Diagnostic Delays Are Common Among Patients With Hepatocellular Carcinoma

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Abstract

Background: Most patients with hepatocellular carcinoma (HCC) present at advanced stages. The prevalence and clinical impact of delays during diagnostic evaluation among patients with HCC is unclear. **Purpose:** To identify and characterize factors associated with diagnostic delays among patients with HCC. **Methods:** Records were reviewed for consecutive patients with cirrhosis and HCC at a large urban hospital between January 2005 and July 2012. Time from presentation to diagnosis was determined using Kaplan-Meier analysis. Diagnostic delay was defined as time to diagnosis exceeding 3 months, and multivariate logistic regression was used to identify correlates of diagnostic delays. **Results:** Among 457 patients with HCC, 226 (49.5%) were diagnosed as outpatients. Among these, median time-to-diagnosis was 2.2 months, with 87 patients (38.5%) experiencing a diagnostic delay. Diagnostic delays were positively associated with the presence of hepatic encephalopathy (odds ratio [OR], 2.29; 95% CI, 1.03–5.07) and negatively associated with presentation after implementation of the electronic medical records (EMR) (OR, 0.28; 95% CI, 0.15–0.52) and presentation with an abnormal ultrasound (OR, 0.36; 95% CI, 0.19–0.67) on multivariate analysis. Higher rates of diagnostic delays were observed among those with hepatic encephalopathy (56% vs 35%), whereas lower rates were seen in those who presented after EMR implementation (26% vs 60%) and those who presented with an abnormal ultrasound with or without an elevated alpha fetoprotein level (27% vs 50%). Among 49 patients with mass-forming HCC and diagnostic delay, 18% had interval tumor growth of 2 cm or greater. **Conclusions:** Nearly 20% of patients with HCC wait more than 3 months from presentation to diagnosis, which can contribute to interval tumor growth. (J Natl Compr Canc Netw 2015;13:543–549)

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death worldwide. Although its incidence is lower in the United States and Europe, its incidence is rapidly increasing because of a growing number of cases of nonalcoholic fatty liver disease (NAFLD) and hepatitis C virus (HCV).¹ Prognosis for patients with HCC depends on tumor stage at diagnosis, with curative options only available for those diagnosed at an early stage. Patients with early HCC achieve 5-year survival rates near 70% with resection or liver transplantation, whereas those with advanced HCC have a median survival of less than 1 year.² Surveillance

at 6-month intervals is recommended in patients with cirrhosis and is associated with improved early detection and overall survival.^{3,4}

Despite the availability of efficacious surveillance tests, only 40% of HCC cases are diagnosed at an early stage nationally.⁵ Tumor stage at diagnosis can be impacted by several factors in clinical practice, including low surveillance rates and delays in follow-up of abnormal screening tests.^{6–9} These issues may be particularly prevalent among racial minorities and socioeconomically disadvantaged patients, potentially contributing to racial and socioeconomic disparities in cancer outcomes.^{10,11}

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Delays in diagnostic testing after presentation with a positive screening test have been well described as a barrier for effective colon and breast cancer screening; however, no studies to date have characterized the prevalence and potential clinical impact of diagnostic delays among patients with HCC.¹² For HCC, delays as little as 3 months in diagnostic follow-up can allow for significant tumor growth and lead to lower chances of effective treatment options.¹³ A better understanding of breakdowns in follow-up is necessary to identify appropriate intervention strategies. Integrated health systems are the ideal setting to study potential failures, because patients are typically followed through the entire continuum of HCC care from presentation to diagnosis to treatment. Therefore, the primary goals of this study were to quantify diagnostic delays among patients diagnosed with HCC and identify factors associated with delays in follow-up testing.

Methods

Study Population

We conducted a retrospective cohort study of patients with cirrhosis diagnosed with HCC at Parkland Memorial Health & Hospital System, the safety net system for Dallas County, between January 2005 and June 2012. With 11 primary care clinics in low-income neighborhoods, Parkland cares for approximately 50% of patients with HCC in Dallas County. Given its integrated structure and function as the safety net institution of Dallas, patients admitted to Parkland Hospital often receive their continuity care through the Parkland Health System clinics. Parkland adopted a comprehensive electronic medical record (EMR), including laboratory and radiology results, for inpatient and outpatient care in 2008. Patients were identified by ICD-9 codes for HCC (155.0 or 155.2), tumor conference presentation lists, and databases of patients who underwent surgical (resection or transplantation) or interventional (transarterial chemoembolization [TACE] or local ablation) treatments for HCC as previously described.¹⁴

Two authors (A.G.S. and A.C.Y.) adjudicated HCC cases to confirm that they met diagnostic criteria based on American Association for the Study of Liver Diseases guidelines.² For tumors larger than 1 cm, diagnosis was made by a typical vascular pattern

on dynamic imaging (arterial enhancement and delayed washout) or histology. This study was approved by the Institutional Review Board of UT Southwestern Medical Center.

Data Collection

Patient demographics, clinical history, laboratory data, and imaging results were obtained through review of EMRs and paper medical records. Two investigators (A.G.S. and N.P.) independently extracted information using standardized forms, with discrepancies resolved through discussion and consensus. Age, sex, race/ethnicity, and lifetime alcohol and smoking history were recorded, with active alcohol abuse defined as drinking more than 40 g/d. Date of first medical encounter and number of primary care and hepatology clinic visits were documented. Data regarding liver disease included underlying etiology and presence of decompensation (ascites or encephalopathy). We classified patients according to liver disease etiology, including HCV, hepatitis B virus, alcohol-related liver disease, NAFLD, and other. NAFLD was often associated with components of the metabolic syndrome (obesity, diabetes, dyslipidemia) but was a diagnosis of exclusion, only made in the absence of other causes of liver disease, including viral hepatitis and alcohol abuse. Laboratory data of interest included platelet count, creatinine, aspartate aminotransferase, alanine aminotransferase, bilirubin, albumin, international normalized ratio, and alpha fetoprotein (AFP) at presentation and diagnosis.

Dates of HCC presentation, diagnosis, and treatment were abstracted. The date of HCC presentation was defined by the presence of any suspicious liver mass on any imaging study, an AFP level greater than 100 ng/mL, or 2 consecutive increasing AFP levels greater than 20 ng/mL. We included a one-time AFP level of 100 ng/mL based on its greater specificity and associated higher level of clinical concern for HCC at this cutoff. For cases with consecutive increasing AFP levels, we defined presentation using the date of the second AFP test. The date of HCC diagnosis was defined as the date of characteristic imaging (as described earlier) or biopsy. Tumor characteristics were determined by imaging studies, which had all been interpreted by radiologists at our institution, and tumor staging was performed using the Barcelona Clinic Liver Cancer (BCLC) staging system. HCC treatments were categorized as liver

transplantation, resection, radiofrequency ablation (RFA), TACE, systemic chemotherapy, or best supportive care. In patients who received multiple treatments, treatment was categorized as the most curative (ie, liver transplantation > resection > RFA > TACE > systemic chemotherapy > best supportive care). All patients with HCC at Parkland are evaluated in a multidisciplinary conference and clinic for evaluation and treatment.¹⁵

Statistical Analysis

Our primary outcome of interest was time from presentation to diagnosis. We used Kaplan-Meier analysis to determine time to diagnosis and Cox multivariate regression analysis to identify factors associated with time to diagnosis. We also analyzed time to diagnosis as a dichotomous outcome, with delayed diagnosis being defined as time from presentation to diagnosis exceeding 3 months (ie, 90 days). The cut-off of 3 months was based on prior studies examining delays in HCC care and tumor doubling time.¹³ Demographics, clinical features, and tumor characteristics were compared between the 2 groups using Fisher exact and Mann-Whitney rank sum tests for categorical and continuous variables, respectively. We assessed patient sociodemographic and clinical characteristics, including age, sex, race/ethnicity, primary language, alcohol abuse, insurance status, performance status, inpatient versus outpatient status, number of primary care visits, receipt of hepatology subspecialty care, cause of liver disease, platelet count, bilirubin, Child-Pugh class, and implementation of the EMR as independent variables. Statistical significance was defined as *P* less than .05 for both univariate and multivariate analysis. All data analysis was performed using Stata 11 (StataCorp, College Station, TX).

Results

Patient Characteristics

Between January 2005 and July 2012, 457 patients with cirrhosis were diagnosed with HCC. Baseline characteristics of the cohort are shown in Table 1. The median age of patients was 56 years (range, 28–92 years), and more than 75% were men. Our population was racially diverse, with 36% African Americans, 30% Hispanic Caucasians, and 26% non-Hispanic Caucasians. Nearly 56% of patients

were uninsured, 18% had Medicaid, and only 25% had Medicare or private health insurance. The most common causes of cirrhosis were HCV infection (69%), alcohol-induced liver disease (12%), and NAFLD (9%). The median Child-Pugh score at time of HCC diagnosis was 7 (range, 5–15), with 37% of patients having Child-Pugh A cirrhosis. Tumor stage at presentation was diverse, with 29% BCLC stage A, 9% BCLC stage B, 29% BCLC stage C, and 33% BCLC stage D.

Presentation Data

Most patients presented initially with an abnormal imaging study, with 219 (48%) presenting with abnormal abdominal ultrasound and 149 (33%) presenting with a mass on CT or MRI. AFP level was elevated in 135 patients (30%) including 67 whose presentation was an elevated AFP level alone (ie, without concomitant abnormal imaging). The other 22 patients presented to an outside hospital and the test at presentation was unknown given the lack of details in the available medical records. Nearly 40% (n=178) presented before the EMR system was implemented, whereas the other 279 presented after its adoption. Initial presentation of HCC occurred as an inpatient in 243 patients (53%), of whom 231 (Group 1) had the diagnostic process completed during the same hospitalization before discharge. The remaining 226 patients (Group 2) either presented or were diagnosed as an outpatient (Figure 1).

Time From Presentation to Diagnosis

The median time from presentation to diagnosis among all patients was 0.6 months. More than 90% (n=214) of patients in Group 1 (ie, inpatients) had a time from presentation to diagnosis of less than 1 week. Only 1 of these 231 patients had HCC diagnosed more than 1 month after initial presentation (ie, 1.5 months). The median time to diagnosis among the 226 patients in Group 2 was 2.2 months, with 87 (39%) being diagnosed more than 3 months after initial presentation.

Overall, 87 patients (39%) were diagnosed more than 3 months after initial presentation. Among the patients with diagnostic delay, 73 (84%) had at least one interval clinic visit to primary care or gastroenterology clinics, during which HCC presentation was not recognized. In fact, 52 patients (60%) had more than 3 visits and 20 (23%) had 10 or more clinic visits before diagnostic workup was completed.

Table 1 Patient Characteristics

Patient Characteristics	Patients With Diagnostic Delays (n=87)	Patients Without Diagnostic Delays (n=370)	P Value
Age (y)	55 (34–93)	56 (28–89)	.42
Gender (% male)	64 (73.6%)	293 (79.2%)	.25
Race/ethnicity			.10
Hispanic	31 (35.6%)	104 (28.1%)	
Caucasian	22 (25.3%)	97 (26.2%)	
Black	31 (35.6%)	131 (35.4%)	
Other	3 (3.5%)	38 (10.3%)	
Cause			.87
Hepatitis C virus infection	61 (70.1%)	246 (66.5%)	
Hepatitis B virus infection	7 (8.1%)	34 (9.2%)	
Alcohol-induced	11 (12.6%)	45 (12.2%)	
Nonalcoholic steatohepatitis	6 (6.9%)	36 (9.7%)	
Other	2 (2.3%)	9 (2.4%)	
Insurance status			.31
Medicare	21 (24.1%)	67 (18.1%)	
Medicaid	13 (15.0%)	71 (19.2%)	
Private insurance	6 (6.9%)	22 (5.9%)	
None	47 (54.0%)	210 (56.8%)	
Alcohol (% active)	22 (25.3%)	114 (30.1%)	.30
Presence of ascites	41 (47.1%)	171 (46.2%)	.88
Presence of hepatic encephalopathy	22 (25.3%)	49 (13.2%)	.005
Platelet count, x 1000/mm ³	114 (6–518)	134 (12–842)	.007
AST (U/L)	96 (6–578)	112 (12–3742)	.34
ALT (U/L)	54 (9–245)	54 (11–601)	.89
Bilirubin (mg/dL)	1.4 (0.3–15.7)	1.4 (0.2–37)	.17
Albumin (g/dL)	3.1 (1.3–4.7)	3.0 (1.2–4.7)	.93
INR	1.3 (0.9–4.8)	1.2 (0.9–5.0)	.86
Functional status (% ECOG 0–1)	74 (85.1%)	312 (84.3%)	.91
Child-Pugh score	7 (5–15)	7 (5–15)	.73
Child-Pugh classification			.56
Child-Pugh A	33 (37.9%)	135 (36.5%)	
Child-Pugh B	32 (36.8%)	157 (42.4%)	
Child-Pugh C	22 (25.3%)	78 (21.1%)	
Tumor stage			.03
BCLC A	37 (42.5%)	93 (25.1%)	
BCLC B	7 (8.1%)	34 (9.2%)	
BCLC C	12 (13.8%)	122 (33.0%)	
BCLC D	31 (35.6%)	121 (32.7%)	
Treatment			.09
Liver transplantation	2 (2.3%)	4 (1.1%)	
Resection	9 (10.3%)	19 (5.1%)	
Radiofrequency ablation	5 (5.7%)	13 (3.5%)	
Transarterial chemoembolization	31 (35.6%)	95 (25.7%)	
Systemic therapy	9 (10.3%)	52 (14.1%)	
Best supportive care	31 (35.6%)	187 (50.5%)	

All data are expressed as median (range) unless otherwise specified.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; INR, international normalized ratio.

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Figure 1 Patient cohorts.

However, 13 patients (15%) with diagnostic delay had at least one missed appointment for diagnostic imaging. Additionally, diagnostic delay could have been related to insensitive diagnostic testing in 25 patients (29%), in whom CT and/or MRI had been performed but was not diagnostic for HCC.

An infiltrative type pattern was seen in 38 patients on follow-up imaging, and therefore interval growth was difficult to accurately determine. Among the 49 patients with diagnostic delays and mass-forming HCC, 9 (18%) were noted to have interval HCC growth of 2 cm or more in maximum diameter. However, no significant difference was seen in receipt of treatment ($P=.68$) between patients with and without diagnostic delays after adjusting for BCLC stage and presentation as an inpatient. Similarly, we did not detect a difference in survival according to the presence of diagnostic delay ($P=.16$) after adjusting for BCLC stage, presentation as an inpatient, and receipt of HCC-directed treatment.

Predictors for Diagnostic Delays

Diagnostic delays among all patients were positively associated with the presence of hepatic encephalopathy (odds ratio [OR], 3.39; 95% CI, 1.72–6.68) and negatively associated with presentation as an inpatient (OR, 0.17; 95% CI, 0.09–0.30), presentation after EMR implementation (OR, 0.33; 95% CI, 0.19–0.57), and presentation with an abnormal ultrasound (OR, 0.39; 95% CI, 0.22–0.67). Higher rates of diagnostic delays were observed among those with hepatic encephalopathy (31% vs 17%), whereas lower rates were seen in those who presented as an inpatient (9% vs 30%), presented after EMR

implementation (13% vs 29%), and those who presented with an abnormal ultrasound with or without elevated AFP (26% vs 12%). Rates of diagnostic delays were 12.3% among those who presented with any abnormal ultrasound, compared with 29.9% for those who presented with an abnormal AFP and 24.8% among those who had an incidental mass discovered on CT/MRI.

Among the subset of patients in Group 2, diagnostic delays were positively associated with the presence of hepatic encephalopathy (OR, 2.29; 95% CI, 1.03–5.07) and negatively associated with presentation after EMR implementation (OR, 0.28; 95% CI, 0.15–0.52) and presentation with an abnormal ultrasound (OR, 0.36; 95% CI, 0.19–0.67). Higher rates of diagnostic delays were observed among those with hepatic encephalopathy (56% vs 35%), whereas lower rates were seen among those who presented after EMR implementation (26% vs 60%) and those who presented with an abnormal ultrasound with or without elevated AFP levels (27% vs 50%). Sex and presentation to primary care or gastroenterology clinic were significant on univariate analysis but failed to reach statistical significance on multivariate analysis.

Discussion

This study is the first to provide in-depth analysis of diagnostic delays in HCC. We found that these delays were common, with nearly 1 in 5 patients experiencing delays exceeding 3 months. Diagnostic delays are particularly common among outpatients,

occurring in more than one-third. These delays may be related to several potential issues, including providers failing to recognize positive surveillance tests, patients missing radiology appointments, and insensitive diagnostic tests. Although we did not find any difference in receipt of HCC-directed treatment, diagnostic delays were associated with potential interval tumor growth in nearly one-fifth of patients.

Most diagnostic delays in our cohort were related to lack of provider orders. The higher rate of diagnostic delays among patients with an incidental mass on imaging and/or elevated AFP level on univariate analysis (data not shown) suggests that providers' lack of awareness of abnormal test results may play an important role. Similarly, the association between implementation of the EMR and a reduction in diagnostic delays may be mediated by increased provider awareness of prior test results and improved communication. Consistent with previous studies showing high levels of patient acceptance for HCC surveillance, this study suggests that patient adherence is not a major barrier to follow-up testing in most patients.^{9,16} Missed radiology appointments were only documented in 15% of those with diagnostic delays. However, missed appointments were significantly more common among patients with hepatic encephalopathy (17% vs 8%; $P=.02$) and may explain the association between hepatic encephalopathy and diagnostic delays. Therefore, it is possible that patient adherence may play a bigger role in certain subsets of patients.

We also found that diagnostic delays may relate to poor sensitivity of diagnostic testing in more than one-fourth of cases. Both CT and MRI have imperfect sensitivity, requiring liver biopsy among cases with suspicious lesions that are not characteristic on imaging.² However, even liver biopsy has imperfect sensitivity, requiring up to 3 biopsies in some cases to make a diagnosis of HCC.¹⁷ The introduction of a tissue-based panel of biomarkers, including glypican 3, heat shock protein 70, and glutamine synthetase, may also help with HCC diagnosis, particularly in small nodules.¹⁸ Similarly, serum-based biomarkers are being evaluated to improve diagnostic accuracy.^{19–21} It is possible that introduction of biomarkers with high diagnostic accuracy may help reduce diagnostic delays in the future.

Several studies have shown that race, socioeconomic status, and underinsurance are important pre-

dictors of screening completion.^{11,22} We found that Hispanic race was a predictor of time-to-diagnosis as a continuous outcome (data not shown), but was not significantly associated with diagnostic delays when dichotomized at 3 months. Similarly, we found that sex was associated with diagnostic delays on univariate analysis but did not remain significant on multivariate analysis. Insurance status did not appear to be associated with diagnostic delays, although this may relate to Parkland's sliding fee scale program, which provides a subsidy for medical care, such as receipt of HCC surveillance and diagnostic testing. Further studies in large racially diverse cohorts are needed to continue exploring potential racial and socioeconomic disparities in HCC surveillance, diagnostic, and treatment processes.

Diagnostic delays were associated with interval tumor growth of at least 2 cm in nearly one-fifth of patients. Although we did not observe any significant difference in overall survival, it is possible that this lack of association could be related to length time bias. Although slow-growing tumors will permit repeat imaging for diagnosis despite diagnostic delays, more aggressive tumors may precipitate liver failure or death before a definite HCC diagnosis can be made. This study only included patients with an established HCC diagnosis; therefore, we could not quantify or characterize those who never completed diagnostic testing after initial presentation.

This study has several limitations. The conclusions reflect a retrospective analysis of patients with HCC seen at a large urban safety net hospital, and therefore may not be generalized to other practice settings. Further studies, with large sample sizes in other health care settings, are necessary to validate the results. Given its retrospective nature, this study could not assess potential determinants of follow-up completion, such as patient knowledge, social support, and/or barriers such as lack of transportation. This study was also limited by possible unmeasured confounders and missing data. Although some patients may have received diagnostic testing at outside institutions, we believe this is unlikely given that Parkland, as the safety net health system for Dallas County, is the only option for most indigent patients. Overall, we believe the limitations of our study are outweighed by its strengths, including its well-characterized cohort, its racially and socioeconomically diverse population, and its relatively large sample size.

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Conclusions

Diagnostic delays seem to be common and may allow interval tumor growth among patients with HCC. This study showed that 1 in 5 patients experienced significant diagnostic delays, allowing for interval tumor growth. Delays in diagnosis are particularly common among patients who present as an outpatient, being present in more than one-third of cases. Furthermore, diagnostic delays may be more common in hospital systems without an EMR, because of higher rates of unrecognized positive surveillance tests. This study highlights that diagnostic delays may be a common issue among patients with HCC, and that further studies in large cohorts are necessary. If confirmed, interventions are needed to improve the timely diagnosis of HCC among patients with cirrhosis and positive surveillance tests.

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