and nonsurgical treatment were associated with increased mortality, and care at an academic center (hazard ratio [HR], 0.27; 95% CI, 0.15–0.48) was associated with reduced mortality in patients with T1 HCC. Liver transplantation (HR, 0.27; 95% CI, 0.20–0.37) and surgical resection (HR, 0.67; 95% CI, 0.48–0.93) were independently associated with improved survival compared with ablation. This is the first study to examine the trend of T1 HCC using the National Cancer Database, which covers approximately 70% of all cancer diagnoses in the United States, using robust statistical analyses. Limitations of the study include a retrospective study design using administrative data and some pertinent data that were not available. **Conclusions:** Despite increases over time, <10% of HCCs are detected at T1 stage. The strongest correlates of survival among patients with T1 HCC are receiving care at an academic institution and surgical treatment.

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Background

A unifocal hepatocellular carcinoma (HCC) measuring <2 cm (T1 HCC) without vascular invasion and extra-hepatic metastasis is the tumor-related component of very early-stage disease.¹ This stage of HCC has a decreased likelihood of satellite nodules or microscopic vascular invasion,² and therefore patients who present at this stage have an excellent prognosis.^{3,4} Studies have shown that tumors detected under surveillance programs are associated with early-stage disease and receipt of potentially curative treatment.^{5,6} Liver ultrasound is a standard surveillance test for HCC^{3,4}; however, its sensitivity for the detection of early-stage HCC remains <50%.⁷ Because of the unsatisfactory performance of liver ultrasound, contrast-enhanced CT or MRI scan is sometimes used as a surveillance test in high-risk individuals.⁸ The American Association for the Study of Liver Diseases (AASLD) endorsed an HCC surveillance program for high-risk patients with its first HCC practice guidelines in 2005.⁹ With improvement in diagnostic imaging technology and increasing implementation of HCC surveillance programs, detection of T1 HCC is expected to increase.⁸ Currently, the extent to which HCCs are detected at this stage in the United States and factors associated with detection at a very early stage remain unknown.

Because patients with HCC often have cirrhosis of the liver, their prognosis is determined by both tumor-related (disease extent and biology) and liver dysfunction-related factors.¹⁰ Although several studies have reported prognostic factors in large cohorts of patients with HCC, factors specifically associated with survival in patients with T1 HCC remain unknown. With the anticipation of

¹Division of Digestive and Liver Diseases, ²Comprehensive Transplant Center, ³Samuel Oschin Comprehensive Cancer Institute, and ⁴Biostatistics and Bioinformatics Research Center, Cedars-Sinai Medical Center, West Hollywood, California; and ⁵Division of Digestive and Liver Diseases, University of Texas Southwestern Medical Center, Dallas, Texas.

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increasing detection of HCC at this early stage, understanding factors related to the survival of these patients is relevant and timely.

The aim of this study was to investigate the trend in detection of T1 HCC, factors associated with detection at this stage, and outcomes of these patients in the United States.

Methods

Database

The National Cancer Database (NCDB) is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society. It is a clinical oncology database sourced from hospital registry data that are collected in >1,500 CoC-accredited facilities. Data represent >70% of newly diagnosed patients with cancer nationwide and >34 million historical records.

Patients and Variables

All patients with HCC diagnosed from 2004 through 2014 were identified from the NCDB. HCC diagnosis was based on ICD-O-3 code C22.0 and histology codes 8170–8175, which include not only microscopically verified HCC but also clinically confirmed HCC. According to the United Network for Organ Sharing staging classification, T1 HCC is defined as a single tumor <2 cm. Patients with missing information on tumor size, follow-up, or treatment type were excluded (supplemental eFigure 1, available with this article at JNCCN.org).

Demographic, socioeconomic, reporting medical facility, and clinical data for patients were extracted from the NCDB. Socioeconomic data included insurance status, income (median household income for patient zip code based on 2000 US Census data, in quartiles), education (median percentage of adults without a high school degree in patient's zip code based on 2000 US Census data), urban/rural location (metropolitan, urban, rural), and travel distance (distance in miles between patient's residence and reporting hospital). Facility data included type (academic: >500 new cancer diagnoses annually and at least 4 postgraduate training programs; comprehensive community: >500 new cancer diagnoses annually; integrated network: no minimum caseload, joint venture with multiple facilities providing integrated cancer care and offering comprehensive services, at least 1 facility being a hospital and a CoC-accredited cancer program; community: 100–500 new cancer diagnoses annually) and geographic region of the medical center. Clinical data included Charlson-Deyo comorbidity score (0, 1, 2, ≥ 3), alpha-fetoprotein (AFP) level (normal vs elevated), Model for End-Stage Liver Disease (MELD) score (available since 2010), diagnosis method,

treatment, and interval from the date of HCC diagnosis (date of initial diagnosis clinically or microscopically) to the date of the most definitive treatment. Given that the Child-Pugh score was not available in the NCDB, a MELD score ≤ 10 was used to reflect preserved liver function. Alternative scoring systems, such as the MELD and albumin-bilirubin (ALBI) scores, have been shown to have good prognostic performance in patients with HCC and are gaining popularity given their increased objectivity compared with using the Child-Pugh score.^{10–13} For patients who received multiple courses of treatments, the most invasive surgical procedure for the primary site (liver transplantation > resection > ablation) was reported in the database.

Statistical Analysis

Baseline characteristics in patients with T1 HCC and others were compared using the Welch *t* test and the Mann-Whitney Wilcoxon test for continuous variables as appropriate. Categorical variables were compared using the Pearson chi-square test. The Cochran-Armitage Trend test was used to determine the statistical significance of the temporal trend of T1 HCC. Survival probabilities were estimated using the Kaplan-Meier method and compared using the log-rank test.

Factors associated with the detection of T1 HCC were determined using univariable and multivariable logistic regression. Factors associated with overall survival (OS) among patients with T1 HCC were determined using univariate and multivariable Cox proportional hazards regression. Time-to-event was defined as the time from HCC diagnosis to last follow-up or death.

In a secondary analysis, OS was compared among patients who received (1) ablation versus resection and (2) ablation versus liver transplantation using inverse probability of treatment-weighting (IPTW) analysis.¹⁴ Although patients with HCC lesions <2 cm do not typically get priority points for liver transplantation, a “wait and not ablate” approach in which these patients are followed until the lesion grows to ≥ 2 cm is commonly used in clinical practice.^{1,15}

The proportional hazards assumption among all survival models was assessed using the scaled Schoenfeld residuals and the goodness-of-fit test as proposed by Grambsch and Therneau.¹⁶ All statistical analyses were performed using R version 3.5.1 (R Foundation for Statistical Computing) with 2-sided tests and a significance level of .05.

Results

Patient Characteristics

A total of 110,182 patients with HCC were identified, of whom 6,261 (5.7%) had a T1 lesion (Table 1). The proportion of patients detected at a very early stage

Table 1. Patient Characteristics

Characteristic	Overall n (%)	Single HCC <2 cm (T1) n (%)	Multifocal HCC or Tumor ≥2 cm (>T1) n (%)	P Value ^a
Total, n	110,182	6,261	103,921	
Demographic factors				
Age, mean (SD), y	63.2 (11.3)	60.7 (9.57)	63.4 (11.3)	<.001
Sex				<.001
Male	83,141 (75.5%)	4,326 (69.1%)	78,815 (75.8%)	
Female	27,041 (24.5%)	1,935 (30.9%)	25,106 (24.2%)	
Race/Ethnicity				.116
Hispanic	18,330 (16.6%)	17,346 (16.7%)	984 (15.7%)	
White	65,667 (59.6%)	61,843 (59.5%)	3,824 (61.1%)	
Black	15,645 (14.2%)	14,776 (14.2%)	869 (13.9%)	
Asian/Other	10,107 (9.17%)	9,551 (9.19%)	556 (8.88%)	
Missing	433 (0.39%)	405 (0.39%)	28 (0.45%)	
Socioeconomic factors				
Insurance status				<.001
Uninsured	6,125 (5.56%)	214 (3.42%)	5,911 (5.69%)	
Private	35,724 (32.4%)	2,386 (38.1%)	33,338 (32.1%)	
Medicaid/Medicare	64,146 (58.2%)	3,442 (55.0%)	60,704 (58.4%)	
Other	1,862 (1.69%)	110 (1.76%)	1,752 (1.69%)	
Missing	2,325 (2.11%)	109 (1.74%)	2,216 (2.13%)	
Median income, annual				<.001
<\$38,000	24,868 (22.6%)	1,393 (22.2%)	23,475 (22.6%)	
\$38,000–\$47,999	26,145 (23.7%)	1,409 (22.5%)	24,736 (23.8%)	
\$48,000–\$62,999	28,453 (25.8%)	1,632 (26.1%)	26,821 (25.8%)	
≥\$63,000	28,902 (26.2%)	1,757 (28.1%)	27,145 (26.1%)	
Missing	1,814 (1.65%)	70 (1.12%)	1,744 (1.68%)	
Without high school degree				<.001
≥21%	27,303 (24.8%)	1,505 (24.0%)	25,798 (24.8%)	
13%–20.9%	30,163 (27.4%)	1,660 (26.5%)	28,503 (27.4%)	
7%–12.9%	31,497 (28.6%)	1,808 (28.9%)	29,689 (28.6%)	
<7%	19,473 (17.7%)	1,221 (19.5%)	18,252 (17.6%)	
Missing	1,746 (1.58%)	67 (1.07%)	1,679 (1.62%)	
Location				<.001
Rural	1,363 (1.24%)	71 (1.13%)	1,292 (1.24%)	
Urban	12,017 (10.9%)	598 (9.55%)	11,419 (11.0%)	
Metropolitan	92,938 (84.3%)	5,424 (86.6%)	87,514 (84.2%)	
Missing	3,864 (3.51%)	168 (2.68%)	3,696 (3.56%)	
Medical facility factors				
Facility type				<.001
Community	5,123 (4.65%)	95 (1.52%)	5,028 (4.84%)	
Comprehensive community	28,428 (25.8%)	884 (14.1%)	27,544 (26.5%)	
Academic	63,423 (57.6%)	4,619 (73.8%)	58,804 (56.6%)	
Integrated network	11,587 (10.5%)	590 (9.42%)	10,997 (10.6%)	
Other/Unknown	1,621 (1.47%)	73 (1.17%)	1,548 (1.46%)	

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Table 1. Patient Characteristics (cont.)

Characteristic	Overall n (%)	Single HCC <2 cm (T1) n (%)	Multifocal HCC or Tumor ≥2 cm (>T1) n (%)	P Value ^a
Region				<.001
South	40,898 (37.1%)	2,074 (33.1%)	38,824 (37.4%)	
Northeast	23,154 (21.0%)	1,548 (24.7%)	21,606 (20.8%)	
Midwest	22,035 (20.0%)	1,319 (21.1%)	20,716 (19.9%)	
West	22,474 (20.4%)	1,247 (19.9%)	21,227 (20.4%)	
Missing	1,621 (1.47%)	73 (1.17%)	1,548 (1.49%)	
Clinical factors				
Charlson-Deyo comorbidity score				<.001
0	50,645 (46.0%)	2,686 (42.9%)	47,959 (46.1%)	
1	30,410 (27.6%)	1,737 (27.7%)	28,673 (27.6%)	
2	12,157 (11.0%)	664 (10.6%)	11,493 (11.1%)	
≥3	16,970 (15.4%)	1,174 (18.8%)	15,796 (15.2%)	
Diagnosis method				<.001
Cytology or histology	72,629 (65.9%)	3,150 (50.3%)	69,479 (66.9%)	
Clinical diagnosis	37,553 (34.1%)	3,111 (49.7%)	34,442 (33.1%)	
Alpha-fetoprotein level				<.001
Normal	22,740 (20.6%)	1,953 (31.2%)	20,787 (20.0%)	
Elevated	62,600 (56.8%)	2,930 (46.8%)	59,670 (57.4%)	
Missing	24,842 (22.5%)	1,378 (22.0%)	23,464 (22.6%)	
MELD				
Median (IQR)	12.0 (8.47–19.3)	11.7 (8.47–18.0)	12.0 (8.47–19.4)	.113
Fibrosis				<.001
Ishak fibrosis score 0–4	5,592 (5.08%)	307 (4.90%)	5,285 (5.09%)	
Ishak fibrosis score 5–6 (cirrhosis)	17,987 (16.3%)	1,597 (25.5%)	16,390 (15.8%)	
Missing	86,603 (78.6%)	4,357 (69.6%)	82,246 (79.1%)	

Abbreviations: IQR, interquartile range; MELD, Model for End-Stage Liver Disease.

^aP values were calculated by Pearson chi-square test for categorical variables and Welch t test for continuous variables.

increased 2.6-fold over time from 2.6% in 2004 to 6.8% in 2014 ($P<.01$) (Figure 1). The proportion of patients with T1 HCC and MELD score ≤ 10 between 2010 (when MELD scores became available) and 2014 minimally increased from 2.6% to 3.1% ($P=.12$) (supplemental eFigure 2). Patients with T1 HCC were younger, less male-preponderant, more likely to have private insurance, had a higher Charlson-Deyo comorbidity score, and lived in areas with higher household income and education levels. Patients with T1 HCC were seen more frequently in academic cancer centers, were more likely to have their cancer diagnosis made clinically (without cytology or histology), and were more likely to have normal AFP levels.

Factors Associated With Detection of T1 HCC

Demographic, socioeconomic, medical facility, and clinical factors associated with the detection of T1 HCC

are summarized in Table 2. Younger age, female sex, and white and black race were associated with detection of T1 HCC. Patients with any type of insurance also had approximately a 2-fold increased likelihood of presenting with T1 HCC. Finally, the type of medical facility was strongly associated with very early detection: patients seen at an academic medical center had a 3.5-fold increased likelihood of having T1 HCC compared with those seen at community programs.

Factors Associated With OS in Patients With T1 HCC

Median survival among patients with T1 HCC was 61 months (95% CI, 57–64), which was superior to a median survival of 14 months observed in patients with HCC at stages beyond T1 (95% CI, 14–14). Older age, lack of insurance, increased comorbidity, higher AFP level, and degree of liver dysfunction were all associated with increased

Figure 1. Temporal trend in the proportion of patients diagnosed with T1 hepatocellular carcinoma.

mortality (Table 3). Hispanic patients had reduced mortality compared with white patients, suggesting the presence of the Hispanic paradox with regard to HCC prognosis. Medical facility factors were one of the strongest drivers of prognosis in patients with T1 HCC. Patients seen at an academic center, integrated network, or comprehensive community cancer program had significantly reduced mortality compared with those seen in community programs.

Impact of Treatment on Survival of Patients With T1 HCC

Type of treatment was strongly associated with OS (Figure 2). Because resection, ablation, and liver transplantation are potentially curative options for T1 HCC, patients who received these types of treatments were further analyzed, and their baseline characteristics are summarized in supplemental eTable 1. Among patients who received potentially curative treatments, the largest proportion of patients received ablation (47%), followed by liver transplantation (37%) and resection (16%). Compared with ablative therapy, surgical resection (adjusted hazard ratio [HR], 0.67; 95% CI, 0.48–0.93) and liver transplantation (adjusted HR, 0.27; 95% CI, 0.20–0.37) were independently associated with reduced mortality (see Table 3). The association between curative surgery (resection or liver transplantation) and improved OS persisted in IPTW analysis: surgical resection had an HR of 0.70 (95% CI, 0.58–0.83) and liver transplantation had an HR of 0.37 (95% CI, 0.30–0.45) versus ablation.

Subgroup analyses were performed among patients with MELD ≤ 10 and >10 . The association between curative surgery (resection or liver transplantation) and improved OS persisted in IPTW analysis in patients with MELD scores >10 : surgical resection had an HR of 0.60 (95% CI, 0.46–0.77) and liver transplantation had an HR of 0.31 (95% CI, 0.25–0.39) versus ablation. In

patients with MELD scores ≤ 10 , resection (HR, 0.91; 95% CI, 0.65–1.26) was no longer associated with improved OS, and liver transplantation (HR, 0.47; 95% CI, 0.27–0.81) was still associated with improved survival compared with ablation in IPTW analysis.

Discussion

This study showed that the proportion of very early-stage HCC increased steadily in the United States from 2004 through 2014, but remained $<10\%$ of all patients with HCC. A slight increase in the proportion of T1 HCC may not be clinically relevant, but it clearly showed an increasing trend over the past 10 years, which may be a reflection of improved HCC surveillance implementation and advances in imaging technology. A steep increase in the proportion of T1 HCC from 2007 through 2010 could have resulted from increased awareness of HCC surveillance after the 2005 AASLD HCC practice guidelines were issued,⁹ in addition to improved diagnostic technology. The results highlight demographic, socioeconomic, and facility disparities in very early detection and outcomes of T1 HCC. The strongest correlates of improved survival among patients with T1 HCC were care at an academic center and receipt of surgical therapy.

The low proportion of patients found at a very early stage contrasts to that found in Japan, where a nationwide intensive HCC surveillance program has been implemented and nearly one-third of HCCs are found at a very early stage.^{3,17} Because of the unsatisfactory performance of liver ultrasound, contrast-enhanced CT or MRI scan has been considered as a surveillance test in high-risk individuals.^{8,18,19} A recent modeling study showed that MRI could be cost-effective as a surveillance test in high-risk patients with cirrhosis.²⁰ In addition to radiologic tests, a new blood-based biomarker has been proposed for early detection of HCC.^{21,22} With the increasing use of highly accurate diagnostic radiology images as a surveillance test in high-risk patients and the development of novel circulating biomarkers, there may be an increase in the very early detection of HCC in the United States in the foreseeable future.

This study demonstrated demographic, socioeconomic, and facility disparities in the very early detection and outcomes of T1 HCC. Type of facility had a strong association with both very early HCC detection and resultant outcomes, perhaps because of the resource-intensive nature of detecting small HCCs and providing optimal treatment modalities.^{23,24} Several studies showed that impact of the facility on OS was larger among patients with earlier-stage versus advanced-stage HCC, likely because of differences in the availability of resources, including liver transplantation programs and multidisciplinary care, which can make

Table 2. Factors Associated With Detection of T1 HCC

	Univariate Analysis		Multivariable Analysis	
	OR (95% CI)	P Value	OR (95% CI)	P Value
Demographic				
Age (10-y change)	0.809 (0.791–0.828)		0.741 (0.705–0.778)	<.001
Sex				
Male	Ref		Ref	
Female	1.404 (1.328–1.484)	<.001	1.769 (1.615–1.937)	<.001
Race/Ethnicity				
Hispanic	Ref		Ref	
White	1.090 (1.014–1.171)	.019	1.244 (1.089–1.422)	.001
Black	1.037 (0.944–1.139)	.451	1.210 (1.026–1.427)	.024
Asian/Other	1.026 (0.922–1.142)	.636	1.089 (0.902–1.314)	.376
Socioeconomic				
Insurance status				
Uninsured	Ref		Ref	
Private	1.977 (1.714–2.280)	<.001	1.792 (1.425–2.254)	<.001
Medicaid/Medicare	1.566 (1.361–1.803)	<.001	1.710 (1.363–2.147)	<.001
Other	1.734 (1.370–2.196)	<.001	1.142 (0.730–1.788)	.56
Median income, annual				
<\$38,000	Ref		Ref	
\$38,000–\$47,999	0.960 (0.890–1.036)	.293	0.998 (0.874–1.141)	.978
\$48,000–\$62,999	1.025 (0.953–1.104)	.504	0.941 (0.816–1.085)	.405
≥\$63,000	1.091 (1.015–1.173)	.019	0.960 (0.814–1.132)	.626
Without high school degree				
≥21%	Ref		Ref	
13%–20.9%	0.998 (0.929–1.073)	.963	0.921 (0.809–1.049)	.217
7%–12.9%	1.044 (0.973–1.120)	.232	1.091 (0.946–1.257)	.231
<7%	1.147 (1.061–1.240)	<.001	1.101 (0.925–1.309)	.279
Location				
Rural	Ref		Ref	
Urban	0.953 (0.740–1.227)	.709	0.823 (0.561–1.209)	.321
Metropolitan	1.128 (0.887–1.434)	.327	0.996 (0.689–1.440)	.985
Medical facility				
Facility type				
Community	Ref		Ref	
Comprehensive community	1.699 (1.372–2.103)	<.001	1.728 (1.123–2.660)	.013
Academic	4.157 (3.386–5.104)	<.001	3.511 (2.310–5.335)	<.001
Integrated network	2.840 (2.281–3.535)	<.001	2.745 (1.771–4.256)	<.001
Region				
South	Ref		Ref	
Northeast	1.341 (1.253–1.435)	<.001	1.116 (0.989–1.260)	.074
Midwest	1.192 (1.110–1.280)	<.001	1.120 (0.995–1.262)	.061
West	1.100 (1.023–1.182)	.010	1.192 (1.054–1.348)	.005

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Table 2. Factors Associated With Detection of T1 HCC (cont.)

	Univariate Analysis		Multivariable Analysis	
	OR (95% CI)	P Value	OR (95% CI)	P Value
Clinical				
Charlson-Deyo comorbidity score				
0	Ref		Ref	
1	1.082 (1.017–1.151)	.013	1.069 (0.964–1.186)	.205
2	1.032 (0.945–1.126)	.486	1.094 (0.952–1.257)	.208
≥3	1.327 (1.236–1.425)	<.001	1.214 (1.083–1.361)	<.001
Alpha-fetoprotein level				
Normal	Ref		Ref	
Elevated	0.523 (0.493–0.555)	<.001	0.505 (0.464–0.551)	<.001
MELD (10-unit change)	0.943 (0.899–0.990)	.017	0.949 (0.899–0.998)	.048

Abbreviations: MELD, Model for End-Stage Liver Disease; OR, odds ratio.

a substantial difference in patient outcomes.^{23–25} Results also showed significant racial/ethnic disparities; Hispanic patients were less likely to present with T1 HCC, although they had longer OS than white patients. Racial/Ethnic disparity in HCC stage and outcome in the current study was consistent with findings from a recent large retrospective cohort study showing that Hispanic patients were less likely to be diagnosed with early-stage HCC compared with non-Hispanic white patients, although they had lower mortality after adjusting for covariates.²⁶ Racial/Ethnic differences in liver disease etiology, recognition of cirrhosis, and use of HCC surveillance may account for this disparity to some extent, but further studies are needed to investigate the reasons for the racial/ethnic disparity in HCC presentation and outcome.

Treatment of T1 HCCs remains unclear because there is no randomized controlled trial (RCT) that has compared the efficacy of different treatment modalities in this specific group of patients. The European Association for the Study of the Liver guideline²⁷ recommends ablation or resection as a primary treatment modality for very early-stage HCC, based on extrapolation of evidence from RCTs in early-stage HCC (including stages beyond T1 HCC), Markov modeling studies, cost-effective analyses, and small retrospective cohort studies.^{28–30} The most recent AASLD guideline, however, recommends resection over ablation for patients with a resectable T1 HCC with Child-Pugh A cirrhosis based on 2 moderate-quality RTCs that showed the superiority of resection over ablative therapy.^{31–33} However, these 2 RTCs included patients with HCC that was beyond very early stage. Similarly, a recent study using the NCDB showed that surgical resection leads to longer OS compared with ablation, but the

authors did not investigate the impact of treatment in the subgroup of patients with T1 HCC.³⁴ Although we found that resection was associated with prolonged survival compared with ablation in T1 HCCs in IPTW analyses, the superiority of resection over ablation was no longer seen in patients with MELD scores ≤10, suggesting that resection and ablation may be equally effective in T1 HCC with preserved liver function.

HCC is the most common indication for liver transplantation in the United States.³⁵ Posttransplantation recurrent HCC was reported in up to 15% of patients, but the risk is smaller in patients with lower tumor burden.³⁶ In contrast, retrospective studies showed that 68% of patients with T1 HCC developed recurrent disease after surgical resection³⁷ and >70% developed recurrent disease after an ablation.³⁸ Currently, patients with T1 HCC are not prioritized for organ allocation by the MELD exception score.³⁹ They have to wait for T1 HCC to grow without cancer treatment until it reaches stage T2, at which point patients are eligible for liver transplantation priority based on their MELD exception score. A single-center retrospective cohort study showed that the “wait and not ablate” approach until tumor growth from T1 to T2 before transplant listing is associated with a <10% risk of tumor progression to directly beyond T2 criteria, suggesting it as a viable treatment strategy under the current liver organ allocation system.¹⁵ In the current study, approximately 38% of patients were diagnosed with HCC at the time of liver transplantation, representing incidental HCC found on explant, and the remaining 62% were diagnosed with HCC before liver transplantation. To which extent these patients with T1 HCC experienced progression beyond T2 HCC remains unclear.

Table 3. Factors Associated With Overall Survival of Patients With T1 HCC

	Univariate Survival Analysis		Multivariable Survival Analysis	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Demographic				
Age (10-y change)	1.299 (1.248–1.351)	<.001	1.207 (1.113–1.308)	<.001
Sex				
Male	Ref		Ref	
Female	0.978 (0.901–1.061)	.593	0.904 (0.784–1.042)	.163
Race/Ethnicity				
Hispanic	Ref		Ref	
White	1.103 (0.992–1.227)	.07	1.262 (1.014–1.570)	.037
Black	1.203 (1.050–1.377)	.008	1.061 (0.810–1.388)	.669
Asian/Other	0.657 (0.549–0.785)	<.001	0.716 (0.510–1.005)	.054
Socioeconomic				
Insurance status				
Uninsured	Ref		Ref	
Private	0.491 (0.403–0.599)	<.001	0.446 (0.320–0.622)	<.001
Medicaid/Medicare	0.756 (0.623–0.917)	.005	0.570 (0.411–0.791)	.001
Other	0.775 (0.563–1.068)	.119	0.525 (0.269–1.027)	.06
Median income, annual				
<\$38,000	Ref		Ref	
\$38,000–\$47,999	0.902 (0.809–1.005)	.062	1.009 (0.819–1.241)	.936
\$48,000–\$62,999	0.787 (0.707–0.876)	<.001	1.032 (0.826–1.289)	.781
≥\$63,000	0.774 (0.697–0.860)	<.001	0.987 (0.760–1.282)	.92
Without high school degree				
≥21%	Ref		Ref	
13%–20.9%	0.980 (0.883–1.088)	.71	0.950 (0.774–1.164)	.618
7%–12.9%	0.909 (0.819–1.008)	.071	0.848 (0.680–1.058)	.144
<7%	0.926 (0.826–1.037)	.184	1.060 (0.808–1.390)	.674
Location				
Rural	Ref		Ref	
Urban	1.144 (0.775–1.688)	.498	0.631 (0.368–1.082)	.094
Metropolitan	1.054 (0.726–1.529)	.784	0.649 (0.391–1.077)	.094
Medical facility				
Facility type				
Community	Ref		Ref	
Comprehensive community	0.712 (0.537–0.944)	.018	0.384 (0.214–0.690)	.001
Academic	0.420 (0.321–0.551)	<.001	0.270 (0.153–0.477)	<.001
Integrated network	0.509 (0.380–0.681)	<.001	0.349 (0.190–0.640)	.001
Region				
South	Ref		Ref	
Northeast	0.857 (0.776–0.948)	.003	1.131 (0.923–1.386)	.236
Midwest	0.922 (0.831–1.022)	.123	1.295 (1.071–1.567)	.008
West	0.984 (0.886–1.092)	.757	1.277 (1.052–1.552)	.014

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Table 3. Factors Associated With Overall Survival of Patients With T1 HCC (cont.)

	Univariate Survival Analysis		Multivariable Survival Analysis	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Clinical				
Charlson-Deyo comorbidity score				
0	Ref		Ref	
1	0.923 (0.842–1.011)	.086	0.997 (0.845–1.176)	.97
2	0.951 (0.837–1.081)	.44	1.117 (0.903–1.383)	.308
≥3	0.989 (0.893–1.096)	.839	1.279 (1.073–1.526)	.006
Alpha-fetoprotein level				
Normal	Ref		Ref	
Elevated	1.258 (1.151–1.376)	<.001	1.255 (1.096–1.438)	.001
MELD (10-unit change)	1.236 (1.153–1.325)	<.001	1.345 (1.242–1.456)	<.001
Treatment type				
Ablation	Ref		Ref	
Resection	0.662 (0.555–0.790)	<.001	0.668 (0.480–0.930)	.017
Transplant	0.378 (0.327–0.438)	<.001	0.273 (0.200–0.372)	<.001
Other	1.639 (1.495–1.798)	<.001	1.564 (1.337–1.830)	<.001

Abbreviations: HR, hazard ratio; MELD, Model for End-Stage Liver Disease

Our study has several limitations. First, this is a retrospective study and some pertinent data were not available or were missing. For example, the Child-Pugh score, the etiology of liver disease, and the mode of HCC detection (surveillance vs incidental) were lacking, and cirrhosis status was missing in a high proportion of patients. However, we anticipated that most patients with T1 HCC would have underlying cirrhosis and that their HCC diagnosis was made under surveillance given

its small size. Although the Child-Pugh score was not available, analyses were conducted using MELD scores, which have been available since 2010. As discussed earlier, the MELD and ALBI scores have been shown to have good prognostic performance in patients with HCC and increased objectivity compared with the Child-Pugh score, leading to increased popularity as alternative measures of liver dysfunction. Second, patients with missing tumor size, follow-up, and treatment information were excluded. Patients with missing tumor size or treatment information had shorter survival than those with T1 HCC (HR, 4.9; 95% CI, 4.7–5.1; $P<.001$), suggesting that the proportion of patients with T1 HCC may be even lower in the United States than what we reported because patients who were excluded had worse survival. Third, patients who underwent liver transplantation had a short interval from time of diagnosis to surgery, and it is unknown whether they had tumor progression beyond the T1 stage and received bridging treatment before transplant. Fourth, the NCDB may have potential issues regarding generalizability because it only covers patients presented at participating institutions.⁴⁰ Fifth, the association between surgical treatment and improved survival should be interpreted carefully, because residual bias may persist despite IPTW analysis. Finally, this study does not contain data on cancer recurrence, subsequent treatment of recurrent cancer, and cause of death. Despite these limitations, this is the first study to examine the trend of very early HCC using the NCDB, which covers approximately 70% of all

Figure 2. Treatment and overall survival in patients with T1 hepatocellular carcinoma.

cancer diagnoses in the United States, using robust statistical analyses.

Conclusions

There is an increasing trend of detecting HCC at a very early stage in the United States; however, <10% of HCC is detected at this stage. Demography, insurance, and facility type are independently associated with detection at a very early stage and patient survival. Receipt of surgical therapy seems to be associated with longer survival compared with ablation in patients with T1 HCC. Continued efforts to improve very early detection of HCC in patients with cirrhosis are needed.

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Data interpretation: All authors. **Manuscript preparation:** Yang. **Statistical analysis:** Luu. **Critical revision of the manuscript:** Luu, Singal, Nouredin, Kuo, Ayoub, Sundaram, Kotler, Kim, Todo, Voidonikolas, Brennan, Kosari, Klein, Hendifar, Lu, Nissen, Gong.

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Correspondence: Ju Dong Yang, MD, MS, Cedars-Sinai Medical Center, 8900 Beverly Boulevard, Los Angeles, CA 90048. Email: judong.yang@cshs.org

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Supplemental online content for:

Factors Associated With Detection and Survival of T1 Hepatocellular Carcinoma in the United States: National Cancer Database Analysis

Ju Dong Yang, MD, MS; Michael Luu, MPH; Amit G. Singal, MD; Mazen Nouredin, MD; Alexander Kuo, MD; Walid S. Ayoub, MD; Vinay Sundaram, MD; Honore Kotler, ACNP; Irene K. Kim, MD; Tsuyoshi Todo, MD; Georgios Voidonikolas, MD; Todd V. Brennan, MD; Kambiz Kosari, MD; Andrew S. Klein, MD; Andrew Hendifar, MD; Shelly C. Lu, MD; Nicholas N. Nissen, MD; and Jun Gong, MD

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eFigure 1: Flowchart of Patient Selection

eFigure 2: Temporal Trend in Proportion of Patients With T1 HCC and MELD Score ≤ 10

eTable 1: Clinical Characteristics of Patients With T1 HCC Who Received Ablation, Resection, or Liver Transplantation

eFigure 1. Flowchart of patient selection.

eFigure 2. Temporal trend in proportion of patients with T1 HCC and MELD score ≤ 10 . Abbreviations: HCC, hepatocellular carcinoma; MELD, Model for End-Stage Liver Disease.

eTable 1. Clinical Characteristics of Patients With T1 HCC Who Received Ablation, Resection, or Liver Transplantation

Characteristic	Overall	Ablation	Resection	Transplant	P Value ^a
Total, n	3,064	1,445	492	1,127	
Demographic factors					
Age, mean (SD), y	60.2 (9.36)	62.2 (9.87)	60.9 (10.6)	57.4 (7.16)	<.001
Sex					<.001
Male	2,172 (70.9%)	971 (67.2%)	339 (68.9%)	862 (76.5%)	
Female	892 (29.1%)	474 (32.8%)	153 (31.1%)	265 (23.5%)	
Race/Ethnicity					<.001
Hispanic	440 (14.4%)	223 (15.4%)	44 (8.94%)	173 (15.4%)	
White	1,902 (62.1%)	850 (58.8%)	273 (55.5%)	779 (69.1%)	
Black	401 (13.1%)	213 (14.7%)	85 (17.3%)	103 (9.14%)	
Asian/Other	305 (9.95%)	147 (10.2%)	88 (17.9%)	70 (6.21%)	
Missing	16 (0.52%)	12 (0.83%)	2 (0.41%)	2 (0.18%)	
Socioeconomic factors					
Insurance status					<.001
Uninsured	75 (2.45%)	52 (3.60%)	10 (2.03%)	13 (1.15%)	
Private	1,283 (41.9%)	490 (33.9%)	226 (45.9%)	567 (50.3%)	
Medicaid/Medicare	1,594 (52.0%)	849 (58.8%)	244 (49.6%)	501 (44.5%)	
Other	61 (1.99%)	32 (2.21%)	7 (1.42%)	22 (1.95%)	
Missing	51 (1.66%)	22 (1.52%)	5 (1.02%)	24 (2.13%)	
Median income, annual					.026
<\$38,000	635 (20.7%)	325 (22.5%)	103 (20.9%)	207 (18.4%)	
\$38,000–\$47,999	656 (21.4%)	304 (21.0%)	97 (19.7%)	255 (22.6%)	
\$48,000–\$62,999	825 (26.9%)	377 (26.1%)	140 (28.5%)	308 (27.3%)	
≥\$63,000	924 (30.2%)	433 (30.0%)	150 (30.5%)	341 (30.3%)	
Missing	24 (0.78%)	6 (0.42%)	2 (0.41%)	16 (1.42%)	
Without high school degree					.002
≥21%	662 (21.6%)	348 (24.1%)	107 (21.7%)	207 (18.4%)	
13%–20.9%	805 (26.3%)	364 (25.2%)	131 (26.6%)	310 (27.5%)	
7%–12.9%	911 (29.7%)	421 (29.1%)	134 (27.2%)	356 (31.6%)	
<7%	662 (21.6%)	306 (21.2%)	118 (24.0%)	238 (21.1%)	
Missing	24 (0.78%)	6 (0.42%)	2 (0.41%)	16 (1.42%)	
Location					.316
Rural	38 (1.24%)	17 (1.18%)	6 (1.22%)	15 (1.33%)	
Urban	302 (9.86%)	122 (8.44%)	52 (10.6%)	128 (11.4%)	
Metropolitan	2,649 (86.5%)	1,272 (88.0%)	420 (85.4%)	957 (84.9%)	
Missing	75 (2.45%)	34 (2.35%)	14 (2.85%)	27 (2.40%)	
Medical facility factors					
Facility type					<.001
Community	22 (0.72%)	13 (0.90%)	8 (1.63%)	1 (0.09%)	
Comprehensive community	322 (10.5%)	175 (12.1%)	80 (16.3%)	67 (5.94%)	
Academic	2,380 (77.7%)	1,097 (75.9%)	359 (73.0%)	924 (82.0%)	
Integrated network	295 (9.63%)	144 (9.97%)	32 (6.50%)	119 (10.6%)	
Other/Unknown	45 (1.47%)	16 (1.11%)	13 (2.64%)	16 (1.42%)	

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eTable 1. Clinical Characteristics of Patients With T1 HCC Who Received Ablation, Resection, or Liver Transplantation (cont.)

Characteristic	Overall	Ablation	Resection	Transplant	P Value ^a
Region					<.001
South	1,014 (33.1%)	402 (27.8%)	150 (30.5%)	462 (41.0%)	
Northeast	738 (24.1%)	380 (26.3%)	152 (30.9%)	206 (18.3%)	
Midwest	676 (22.1%)	312 (21.6%)	118 (24.0%)	246 (21.8%)	
West	591 (19.3%)	335 (23.2%)	59 (12.0%)	197 (17.5%)	
Missing	45 (1.47%)	16 (1.11%)	13 (2.64%)	16 (1.42%)	
Clinical factors					
Charlson-Deyo comorbidity score					<.001
0	1,221 (39.8%)	662 (45.8%)	234 (47.6%)	325 (28.8%)	
1	866 (28.3%)	405 (28.0%)	154 (31.3%)	307 (27.2%)	
2	362 (11.8%)	164 (11.3%)	56 (11.4%)	142 (12.6%)	
≥3	615 (20.1%)	214 (14.8%)	48 (9.76%)	353 (31.3%)	
Diagnosis method					<.001
Cytology or histology	2,179 (71.1%)	602 (41.7%)	489 (99.4%)	1,088 (96.5%)	
Clinical diagnosis	885 (28.9%)	843 (58.3%)	3 (0.61%)	39 (3.46%)	
Alpha-fetoprotein level					<.001
Normal	1,368 (44.6%)	720 (49.8%)	211 (42.9%)	437 (38.8%)	
Elevated	960 (31.3%)	438 (30.3%)	146 (29.7%)	376 (33.4%)	
Missing	736 (24.0%)	287 (19.9%)	135 (27.4%)	314 (27.9%)	
MELD					
Median (IQR)	11.5 (8.47–18.5)	10.4 (8.41–14.2)	8.94 (6.43–12.7)	16.6 (11.3–24.1)	<.001
Fibrosis					<.001
Ishak fibrosis score 0–4	194 (6.33%)	67 (4.64%)	67 (13.6%)	60 (5.32%)	
Ishak fibrosis score 5–6 (cirrhosis)	849 (27.7%)	400 (27.7%)	87 (17.7%)	362 (32.1%)	
Missing	2021 (66.0%)	978 (67.7%)	338 (68.7%)	705 (62.6%)	
Time to treatment, days ^b					
Median (IQR)	53.0 (12.0–126)	56.0 (29.0–98.0)	33.0 (0.00–64.2)	79.5 (0.00–235)	<.001

Abbreviations: HCC, hepatocellular carcinoma; IQR, interquartile range; MELD, Model for End-Stage Liver Disease.

^aP values were calculated by Pearson chi-square test for categorical variables and Welch t test for continuous variables.

^bAmong patients who underwent liver transplantation, a total of 424 patients had an HCC diagnosis at the time of transplant surgery date.