Diagnostic and Therapeutic Delays in Patients With Hepatocellular Carcinoma

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ABSTRACT

Background: Delays in diagnosis and treatment have been reported for many cancers, with resultant stage migration and worse survival; however, few data exist in patients with hepatocellular carcinoma (HCC). These data are of particular importance in light of the COVID-19 pandemic, which has caused disruptions in healthcare processes and may continue to impact cancer care for the foreseeable future. The aim of our study was to characterize the prevalence and clinical significance of diagnostic and treatment delays in patients with HCC. **Methods:** We performed a retrospective cohort study of consecutive patients diagnosed with HCC between January 2008 and July 2017 at 2 US health systems. Diagnostic and treatment delays were defined as >90 days between presentation and HCC diagnosis and between diagnosis and treatment, respectively. We used multivariable logistic regression to identify factors associated with diagnostic and treatment delays and Cox proportional hazard models to identify correlates of overall survival. **Results:** Of 925 patients with HCC, 39.0% were diagnosed via screening, 33.1% incidentally, and 27.9% symptomatically. Median time from presentation to diagnosis was 37 days (interquartile range, 18–94 days), with 120 patients (13.0%) experiencing diagnostic delays. Median time from HCC diagnosis to treatment was 46 days (interquartile range, 29–74 days), with 17.2% of patients experiencing treatment delays. Most (72.5%) diagnostic delays were related to provider-level factors (eg, monitoring indeterminate nodules), whereas nearly half (46.2%) of treatment delays were related to patient-related factors (eg, missed appointments). In multivariable analyses, treatment delays were not associated with increased mortality (hazard ratio, 0.90; 95% CI, 0.60–1.35); these results were consistent across subgroup analyses by Barcelona Clinic Liver Cancer stage and treatment modality. **Conclusions:** Diagnostic and therapeutic delays exceeding 3 months are common in patients with HCC; however, observed treatment delays do not seem to significantly impact overall survival.

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Background

Hepatocellular carcinoma (HCC) mortality continues to increase in many countries, including the United States.[1] The 5-year survival for HCC remains <20%, in part related to failures in care delivery across the screening and treatment continuum. For example, there is underuse of HCC screening in practice, with only 24% of at-risk patients undergoing screening as recommended by society guidelines.[2] Even among patients who undergo screening, downstream failures in the care continuum can result in stage migration and worse prognosis.[3] Although it is conceptually simple, the HCC care continuum consists of several steps, including screening, recognition of abnormal results, appropriate diagnostic testing, accurate interpretation of diagnostic tests, referral for treatment, adherence to clinic visits, and appropriate treatment recommendations.[3,4] Failures can occur as a result of a combination of patient-, provider-, and system-level factors at any step.[5,6]

The prevalence and significance of diagnostic and therapeutic delays has been well studied in many malignancies but remains controversial.[7,8] For instance, in breast and colorectal cancer, diagnostic and treatment delays have been associated with stage migration and worse survival,[9–13] whereas other studies have failed to show an association between delays and worse prognosis.[14–18] In HCC, few studies have explored the prevalence and clinical impact of diagnostic and therapeutic delays.[19,20] Although one prior study reported HCC treatment delays in nearly one-third of patients, it was a single-center study with only 165 patients, precluding precise prevalence estimates or robust conclusions.[19] Improving our understanding of the prevalence, determinants, and impact of delays in HCC care is timely in light of the ongoing COVID-19 pandemic and its impact on healthcare delivery. In a recent American Cancer Society survey, 50% of patients with cancer reported disrupted access to healthcare, including 27% reporting delays in cancer treatment.[21] Similarly, many health systems have deferred cancer screening examinations and even


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delayed diagnostic tests in patients with abnormal screening results. In light of ASCO recommendations for HCC treatment to proceed without delay because the benefits likely outweigh the risk of COVID-19 exposure,[22,23] data evaluating the impact of diagnostic and therapeutic delays on prognosis are needed. Therefore, the primary aims of our study were to enumerate the prevalence of diagnostic and therapeutic delays, identify factors associated with delays, and characterize the impact of delays on outcomes, including tumor stage and overall survival (OS).

Methods

Study Population

We conducted a retrospective cohort study of consecutive patients diagnosed with HCC between January 2008 and July 2017 at 2 large US health systems: UT Southwestern Medical Center and Parkland Health and Hospital System. UT Southwestern is a university-affiliated tertiary care referral center, that cares for patients with HCC referred from across Texas and neighboring states. Parkland is the safety-net system for Dallas County and provides care to a socioeconomically disadvantaged population of patients with HCC. Patients at both sites are cared for by the same group of providers, with each patient discussed at a shared multidisciplinary conference.[24] HCC diagnoses were confirmed using American Association for the Study of Liver Diseases (AASLD) criteria (ie, characteristic imaging [LI-RADS 5] or histopathologic confirmation).[25] We excluded patients (1) with liver masses without characteristic imaging or histology, (2) for whom the date of HCC presentation and/or diagnosis could not be ascertained from the electronic medical record, and (3) who had received HCC treatment at an outside facility before presentation at a study site. This study was approved by the Institutional Review Board of UT Southwestern Medical Center.

Data Collection

We obtained patient demographics, clinical history, laboratory data, and imaging results at HCC presentation, diagnosis, and treatment from the electronic medical record. Variables of interest included age, sex, race/ethnicity, insurance status, etiology of cirrhosis, Child-Pugh class, tumor burden, and receipt of hepatology care. Race/ethnicity was categorized as non-Hispanic White (White), non-Hispanic Black (Black), Hispanic, Asian, or other.[26] Medical history included the presence of metabolic syndrome, lifetime alcohol history, lifetime smoking history, and ECOG performance status. Data regarding liver disease included liver disease etiology (hepatitis C virus [HCV], hepatitis B virus [HBV], alcohol-related liver disease, and nonalcoholic fatty liver disease)[27] and liver function (Child-Pugh score). Laboratory data at presentation, diagnosis, and treatment included bilirubin, international normalized ratio, albumin, platelet count, creatinine, and alpha fetoprotein (AFP). Healthcare utilization included contact with gastroenterology/hepatology clinic and receipt of HCC screening in the prior 12 months.

Dates of HCC presentation, diagnosis, and treatment initiation were abstracted. HCC presentation was defined as a suspicious liver mass on an imaging study, a new increase in AFP level exceeding 20 ng/mL, or a persistently elevated AFP level exceeding 20 ng/mL on 2 consecutive visits. Type of initial presentation was classified as screening (including follow-up of indeterminate nodules), symptomatic (eg, presence of abdominal pain, jaundice, weight loss), or incidental (eg, evaluation of abnormal liver biochemistries or imaging performed in the emergency department for other reasons). HCC diagnosis was defined by the date when lesions met HCC criteria per AASLD guidelines.[25] Tumor staging was performed using the Barcelona Clinic Liver Cancer (BCLC) staging system.[28] Date of treatment was defined by the first delivered HCC therapy, including liver transplantation, surgical resection, local ablative therapy, stereotactic body radiation therapy, embolization techniques (eg, transarterial chemoembolization or radioembolization), or systemic therapy.

Diagnostic and treatment delays were defined as >90 days from presentation to diagnosis and from diagnosis to treatment, respectively. The 90-day cutoff was selected as a clinically relevant timepoint based on prior literature.[19,29] If diagnostic and/or treatment delays were present, we classified the reasons for delay as patient-level (eg, patient choice, missed appointment, clinical decompensation, lost to follow-up), provider-level (eg, provider decisions including monitoring indeterminate nodules, failure to place orders), or system-level (eg, follow-up testing/treatment ordered but not completed within 3 months).

Statistical Analysis

Variables were stratified by type of HCC presentation, and the Kruskal-Wallis test was used to compare groups. Times to HCC diagnosis and to HCC treatment were determined using Kaplan-Meier analysis. Diagnostic and treatment delays were evaluated as dichotomous outcomes, and we used logistic regression models to evaluate factors associated with delays. Variables of a priori clinical importance (eg, Child-Pugh class) and those associated with delays in univariable analyses ($P<.25$) were included in multivariable models.

Using Kaplan-Meier analysis, transplant-free OS was estimated from the date of HCC diagnosis to death, liver transplantation, last known follow-up, or end of study period (July 1, 2017). Univariable and multivariable Cox proportional hazard models were used to identify factors associated with OS. Log-rank tests were used to compare

survival distributions between groups. A landmark analysis was performed to evaluate the association between treatment delays and OS, accounting for immortal time bias, with OS calculated from a landmark date of 150 days after HCC diagnosis (selected a priori). In this analysis, timely treatment was defined as <90 days and delayed treatment as 90 to 150 days; patients who died before the landmark and those who received HCC treatment after the landmark were excluded. All tests were 2-sided and performed with a 5% significance level. Statistical analysis was performed utilizing STATA, version 14.0 (StataCorp LLP).

Results

Patient Characteristics

Of 1,206 consecutive patients with HCC, 925 met inclusion criteria (Table 1, and supplemental eFigure 1, available with this article at JNCCN.org). The median age of patients was 58.8 years, 78.3% were men, and the population was racially and ethnically diverse (30.0% White, 35.1% Black, and 29.0% Hispanic). The most common etiology of cirrhosis was HCV (65.5%), followed by alcohol-related cirrhosis (14.6%), nonalcoholic fatty liver disease (11.6%), and HBV (5.0%).

A total of 360 patients (39.0%) were diagnosed via screening, whereas 308 (33.1%) were diagnosed incidentally and 257 (27.9%) symptomatically. In those with symptomatic presentation, the most common symptoms were abdominal pain (88.7%), constitutional symptoms (20.6%), and jaundice (9.3%). A higher proportion of tumors was detected symptomatically (vs incidental or screening) in Black and Hispanic patients (43.2% and 28.8%) compared with White patients (21.0%; $P=.003$). Furthermore, a higher proportion of symptomatic presentations occurred in patients in the safety-net health system ($P<.001$), those who were unemployed ($P<.001$), and those who were uninsured ($P<.001$). Among patients diagnosed symptomatically, only 26.9% and 11.7% had a primary care physician or gastroenterology/hepatology visit within the prior 12 months, respectively, and only 7.8% had received abdominal imaging in the 12 months prior to HCC diagnosis.

As expected, type of presentation was associated with tumor stage ($P<.001$), with most patients with BCLC stage 0/A disease presenting via screening (59.2%) and a higher proportion of patients with BCLC stage C and D disease presenting symptomatically (43.2% and 26.9%, respectively).

Diagnostic Delays

Overall, the median time from presentation to HCC diagnosis was 7 days (interquartile range [IQR], 1–42 days). Among the subset of patients diagnosed in an outpatient setting (n=468), median time from presentation to diagnosis was 37 days (IQR, 18–94 days), with 120 patients (13.0%) experiencing a diagnostic delay. Nearly two-thirds (62.4%) of patients with a diagnostic delay presented as an outpatient. The most common reasons for diagnostic delays are detailed in Figure 1A. In brief, 15.1%, 72.5%, and 10.8% of delays were classified as being related to patient-, provider-, and system-level factors, respectively. Provider decisions to monitor indeterminate nodules on imaging (38.3%) or false-negative findings on biopsy (7.5%) accounted for nearly half of diagnostic delays, whereas missed visits (11.7%) and scheduling issues (5.0%) accounted for fewer delays.

In univariable analyses (supplemental eTable 1), symptomatic presentation, Child-Pugh class C cirrhosis, and receiving care at the university health system were associated with lower odds of diagnostic delay. In multivariable analysis, diagnostic delays were inversely associated with symptomatic presentation (odds ratio [OR], 0.14; 95% CI, 0.07–0.32), Child-Pugh class C cirrhosis (OR, 0.38; 95% CI, 0.17–0.85), and care at the university health system (OR, 0.34; 95% CI, 0.18–0.65).

Diagnostic delays were associated with early-stage (BCLC 0/A) HCC at diagnosis, which remained significant after adjusting for age, sex, race/ethnicity, Child-Pugh class, and type of initial presentation (OR, 2.31; 95% CI, 1.44–3.71). Early-stage detection was higher among patients with delays due to monitoring of indeterminate nodules than among those with delays for other reasons (77.8% vs 62.9%; Figure 1A).

Treatment Receipt and Delays

Of 610 patients with HCC who received treatment, surgical resection or liver transplantation was performed as the initial therapy in 18.4%, locoregional therapy in 64.9%, and systemic therapy in 16.7%. A total of 315 patients received no treatment, including 10.6% with BCLC stage 0/A HCC and 17.0%, 51.3%, and 80.6% with BCLC stage B, C, and D HCC, respectively. Lack of treatment was independently associated with lack of insurance coverage (OR, 2.91; 95% CI, 1.16–7.31), symptomatic presentation (OR, 1.79; 95% CI, 1.03–3.09), Child-Pugh class B (OR, 3.67; 95% CI, 2.42–5.57) or class C cirrhosis (OR, 23.75; 95% CI, 13.10–43.07), AFP level >200 ng/mL (OR, 1.89; 95% CI, 1.20–2.98), and infiltrative-type tumors (OR, 2.70; 95% CI, 1.62–4.48) (supplemental eTable 2).

Median time from diagnosis to treatment was 46 days (IQR, 29–74 days). Among the 104 (17.2%) patients with a treatment delay, 25 (25.5%) also experienced a diagnostic delay. The most common reasons for treatment delays are detailed in Figure 1B. Nearly half (46.2%) of treatment delays were related to patient-level factors, whereas 31.7% and 12.5% were attributed to provider- and system-level factors, respectively. The most common

Table 1. Patient and Tumor Characteristics (N=925)[a]

Variable	Screening n (%)	Incidental n (%)	Symptomatic n (%)	*P* Value
Total, n	360	308	257	
Age, mean (SD), y	59.7 (8.2)	60.3 (8.9)	58.6 (9.7)	.06
Male sex	278 (77.2)	240 (77.9)	206 (80.2)	.67
Race/Ethnicity				.003
White	115 (31.9)	108 (35.1)	54 (21.0)	
Black	123 (34.2)	91 (29.6)	111 (43.2)	
Hispanic	103 (28.6)	91 (29.6)	74 (28.8)	
Asian	15 (4.2)	12 (3.9)	17 (6.6)	
Other	4 (1.1)	6 (2.0)	1 (0.4)	
Health system				<.001
Parkland	279 (77.5)	214 (69.5)	219 (85.2)	
UT Southwestern	81 (22.5)	94 (30.5)	38 (14.8)	
Primary language				.38
English	296 (82.2)	246 (79.9)	191 (74.6)	
Spanish	49 (13.6)	45 (14.6)	17 (6.7)	
Other/Unknown/Not reported	15 (4.2)	17 (5.5)	48 (18.8)	
Insurance status				<.001
Medicare	113 (31.4)	95 (30.8)	41 (15.9)	
Medicaid	71 (19.7)	62 (20.1)	71 (27.6)	
Other/Parkland	101 (28.1)	83 (26.9)	89 (24.6)	
Private	49 (13.6)	41 (13.3)	21 (8.2)	
Uninsured	26 (7.2)	27 (8.8)	35 (13.6)	
PCP visit in the past 1 year	239 (66.6)	111 (36.0)	69 (26.9)	<.001
Gastroenterology/Hepatology visit in past 1 year	174 (48.5)	83 (27.0)	20 (11.7)	<.001
Receipt of any abdominal imaging in 12 mo before HCC diagnosis	113 (31.4)	63 (20.5)	20 (7.8)	<.001
Liver disease etiology				.01
HCV	254 (70.9)	192 (62.3)	158 (61.7)	
NAFLD	29 (8.1)	45 (14.6)	33 (12.9)	
Alcohol-related	45 (12.6)	52 (16.9)	38 (14.8)	
HBV	22 (6.2)	7 (2.3)	17 (6.6)	
Other/Unknown	8 (2.2)	12 (3.9)	10 (3.9)	
Child-Pugh class				<.001
A	206 (57.2)	123 (39.9)	94 (36.9)	
B	112 (31.1)	145 (47.1)	104 (40.8)	
C	42 (11.7)	40 (13.0)	57 (22.4)	
ECOG performance status				<.001
0	216 (64.7)	145 (51.4)	89 (36.3)	
1	78 (23.4)	88 (31.2)	80 (32.7)	
2	36 (10.8)	36 (12.8)	53 (21.6)	
3 or 4	4 (1.2)	13 (4.6)	23 (9.4)	
Unknown/Not reported	26 (7.2)	26 (9.2)	12 (4.7)	
Ascites				.001
None	222 (61.7)	152 (49.4)	117 (45.5)	
Mild/Controlled	110 (30.6)	127 (41.2)	106 (41.3)	
Severe/Uncontrolled	28 (7.8)	29 (9.4)	34 (13.2)	

(*continued on next page*)

Table 1. Patient and Tumor Characteristics (N=925)[a] (cont.)

Variable	Screening n (%)	Incidental n (%)	Symptomatic n (%)	*P* Value
Hepatic encephalopathy				.13
None	288 (80.0)	243 (78.9)	215 (83.7)	
Mild/Controlled	64 (17.8)	61 (19.8)	38 (14.8)	
Severe/Uncontrolled	8 (2.2)	4 (1.3)	2 (0.8)	
Platelet count, median (IQR), 10^9/L	106 (70–155)	129 (79–190)	142 (94–221)	<.001
AFP, median (IQR), ng/mL	35 (8–336)	19 (5–267)	275 (14–7,270)	<.001
AFP, ng/mL				<.001
<20	150 (41.7)	155 (50.3)	75 (29.3)	
20–200	107 (29.7)	67 (21.8)	46 (18.0)	
>200	103 (28.6)	86 (27.9)	135 (52.7)	
Number of tumors at diagnosis				<.001
1	222 (61.8)	167 (54.4)	93 (36.2)	
2	68 (18.9)	49 (16.0)	30 (11.7)	
≥3	33 (9.2)	29 (9.5)	24 (9.3)	
Infiltrative and/or innumerable	36 (10.0)	62 (20.2)	110 (42.8)	
Largest tumor diameter, cm				<.001
<2	71 (19.7)	45 (14.6)	13 (5.1)	
2–5	204 (56.7)	141 (45.8)	69 (26.9)	
>5	85 (23.6)	122 (39.6)	175 (68.1)	
Extrahepatic metastases	17 (4.7)	35 (11.4)	62 (24.1)	<.001
BCLC stage at diagnosis				<.001
0/A	213 (59.2)	137 (44.5)	46 (17.9)	
B	53 (14.7)	51 (16.6)	31 (12.1)	
C	51 (14.2)	67 (21.8)	111 (43.2)	
D	43 (11.9)	53 (17.2)	69 (26.9)	
Treated	281 (78.1)	210 (68.2)	119 (46.3)	<.001
Initial HCC treatment				<.001
Resection	58 (16.1)	29 (9.4)	15 (5.8)	
Ablation	45 (12.5)	24 (7.8)	7 (2.7)	
Liver transplantation	3 (0.8)	7 (2.3)	0 (0.0)	
TACE/TARE/SBRT	151 (41.9)	116 (37.7)	53 (20.6)	
Systemic therapy	24 (6.7)	34 (11.0)	44 (17.1)	
None/BSC	79 (21.9)	98 (31.8)	138 (57.0)	
Diagnostic delay >90 days	67 (18.6)	45 (14.6)	8 (3.1)	<.001
Treatment delay >90 days	51 (18.2)	38 (18.3)	15 (12.8)	.38

Abbreviations: AFP, alpha fetoprotein; BCLC, Barcelona Clinic Liver Cancer; BSC, best supportive care; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IQR, interquartile range; NAFLD, nonalcoholic fatty liver disease; PCP, primary care physician; SBRT, stereotactic body radiation therapy; TACE, transarterial chemoembolization; TARE, transarterial radioembolization.
[a]<5% missing data for all variables unless otherwise specified.

reasons included missed appointments (25.0%) and scheduling delays (7.7%).

On univariable analysis, more-aggressive tumor characteristics were associated with lower odds of treatment delays, including AFP level >200 ng/mL, maximum tumor diameter 2 to 5 cm, maximum tumor diameter >5 cm, infiltrative-type and/or innumerable tumors, and presence of extrahepatic metastases (supplemental eTable 3). On multivariable analysis, maximum tumor diameter 2 to 5 cm (OR, 0.56; 95% CI, 0.33–0.95), maximum tumor diameter >5 cm (OR, 0.34; 95% CI, 0.15–0.75), and care at the university health system (OR, 0.55; 95% CI, 0.30–0.99) were inversely

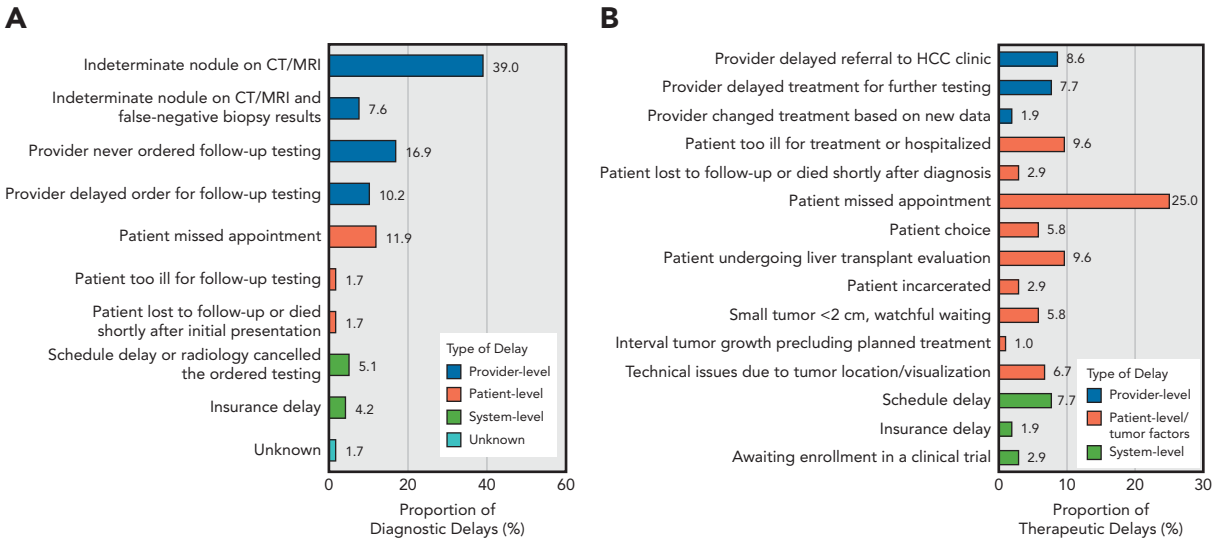

Figure 1. Reasons for (A) diagnostic (n=120) and (B) treatment delays (n=104).
Abbreviation: HCC, hepatocellular carcinoma.

associated with treatment delays, whereas Child-Pugh class B/C cirrhosis (OR, 1.66; 95% CI, 1.02–2.67) was associated with increased treatment delay. The presence of a diagnostic delay was associated with treatment delay on univariable analysis; however, it was not significant on multivariable analysis (OR, 1.41; 95% CI, 0.82–2.44). Patients treated with locoregional therapy (OR, 3.29; 95% CI, 1.60–6.77) had higher odds of experiencing treatment delays than those treated with surgical therapy, whereas there was no increased delay among those receiving systemic therapy (OR, 0.87; 95% CI, 0.31–2.43).

Treatment Delays and OS

In unadjusted analysis, patients with treatment delays had better survival compared with those without delays (31.4 vs 20.7 months; hazard ratio [HR], 0.76; 95% CI, 0.58–1.00). On multivariable analysis, treatment delays were no longer significantly associated with improved survival (HR, 0.81; 95% CI, 0.60–1.09) after adjusting for age, sex, race/ethnicity, health system, presentation type, tumor burden, AFP level, Child-Pugh class, and type of HCC treatment (Table 2).

In the landmark analysis at the 150-day timepoint, 460 patients (75.4%) had received HCC treatment, with 52 (11.3%) having experienced a treatment delay. In unadjusted analyses, there was no significant difference in OS between patients who experienced a treatment delay and those who did not (32.9 vs 27.6 months; HR, 0.94; 95% CI, 0.64–1.37; Figure 2). Results were similar on multivariable analysis after adjusting for age, sex, race/ethnicity, health system, presentation type, tumor burden, AFP level, Child-Pugh class, and type of initial HCC treatment (HR, 0.90; 95% CI, 0.60–1.35). Results were consistent by BCLC stage and HCC treatment modality.

Discussion

This is the largest study to evaluate diagnostic and therapeutic delays in HCC. In our study of >900 patients with HCC, we found that nearly 1 in 7 experienced a diagnostic delay and nearly 1 in 5 experienced a treatment delay. The most common reasons for diagnostic delays were provider-related factors, and nearly half of treatment delays were connected to patient-related factors. We failed to find a significant association between treatment delays and OS.

Although we hypothesized that patient-, provider-, or system-level factors would each contribute to diagnostic delays based on the literature from HCC screening and diagnostic evaluation in other cancers,[2,30–37] we found that nearly three-fourths of diagnostic delays were attributed to provider-related factors. Furthermore, although some diagnostic delays may have been related to provider knowledge gaps or competing clinical demands, others seemed intentional, including monitoring of indeterminate nodules.[33] Our finding that monitoring of indeterminate lesions was a common cause of diagnostic delays is consistent with the results of a recent Veterans Affairs study, which found that 46.9% of patients experienced a diagnostic delay after a "red flag" on imaging, including indeterminate nodules.[20] This mixed rationale for diagnostic delays may explain the association between diagnostic delays and increased early-stage diagnosis. However, a lack of stage migration does not exclude potential other harms, such as increased costs from repetitive testing and psychological distress from prolonged diagnostic evaluation.[38,39] The high prevalence of indeterminate nodules in patients with cirrhosis[40] highlights the need for better diagnostic tools.[41,42]

Table 2. Correlates of Overall Survival Among Patients Receiving HCC Treatment

Variable	Univariate HR (95% CI)	Multivariate[a] (n=601) aHR (95% CI)
Female sex	0.76 (0.59–0.98)	0.83 (0.64–1.08)
Age	1.00 (0.99–1.01)	1.01 (1.00–1.03)
Race/Ethnicity		
White	Ref	Ref
Black	0.95 (0.74–1.21)	0.85 (0.64–1.11)
Hispanic	0.81 (0.62–1.06)	0.61 (0.45–0.83)
Health system		
Parkland	Ref	Ref
UT Southwestern	1.25 (0.99–1.59)	1.17 (0.89–1.53)
Gastroenterology/ Hepatology care in year before diagnosis	0.75 (0.45–1.26)	
Presentation type		
Screening	Ref	Ref
Incidental	1.42 (1.12–1.79)	1.28 (1.00–1.65)
Symptomatic	2.01 (1.54–2.63)	1.21 (0.89–1.63)
Child-Pugh class		
A	Ref	Ref
B	1.85 (1.49–2.30)	1.80 (1.41–2.31)
C	3.10 (1.90–5.04)	3.25 (1.91–5.53)
Liver disease etiology		
HCV	Ref	
Alcohol-related	0.90 (0.64–1.25)	
NAFLD	0.96 (0.69–1.32)	
HBV	0.95 (0.59–1.51)	
Other	0.96 (0.54–1.71)	
AFP, ng/mL		
<20	Ref	Ref
20–200	1.47 (1.14–1.89)	1.57 (1.41–2.30)
>200	2.72 (2.12–3.48)	1.85 (1.91–5.53)
Tumor number		
1	Ref	Ref
2	1.69 (1.28–2.25)	1.30 (0.96–1.75)
≥3	2.72 (1.94–3.81)	1.81 (1.27–2.60)
Infiltrative and/or innumerable	4.72 (3.54–6.29)	1.61 (1.11–2.35)
Maximum tumor diameter, cm		
<2	Ref	Ref
2–5	1.45 (1.05–1.99)	1.27 (0.91–1.76)
>5	3.40 (2.44–4.75)	2.13 (1.46–3.10)
Treatment		
Surgical	Ref	Ref
Locoregional	3.03 (2.13–4.33)	2.45 (1.66–3.61)
Systemic	12.65 (8.46–18.94)	5.79 (3.54–9.46)
Presence of treatment delay >90 days	0.76 (0.58–1.00)	0.81 (0.60–1.09)

Multivariate model adjusted for age, sex, race/ethnicity, hospital system, HCC presentation type, Child-Pugh class, AFP, tumor number, maximum tumor diameter, HCC treatment received, and presence of treatment delay >90 days.
Abbreviations: AFP, alpha fetoprotein; aHR, adjusted hazard ratio; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; NAFLD, nonalcoholic fatty liver disease.

We also observed that one-third of patients received no HCC treatment and that therapeutic delays were present in 17% of those who were treated. Treatment delays were related to a combination of patient-, provider-, and system-level factors,[43] but nearly half were related to patient-level factors. Increasingly, data highlight issues such as financial toxicity of cancer treatment and medical mistrust, which can both lead to nonadherence with provider recommendations.[44,45] Treatment delays may be anticipated for HCC given the complex nature of treatment, including transitions between subspecialty providers and potential changes in liver dysfunction.[24] For instance, among patients who are candidates for liver transplantation, locoregional therapy for HCC may be delayed in those with severe liver dysfunction until they are waitlisted, given the risk for further hepatic decompensation. Similarly, under the current organ allocation system, patients with small T1 HCC (tumors <2 cm) may not receive immediate treatment and instead may be managed with watchful waiting until tumors are classified as T2 (>2 cm), thereby meeting the criteria for United Network for Organ Sharing exception points.[46]

Several studies in other cancers have shown an association between treatment delays and increased mortality. For example, in breast cancer, shorter time to treatment has been shown to improve disease-specific survival and OS.[11,13,47] In HCC, data are conflicted on the relationship between treatment delays and survival. In one US study, treatment delays were associated with worse survival.[19] Smaller studies in Taiwan[29,48] and Canada[49] have also shown the adverse impact of delays in locoregional therapy on treatment response and survival. In contrast, studies have found that delays in surgical therapy have no impact[50] or are associated with improved survival compared with no delays.[51] In our study, patients with treatment delays had better crude survival, but delays were not associated with survival after adjusting for other prognostic factors. The reasons underlying these findings may

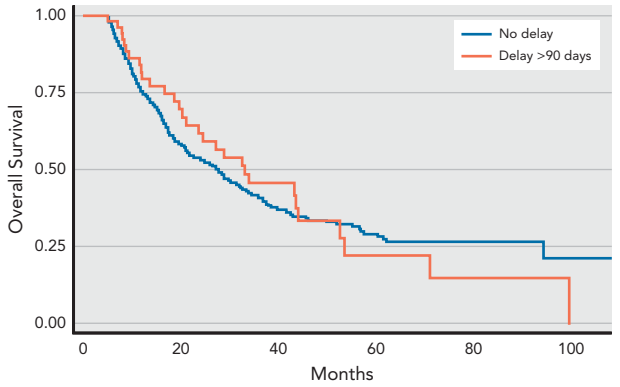

Figure 2. Overall survival by presence of treatment delays in landmark analysis (n=460).

be partly due to provider behavior, wherein patients who are perceived to have more aggressive tumors are prioritized for treatment but still have worse outcomes than those with favorable tumor biology.

Although our study has several strengths, including its large sample size and racially/ethnically and socioeconomically diverse population, it has recognized limitations. First, there is the potential for missing data, measurement bias, and unmeasured confounders given our study's retrospective nature. Second, although we included patients from 2 large health systems, our findings may not be generalizable to other settings. Third, our study must be interpreted in the context of the inherent complexity in studying cancer care delays.[52] Although we performed a landmark analysis, with consistent results, it can still be difficult to fully account for lead time and immortal time biases. Finally, tumor biology may vary between cancer types and even 2 patients with the same cancer,[53,54] resulting in different outcomes despite similar management. Perceived tumor biology may also influence provider management, which cannot be adjusted.

Conclusions

Diagnostic and therapeutic delays >3 months are common in patients with HCC. Most diagnostic delays in this study were due to provider-level factors or decision-making, whereas nearly half of treatment delays were related to patient-level factors. Although the clinical significance of delays remains unclear, interventions should aim to improve timely diagnosis and treatment among patients with HCC.

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References

1. Hashim D, Boffetta P, La Vecchia C, et al. The global decrease in cancer mortality: trends and disparities. Ann Oncol 2016;27:926–933.
2. Wolf E, Rich NE, Marrero JA, et al. Utilization of hepatocellular carcinoma surveillance in patients with cirrhosis: a systematic review and meta-analysis [published online May 8, 2020]. Hepatology, doi: 10.1002/hep.31309
3. Singal AG, Yopp AC, Gupta S, et al. Failure rates in the hepatocellular carcinoma surveillance process. Cancer Prev Res (Phila) 2012;5:1124–1130.
4. Singal AG, El-Serag HB. Hepatocellular carcinoma from epidemiology to prevention: translating knowledge into practice. Clin Gastroenterol Hepatol 2015;13:2140–2151.
5. Zapka JG, Taplin SH, Solberg LI, et al. A framework for improving the quality of cancer care: the case of breast and cervical cancer screening. Cancer Epidemiol Biomarkers Prev 2003;12:4–13.
6. Taplin SH, Anhang Price R, Edwards HM, et al. Introduction: understanding and influencing multilevel factors across the cancer care continuum. J Natl Cancer Inst Monogr 2012;2012:2–10.
7. Tørring ML, Frydenberg M, Hansen RP, et al. Evidence of increasing mortality with longer diagnostic intervals for five common cancers: a cohort study in primary care. Eur J Cancer 2013;49:2187–2198.
8. Yun YH, Kim YA, Min YH, et al. The influence of hospital volume and surgical treatment delay on long-term survival after cancer surgery. Ann Oncol 2012;23:2731–2737.
9. Smith EC, Ziogas A, Anton-Culver H. Delay in surgical treatment and survival after breast cancer diagnosis in young women by race/ethnicity. JAMA Surg 2013;148:516–523.
10. Tørring ML, Frydenberg M, Hamilton W, et al. Diagnostic interval and mortality in colorectal cancer: U-shaped association demonstrated for three different datasets. J Clin Epidemiol 2012;65:669–678.
11. Bleicher RJ, Ruth K, Sigurdson ER, et al. Time to surgery and breast cancer survival in the United States. JAMA Oncol 2016;2:330–339.
12. Corley DA, Jensen CD, Quinn VP, et al. Association between time to colonoscopy after a positive fecal test result and risk of colorectal cancer and cancer stage at diagnosis. JAMA 2017;317:1631–1641.
13. Richards MA, Westcombe AM, Love SB, et al. Influence of delay on survival in patients with breast cancer: a systematic review. Lancet 1999;353:1119–1126.
14. Ramos M, Esteva M, Cabeza E, et al. Relationship of diagnostic and therapeutic delay with survival in colorectal cancer: a review. Eur J Cancer 2007;43:2467–2478.
15. Ramos M, Esteva M, Cabeza E, et al. Lack of association between diagnostic and therapeutic delay and stage of colorectal cancer. Eur J Cancer 2008;44:510–521.
16. Fisher DA, Zullig LL, Grambow SC, et al. Determinants of medical system delay in the diagnosis of colorectal cancer within the Veteran Affairs Health System. Dig Dis Sci 2010;55:1434–1441.

17. Pruitt SL, Harzke AJ, Davidson NO, et al. Do diagnostic and treatment delays for colorectal cancer increase risk of death? Cancer Causes Control 2013;24:961–977.
18. Ho PJ, Cook AR, Binte Mohamed Ri NK, et al. Impact of delayed treatment in women diagnosed with breast cancer: a population-based study. Cancer Med 2020;9:2435–2444.
19. Singal AG, Waljee AK, Patel N, et al. Therapeutic delays lead to worse survival among patients with hepatocellular carcinoma. J Natl Compr Canc Netw 2013;11:1101–1108.
20. Choi DT, Davila JA, Sansgiry S, et al. Factors associated with delay of diagnosis of hepatocellular carcinoma in patients with cirrhosis [published online July 18, 2020]. Clin Gastroenterol Hepatol, doi: 10.1016/j.cgh.2020.07.026
21. American Cancer Society Cancer Action Network. COVID-19 pandemic early effects on cancer patients and survivors: April 2020. Accessed November 25, 2020. Available at: https://www.fightcancer.org/policy-resources/covid-19-pandemic-early-effects-cancer-patients-and-survivors-april-2020
22. American Society of Clinical Oncology. ASCO special report: a guide to cancer care delivery during the COVID-19 pandemic. Accessed November 25, 2020. Available at: https://www.asco.org/sites/new-www.asco.org/files/content-files/2020-ASCO-Guide-Cancer-COVID19.pdf
23. Fix OK, Hameed B, Fontana RJ, et al. Clinical best practice advice for hepatology and liver transplant providers during the COVID-19 pandemic: AASLD expert panel consensus statement. Hepatology 2020;72:287–304.
24. Yopp AC, Mansour JC, Beg MS, et al. Establishment of a multidisciplinary hepatocellular carcinoma clinic is associated with improved clinical outcome. Ann Surg Oncol 2014;21:1287–1295.
25. Marrero JA, Kulik LM, Sirlin CB, et al. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American Association for the Study of Liver Diseases. Hepatology 2018;68:723–750.
26. Rich NE, Hester C, Odewole M, et al. Racial and ethnic differences in presentation and outcomes of hepatocellular carcinoma. Clin Gastroenterol Hepatol 2019;17:551–559.e1.
27. Hester CA, Rich NE, Augustine MM, et al. Clinicopathological factors and curative treatment receipt differ amongst nonalcoholic steatohepatitis-, viral hepatitis-, and alcohol liver disease-related HCC. J Am Coll Surg 2018;227:e170–171.
28. Llovet JM, Brú C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis 1999;19:329–338.
29. Huo TI, Huang YH, Chiang JH, et al. Survival impact of delayed treatment in patients with hepatocellular carcinoma undergoing locoregional therapy: is there a lead-time bias? Scand J Gastroenterol 2007;42:485–492.
30. Dobson CM, Russell AJ, Rubin GP. Patient delay in cancer diagnosis: what do we really mean and can we be more specific? BMC Health Serv Res 2014;14:387.
31. McGowan CE, Edwards TP, Luong MU, et al. Suboptimal surveillance for and knowledge of hepatocellular carcinoma among primary care providers. Clin Gastroenterol Hepatol 2015;13:799–804.
32. Simmons OL, Feng Y, Parikh ND, et al. Primary care provider practice patterns and barriers to hepatocellular carcinoma surveillance. Clin Gastroenterol Hepatol 2019;17:766–773.
33. Dalton-Fitzgerald E, Tiro J, Kandunoori P, et al. Practice patterns and attitudes of primary care providers and barriers to surveillance of hepatocellular carcinoma in patients with cirrhosis. Clin Gastroenterol Hepatol 2015;13:791–798.e1.
34. Sharma P, Saini SD, Kuhn LB, et al. Knowledge of hepatocellular carcinoma screening guidelines and clinical practices among gastroenterologists. Dig Dis Sci 2011;56:569–577.
35. Kanwal F, Singal AG. Surveillance for hepatocellular carcinoma: current best practice and future direction. Gastroenterology 2019;157:54–64.
36. Singal AG, Tiro JA, Murphy CC, et al. Patient-reported barriers are associated with receipt of hepatocellular carcinoma surveillance in a multicenter cohort of patients with cirrhosis [published online July 3, 2020]. Clin Gastroenterol Hepatol, doi: 10.1016/j.cgh.2020.06.049
37. Martin J, Halm EA, Tiro JA, et al. Reasons for lack of diagnostic colonoscopy after positive result on fecal immunochemical test in a safety-net health system. Am J Med 2017;130:93.e1–7.
38. Rich NE, Parikh ND, Singal AG. Overdiagnosis: an understudied issue in hepatocellular carcinoma surveillance. Semin Liver Dis 2017;37:296–304.
39. Wu GX, Raz DJ, Brown L, et al. Psychological burden associated with lung cancer screening: a systematic review. Clin Lung Cancer 2016;17:315–324.
40. Konerman MA, Verma A, Zhao B, et al. Frequency and outcomes of abnormal imaging in patients with cirrhosis enrolled in a hepatocellular carcinoma surveillance program. Liver Transpl 2019;25:369–379.
41. Roberts LR, Sirlin CB, Zaiem F, et al. Imaging for the diagnosis of hepatocellular carcinoma: a systematic review and meta-analysis. Hepatology 2018;67:401–421.
42. Forner A, Vilana R, Ayuso C, et al. Diagnosis of hepatic nodules 20 mm or smaller in cirrhosis: prospective validation of the noninvasive diagnostic criteria for hepatocellular carcinoma. Hepatology 2008;47:97–104.
43. Taplin SH, Clauser S, Rodgers AB, et al. Interfaces across the cancer continuum offer opportunities to improve the process of care. J Natl Cancer Inst Monogr 2010;2010:104–110.
44. Zafar SY, Abernethy AP. Financial toxicity, part I: a new name for a growing problem. Oncology (Williston Park) 2013;27:80–81.
45. Davis JL, Bynum SA, Katz RV, et al. Sociodemographic differences in fears and mistrust contributing to unwillingness to participate in cancer screenings. J Health Care Poor Underserved 2012;23:67–76.
46. Mehta N, Sarkar M, Dodge JL, et al. Intention to treat outcome of T1 hepatocellular carcinoma with the "wait and not ablate" approach until meeting T2 criteria for liver transplant listing. Liver Transpl 2016;22:178–187.
47. Polverini AC, Nelson RA, Marcinkowski E, et al. Time to treatment: measuring quality breast cancer care. Ann Surg Oncol 2016;23:3392–3402.
48. Chen WT, Fernandes ML, Lin CC, et al. Delay in treatment of early-stage hepatocellular carcinoma using radiofrequency ablation may impact survival of cirrhotic patients in a surveillance program. J Surg Oncol 2011;103:133–139.
49. Brahmania M, Ahmed O, Kelley M, et al. Wait time for curative intent radio frequency ablation is associated with increased mortality in patients with early stage hepatocellular carcinoma. Ann Hepatol 2017;16:765–771.
50. Lim C, Bhangui P, Salloum C, et al. Impact of time to surgery in the outcome of patients with liver resection for BCLC 0-A stage hepatocellular carcinoma [published online October 6, 2017]. J Hepatol, doi: 10.1016/j.jhep.2017.09.017
51. Xu K, Watanabe-Galloway S, Rochling FA, et al. Surgical delay is associated with improved survival in hepatocellular carcinoma: results of the National Cancer Database. J Gastrointest Surg 2019;23:933–943.
52. Singal AG, Lok AS, Feng Z, et al. Conceptual model for the hepatocellular carcinoma screening continuum: current status and research agenda. [published online September 19, 2020]. Clin Gastroenterol Hepatol, doi.org/10.1016/j.cgh.2020.09.036
53. Rich NE, John BV, Parikh ND, et al. Hepatocellular carcinoma demonstrates heterogeneous growth patterns in a multi-center cohort of patients with cirrhosis. Hepatology 2020;72:1654–1665.
54. Nathani P, Gopal P, Rich N, et al. Hepatocellular carcinoma tumour volume doubling time: a systemic review and meta-analysis. Gut 2021;70:401–407.

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Diagnostic and Therapeutic Delays in Patients With Hepatocellular Carcinoma

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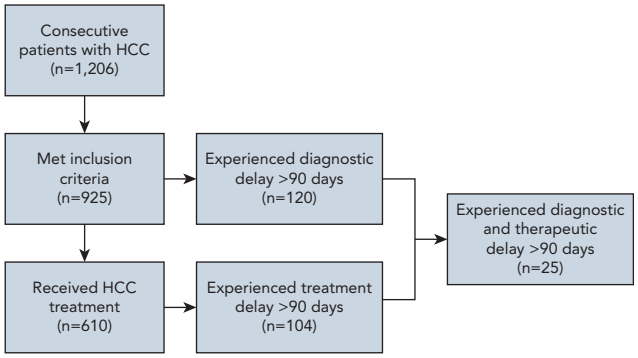

eFigure 1. Study flow diagram.
Abbreviation: HCC, hepatocellular carcinoma.

eTable 1. Correlates of Diagnostic Delays

Variable	Univariate OR (95% CI)	Multivariate (n=908) aOR (95% CI)
Female sex	1.11 (0.71–1.75)	1.12 (0.67–1.87)
Age	0.98 (0.96–0.99)	0.97 (0.95–1.00)
Race/Ethnicity		
White	Ref	Ref
Black	1.02 (0.63–1.64)	0.89 (0.53–1.51)
Hispanic	1.07 (0.65–1.76)	1.04 (0.60–1.80)
Asian	0.49 (0.14–1.66)	0.38 (0.10–1.45)
Health system		
Parkland	Ref	Ref
UT Southwestern	0.44 (0.25–0.77)	0.34 (0.18–0.65)
Insurance status		
Private	Ref	
Medicare	1.44 (0.72–2.88)	
Medicaid	0.90 (0.42–1.91)	
Other/Parkland	1.45 (0.73–2.89)	
Uninsured	1.06 (0.43–2.58)	
Gastroenterology/Hepatology care in year before diagnosis	0.69 (0.24–1.97)	
Presentation type		
Screening imaging	Ref	Ref
Screening AFP	0.94 (0.54–1.64)	1.05 (0.59–1.86)
Incidental	0.72 (0.45–1.14)	0.87 (0.54–1.41)
Symptomatic	0.14 (0.06–0.30)	0.14 (0.07–0.32)
Liver disease etiology		
HCV	Ref	Ref
Alcohol-related	0.87 (0.49–1.54)	0.90 (0.47–1.71)
NAFLD	0.45 (0.20–1.01)	0.61 (0.25–1.50)
HBV	1.79 (0.86–3.75)	2.29 (0.99–5.32)
Other	1.29 (0.48–3.47)	2.59 (0.82–8.18)
Child-Pugh class		
A	Ref	Ref
B	0.82 (0.55–1.24)	0.88 (0.57–1.39)
C	0.34 (0.16–0.72)	0.38 (0.17–0.85)

Abbreviations: AFP, alpha fetoprotein; aOR, adjusted odds ratio; HBV, hepatitis B virus; HCV, hepatitis C virus; NAFLD, nonalcoholic fatty liver disease; OR, odds ratio.

eTable 2. Correlates of Untreated HCC Among Entire Cohort

Variable	Univariate OR (95% CI)	Multivariate (n=857) aOR (95% CI)
Female sex	0.86 (0.61–1.20)	1.22 (0.77–1.95)
Age	0.99 (0.98–1.01)	1.02 (0.99–1.04)
Race/Ethnicity		
White	Ref	Ref
Black	1.33 (0.95–1.88)	1.04 (0.63–1.70)
Hispanic	1.22 (0.85–1.75)	0.73 (0.44–1.22)
Asian	1.47 (0.76–2.84)	0.98 (0.40–2.40)
Health system		
Parkland	Ref	Ref
UT Southwestern	0.53 (0.38–0.76)	0.55 (0.29–1.04)
Insurance status		
Private	Ref	Ref
Medicare	1.18 (0.71–1.97)	0.93 (0.44–1.94)
Medicaid	1.76 (1.05–2.94)	0.87 (0.38–1.99)
Other/Parkland	1.39 (0.84–2.28)	0.73 (0.32–1.65)
Uninsured	4.49 (2.45–8.22)	2.91 (1.16–7.31)
Gastroenterology/Hepatology care in year before diagnosis	0.31 (0.13–0.74)	0.42 (0.14–1.21)
Presentation type		
Screening	Ref	Ref
Incidental	2.01 (1.33–3.04)	1.34 (0.80–2.25)
Symptomatic	5.10 (3.37–7.74)	1.79 (1.03–3.09)
Liver disease etiology		
HCV	Ref	Ref
Alcohol-related	1.50 (1.02–2.19)	1.13 (0.65–1.94)
NAFLD	0.99 (0.64–1.54)	0.97 (0.49–1.91)
HBV	0.99 (0.52–1.88)	0.74 (0.30–1.82)
Other	0.88 (0.40–1.95)	0.95 (0.33–2.70)
AFP, ng/mL		
<20	Ref	Ref
20–200	0.80 (0.54–1.20)	0.78 (0.46–1.31)
>200	3.77 (2.73–5.20)	1.89 (1.20–2.98)
Tumor number		
1	Ref	Ref
2	1.14 (0.75–1.74)	1.02 (0.61–1.71)
≥3	1.44 (0.87–2.38)	0.80 (0.42–1.53)
Infiltrative and/or innumerable	5.37 (3.78–7.62)	2.70 (1.62–4.48)
Maximum tumor diameter, cm		
<2	Ref	Ref
2–5	1.05 (0.65–1.70)	0.88 (0.49–1.57)
>5	4.07 (2.54–6.50)	1.85 (0.97–3.51)
Child-Pugh class		
A	Ref	Ref
B	3.03 (2.18–4.23)	3.67 (2.42–5.57)
C	15.92 (0.99–25.39)	23.75 (13.10–43.07)

Abbreviations: AFP, alpha fetoprotein; aOR, adjusted odds ratio; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; NAFLD, nonalcoholic fatty liver disease; OR, odds ratio.

eTable 3. Correlates of Treatment Delays

Variable	Univariate OR (95% CI)	Multivariate (n=599) aOR (95% CI)
Female sex	1.31 (0.81–2.12)	1.29 (0.77–2.16)
Age	0.99 (0.97–1.02)	1.00 (0.98–1.03)
Race/Ethnicity		
White	Ref	Ref
Black	0.78 (0.47–1.30)	0.83 (0.46–1.48)
Hispanic	0.82 (0.48–1.39)	0.63 (0.34–1.16)
Asian	0.71 (0.23–2.17)	0.83 (0.25–2.74)
Health system		
Parkland	Ref	Ref
UT Southwestern	0.66 (0.39–1.11)	0.55 (0.30–0.99)
Insurance status		
Private	Ref	
Medicare	1.12 (0.55–2.27)	
Medicaid	1.27 (0.61–2.65)	
Other/Parkland	0.93 (0.46–1.91)	
Uninsured	1.31 (0.47–3.62)	
Gastroenterology/ Hepatology care in year before diagnosis	0.64 (0.22–1.86)	
Liver disease etiology		
HCV	Ref	
Alcohol-related	0.85 (0.44–1.65)	
NAFLD	0.83 (0.42–1.65)	
HBV	0.71 (0.24–2.09)	
Other	1.44 (0.51–4.05)	

(*continued*)

eTable 3. Correlates of Treatment Delays (cont.)

Variable	Univariate OR (95% CI)	Multivariate (n=599) aOR (95% CI)
AFP, ng/mL		
<20	Ref	Ref
20–200	0.67 (0.41–1.10)	0.73 (0.43–1.23)
>200	0.42 (0.23–0.77)	0.66 (0.34–1.28)
Tumor number		
1	Ref	Ref
2	0.69 (0.38–1.25)	0.68 (0.36–1.27)
≥3	0.72 (0.34–1.54)	0.79 (0.35–1.74)
Infiltrative and/or innumerable	0.28 (0.11–0.72)	0.64 (0.21–1.93)
Maximum tumor diameter, cm		
<2	Ref	Ref
2–5	0.50 (0.31–0.84)	0.56 (0.33–0.95)
>5	0.21 (0.11–0.41)	0.34 (0.15–0.75)
Presence of extrahepatic metastases	0.24 (0.06–1.00)	0.50 (0.11–2.30)
Child-Pugh class		
A	Ref	Ref
B/C	1.44 (0.94–2.20)	1.66 (1.02–2.67)
Presence of diagnostic delay >90 days	1.86 (1.11–3.10)	1.41 (0.82–2.44)

Abbreviations: AFP, alpha fetoprotein; aOR, adjusted odds ratio; HBV, hepatitis B virus; HCV, hepatitis C virus; NAFLD, nonalcoholic fatty liver disease; OR, odds ratio.