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Hepatocellular carcinoma diagnosis and management in 2021: a national VA quality improvement project

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Abstract

Background & Aims—The COVID-19 pandemic has profoundly disrupted preventative health care services including cancer screening. As the largest provider of cirrhosis care in the United States, the Veterans Affairs (VA) National Gastroenterology and Hepatology Program aimed to assess factors associated with hepatocellular carcinoma (HCC) stage at diagnosis, treatment, and survival.

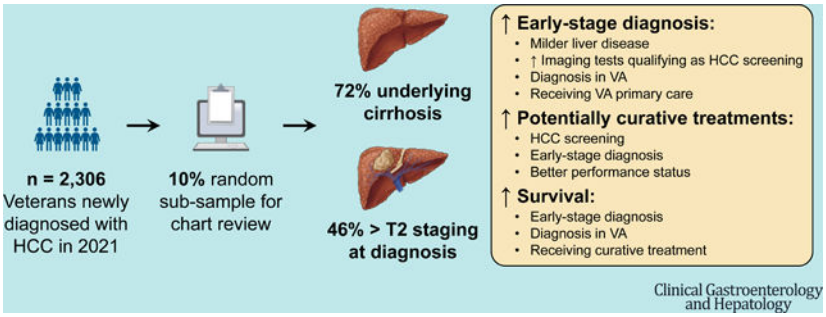
Methods—Veterans with a new diagnosis of HCC in 2021 were identified from electronic health records (n=2306). Structured medical record extraction was performed by expert reviewers in a 10% random sub-sample of Veterans with new HCC diagnoses. Factors associated with stage at diagnosis, receipt of treatment and survival were assessed using multivariable models.

Results—Among 199 patients with confirmed HCC, the average age was 71 and most (72%) had underlying cirrhosis. More than half (54%) were at early stage (T1 or T2) at diagnosis. Less advanced liver disease; number of imaging tests adequate for Hepatocellular Carcinoma screening (“HCC screening”); HCC diagnosis in VA; and receipt of VA primary care were significantly associated with early-stage diagnosis. HCC-directed treatments were administered to 145 (73%) patients after a median of 37 (IQR 19–54) days from diagnosis, including 70 (35%) receiving potentially curative treatments. Factors associated with potentially curative (versus no) treatments included: HCC screening, early-stage at diagnosis, and better performance status. Having fewer comorbidities and better performance status were significantly associated with

non-curative (versus no) treatment. Early-stage diagnosis, diagnosis in the VA system, and receipt of curative treatment were significantly associated with survival.

Conclusions—These results highlight the importance of HCC screening and engagement in care for HCC diagnosis, treatment, and survival while demonstrating the feasibility of developing a national quality improvement agenda for HCC screening, diagnosis, and treatment.

Graphical Abstract



Keywords

COVID-19; Veterans; liver cancer; cirrhosis

Introduction

Hepatocellular carcinoma (HCC) is the third most common cause of cancer death.[1,2] Locoregional and systemic treatments for HCC are available, in addition to curative treatments like surgical resection and transplantation.[3] However, treatment eligibility and survival rely on early-stage diagnosis.[4–6] While guidelines recommend HCC screening for people with cirrhosis, advanced stage disease at diagnosis is common, likely due to under recognition of cirrhosis, low HCC screening rates, and suboptimal performance characteristics of current HCC screening tests.[7] COVID-19 has caused widespread disruptions in access to various aspects of health care, including cancer screening and treatment.[8] Many studies have evaluated HCC screening and treatment using ICD codes alone or evaluating single center data.[9–11] However, detailed, validated data regarding current HCC diagnosis, treatment, and survival in large healthcare systems are lacking and needed to develop plans to address gaps in care, especially after the pandemic of COVID-19.

The US Department of Veterans Affairs (VA) National Gastroenterology and Hepatology Program (NGHP) established an HCC Field Advisory Board (HCC FAB) tasked with monitoring and providing recommendations for improving HCC care. As part of a quality improvement project, the VA HCC FAB collected data about stage at HCC diagnosis, receipt of cancer-directed therapies, and survival in a random sample of VA enrollees diagnosed with HCC in calendar year (CY) 2021. Based on a critical interpretation of these data, the HCC FAB aimed to identify opportunities to improve early detection and timely delivery of appropriate cancer-directed treatments across VA. This manuscript aims to 1) describe the process of developing a data surveillance program; and 2) identify processes of care and outcomes for Veterans with HCC diagnosed in 2021.

Methods

This project was approved, authorized, and executed as a quality improvement project by the VA National Gastroenterology and Hepatology Program. The VA Pittsburgh Healthcare system approved this project as QI. Hence, no Institutional Review Board (IRB) approvals were required. Below we present the process for developing our iterative data monitoring system for quality improvement, following system redesign principles.[12]

Study population: Patients with a new HCC diagnosis in calendar year 2021 (CY2021) were included.

VA utilizes a single electronic health record system (EHR), which enables cross-facility record access to other VA facilities, the Department of Defense, and non-VA facilities through a system called Joint Legacy Viewer. All patients with a new diagnosis of HCC (n=2306) in CY2021 were identified in VA's Corporate Data Warehouse (CDW). New diagnosis of HCC was defined as first documentation of International Classification of Diseases (ICD)-10 code C22.0 in CY2021 in ≥2 outpatient or ≥1 inpatient records without prior HCC ICD codes. We used a random number generator to identify 20 patients from each of the 14 VA facilities represented by HCC FAB members. The number of patients allowed members to complete an in-depth review of patients, resulting in a 10% sample of all Veterans in VA care with new HCC diagnoses (239 chart reviews were completed; 2306 patients in VA nationally had new HCC diagnoses in the year). CDW data collected included: alpha fetoprotein (AFP) at diagnosis, number of gastroenterology/hepatology visits, abdominal imaging tests in the two years prior to the HCC diagnosis, baseline Charlson comorbidity index scores, and date of death.[13,14] CDW data were collected through 9/13/2022.

Composition and structure of the VA HCC FAB

The VA HCC FAB consists of 14 hepatology experts representing unique VA facilities around the country. The group meets monthly and is overseen by NGHP. Each HCC FAB member was asked to complete in-depth chart reviews of 20 patients with a new diagnosis code for HCC randomly selected from their facility, using collaboratively developed data collection instrument, implemented in REDCap© (Supplemental Figure 1). This instrument guided clinicians to complete a structured EHR extraction to confirm the diagnosis of HCC and to determine staging and treatment characteristics. The process is illustrated in Figure 1.

Data definitions

HCC was confirmed by 1) a Liver Radiology And Diagnostic System (LI-RADS) 5 lesion on a multiphasic, contrasted imaging[15] or 2) liver biopsy consistent with HCC. In rare cases, when these two criteria were not met, a multidisciplinary tumor board consensus of diagnosis was considered sufficient. For Veterans with confirmed HCC, other data were collected, including sociodemographic characteristics, underlying liver disease, diagnosis site, stage, HCC treatment, and healthcare utilization. HCC was categorized into stages, following standard Tumor-Node-Metastasis (TNM) criteria, which define T1 lesions as <2cm without vascular invasion, T2 lesions as either one 2–5 cm tumor or 2–3 lesions ≤3 cm, and beyond T2 as not meeting these criteria.[16] Other characteristics were assessed

including lymph node and distant metastases, vascular invasion, and infiltration (making size calculation challenging). Additionally, we collected information about Model for End-Stage Liver Disease-Sodium (MELD-Na) and Child-Turcotte-Pugh (CTP) scores using chart data and documented the performance status using the Eastern Cooperative Oncology Group (ECOG) performance status, where 0 is the best performance status.[17–19] In a subgroup of patients, additional data fields were collected to include documentation of cirrhosis diagnosis, whether HCC was diagnosed because of screening or not, and reasons for non-treatment or delay in HCC treatment.

HCC-directed treatment was categorized as locoregional, radiation, surgical resection, systemic therapies, and liver transplantation. Treatment with curative intent ("Curative treatment") was further defined as any of the following: liver transplantation, surgical resection, percutaneous or laparoscopc ablation (alone or combined with transarterial chemoembolization [TACE]), while other treatments were classified as non-curative treatments (e.g., chemotherapy, radiation, TACE alone). SBRT is considered a potential alternative to ablation.

Statistical Analysis

The cohort of patients with new HCC was characterized using descriptive statistics. Subsequently, we evaluated the factors associated with 1) diagnosis at an early (T1 or T2) vs. late stage (beyond T2); 2) receipt of HCC treatment, and 3) overall survival. These analyses were completed using only patients with complete data (n=187), first with univariate and then multivariable models. Logistic regression models were developed to evaluate the univariate associations between covariates and early-stage diagnosis (T1 or T2). Final estimates for each association adjusted for factors significant in univariate models. Multinomial models were used to assess the factors associated with curative or non-curative treatment vs. no treatment. Cox proportional hazards models were used to assess the factors associated with time from diagnosis to death or end of data collection (9/13/22).

Results

Cohort Characteristics

Of 239 patients with ICD10 code C22.0 recorded in the EHR, 199 (83%) were confirmed to have a *new* diagnosis of HCC in 2021 and are included in this report. Forty patients were excluded for: having an initial HCC diagnosis before 01/01/2021 (n=6), suspected HCC but not meeting our strict diagnostic criteria (n=9), diagnosis of a cancer other than HCC (n=12), and other or unclear reason for the HCC code (n=13). The final cohort of 199 patients was predominantly male (98%), an average of 71 years old, and represented diverse races and ethnicities (Table 1).

Liver disease etiology and stage

The most common etiology of liver disease was cured hepatitis C virus (HCV, 47%) followed by non-alcoholic fatty-liver disease (NAFLD, 31%), alcohol (16%), active HCV (16%), and other etiologies (6%). Among patients with cured HCV, the number of years between HCV eradication and HCC diagnosis ranged from less than 1 year up to 19

years, with a median of 5 years (IQR 3,6). Cirrhosis was documented in 154 of these 199 patients (77%), with most (n=120) diagnoses occurring prior to and a few (n=34) discovered at or after the diagnosis of HCC. Of the 154 patients with cirrhosis, 30% (n=46) had Child-Turcotte-Pugh (CTP) Class B cirrhosis and 6% (n=10) had CTP Class C disease. The mean MELD-Na at diagnosis was 11±5.

Comorbidities and performance status

ECOG performance status was recorded in the chart in 161 (81%) patients and categorized as 0 (n=70), 1 (n=64), 2 (n=10), 3 (n=13), and 4 (n=2). The median Charlson comorbidity score for the cohort was 2 (IQR=1,3). Active alcohol use at HCC diagnosis was noted in 56 patients (28% of the cohort).

Care and screening prior to diagnosis

Based on chart reviews, 131 patients (66%) received VA liver care within 2 years prior to their HCC diagnosis, 15 (8%) received non-VA liver care, and 53 (27%) had no liver care. Most (n=172, 86%) had an assigned VA primary care provider (PCP); 16 (8%) had a non-VA PCP, and 11 (6%) did not have a documented PCP. In the two years prior to HCC diagnosis, 47 (24%) patients had 0–1 imaging tests that would qualify as HCC screening tests, including abdominal ultrasounds or contrast enhanced MRI or CT; 87 (44%) had 2–3 tests, and 65 (33%) had at least 4 tests (indicating imaging studies were being performed at recommended HCC screening intervals). Among the 120 Veterans diagnosed with cirrhosis prior to HCC, only two had not undergone abdominal imaging in the prior 2 years. Sixty (50%) received 1–3 tests, and 58 (48%) received at least 4 tests.

HCC Diagnosis and Stage

Most HCC diagnoses (87%) were made within the VA system. Tumor stage at diagnosis was available for 197 of 199 patients, among whom n=28 (14.2%) were classified as T1, n=79 (40.1%) as T2, and n=90 (46%) as beyond T2. Sixty-one patients (31%) had at least one high-risk tumor characteristic, with some patients having more than one high-risk characteristic, including infiltrative HCC (n=37, 19%), vascular invasion (n=36, 18.1%), lymph node metastases (n=20, 10%) and/or distal metastases (n= 19, 10%). Of the 187 patients with an AFP at diagnosis, 109 (58%) had an AFP<20 and 78 (42%) had AFP ≥20 ng/ml. The median size of the largest lesion was 3.6 cm (IQR 2.2–6.2), and 68% of patients had unifocal HCC at the time of diagnosis.

Factors associated with earlier stage at HCC diagnosis (T1 or T2 versus >T2) in univariate analyses (Table 2) included prior cirrhosis diagnosis (OR=1.80, 95% CI 1.02–3.22), less severe liver disease (Child A or no cirrhosis vs. Child B or C cirrhosis=2.13, 95% CI=1.14–4.16), more imaging tests in the two years prior to diagnosis that would qualify as HCC screening (OR=2.65, 95% CI=1.25–5.81 for 2–3 tests; OR=7.35, 95% CI=3.16–18.08 for ≥4 vs. 0–1 tests), better performance status (ECOG>0 OR=0.49, 95% CI=0.26–0.94), pre-HCC VA liver care (OR=3.35, 95% CI=1.79–6.40), pre-HCC VA primary care (OR=7.73, 95% CI=2.78–27.52), and being diagnosed in VA (OR=5.82, 95% CI=2.03–21.01). In multivariable models, factors associated with earlier-stage diagnosis were liver disease severity (aOR=2.17, 95% CI=1.11–4.34), imaging tests (aOR=2.60, 95% CI=1.21–5.78 for

2–3 tests; OR=6.34, 95% CI=2.54–16.67 for ≥4 imaging tests); diagnosis in VA (aOR=3.92, 95% CI=1.21–15.33), and VA primary care (aOR=4.81, 95% CI=1.56–18.19).

HCC-directed Treatment

Most patients were referred to a tumor board (n=155) and 147 (74%) received HCC-directed treatment after a median of 37 (IQR: 19–54) days from diagnosis (Figure 1). The most common first treatment was ablation (18%), followed by TACE (18%), transarterial radioembolization (TARE) (13%), surgical resection (9%), systemic therapy (8%) and stereotactic body radiation therapy, SBRT (5%). Over follow-up, 18 patients (9%) were referred for liver transplantation, 8 were listed, and 2 underwent transplantation. Listing was higher among those referred in the VA system (7 of 11) versus outside facilities (1 of 7).

Table 3 illustrates the factors associated with receipt of potentially curative (70/199, 35%) and non-curative (77/199, 39%) treatment, compared to no HCC-directed treatment (52/199, 26%). In univariate multinomial models, factors significantly associated with receipt of potentially curative treatment (vs. no treatment) included earlier stage of diagnosis, cured (vs. active) HCV, pre-existing cirrhosis diagnosis, prior imaging tests that would qualify as HCC screening, performance status, and having VA primary care and liver care prior to diagnosis. In multivariable models, factors associated with potentially curative treatment included greater number of imaging tests [adjusted incident rate ratio (aIRR=2.96, 95% CI=1.20–16.57 for 2–3 tests; aIRR=7.03, 95% CI=1.53–32.26 for ≥4 tests) versus 0–1 tests], better performance status (aIRR=5.00, 95% CI=1.53–16.57), and earlier stage HCC (aIRR=24.74, 95% CI=7.60–80.55). Factors associated with non-curative (vs. no) treatment included earlier stage at diagnosis, lower comorbidity score, and better performance status. Two factors remained significant after controlling for potential confounders: lower comorbidity score (aIRR=1.43, 95% CI=−1.04–1.96) and better performance status (aIRR=8.33, 95% CI=2.86–25). In addition, palliative care consultation was received by 32% overall and was higher among patients receiving non-curative (53%) vs. curative treatment (40%).

Survival—Over a median follow-up of 245 days (IQR=239–385), 82 patients died (41%). Survival time was significantly associated with HCC-directed treatment, a pre-existing cirrhosis diagnosis, having more imaging tests consistent with HCC screening, better performance status, VA primary and liver care prior to HCC diagnosis (Table 4). In multivariable models, factors independently associated with *lower* mortality included early stage at diagnosis (aHR=0.31, 95% CI=0.16–0.57) and HCC-targeted therapy, including both curative (aHR=0.46, 95% CI=0.22–0.99) and non-curative (aHR=0.46, 95% CI=0.26–0.82) treatment.

Subset with further review—The HCC FAB conducted two rounds of chart abstraction (Figure 1). We added several questions to the second-round abstraction form to better understand how the HCC was diagnosed and the potential reasons for non-treatment. Among the 88 patients in the second abstraction (Figure 2), the reasons for non-treatment included comorbidities, poor performance status, and advanced stage of liver disease and HCC.

Treatment was delayed >60 days in 18 patients (26%) for a variety of reasons, with patient preference (n=7) and scheduling outside the VA (n=7) as the most frequent explanations.

Discussion

This quality improvement effort identified factors and processes associated with HCC stage of diagnosis, treatment and survival, and resulted in a system for collecting real-time information to inform VA policy and HCC management nationally. This demonstrates the feasibility of conducting such periodic evaluations in a large integrated healthcare system to better understand potential areas for system-level intervention and care improvement. These data guide ongoing implementation efforts in the VA and may be relevant to other healthcare systems.

These findings reaffirm the importance HCC screening for early detection, treatment, and survival. Diagnosis stage was strongly associated with receipt of curative treatment and survival. Yet, almost half of Veterans were diagnosed at a late stage, which contributed to the high observed mortality. While there have been other published evaluations using chart review to understand the role of screening, this study is unique because we assessed additional predictors in a national cohort after the onset of COVID. For example, Parikh et al. reviewed diagnoses of HCC 2014–2018 outside of VA and confirmed the importance of receipt of HCC screening for treatment but not overall survival.[7] In addition to evaluating more recent data, this study is novel because it is linked to a plan to improve the quality of care in a national healthcare system, where we found that fragmentation of care and under-diagnosis of cirrhosis are problematic for this vulnerable population.

Engagement in VA care and ongoing imaging screening for HCC were both associated with earlier stage of diagnosis. Among patients with known cirrhosis, nearly all had received imaging tests that would qualify as screening tests for HCC in the 2 years prior, with half receiving the recommended four tests. However, 17% of patients were diagnosed with cirrhosis after HCC, highlighting the frequent under recognition of cirrhosis.[20] Conversely, we also identified patients with HCC in the absence of cirrhosis, aligned with increasing recognition of HCC associated with non-cirrhotic NASH and HCV.[21–24] While VA generally outperforms non-VA in most measures, including HCC screening, the COVID-19 pandemic likely influenced these results by delaying access to screening.[25–27] In response, VA is engaging in ongoing, proactive efforts to identify Veterans with cirrhosis and to increase HCC screening rates using educational outreach, population health approaches to identifying at risk patients, and a large national trial of the comparative effectiveness of HCC screening modalities.[28,29]

Receipt of clinical care in the VA, including both primary care and liver care were also associated with earlier stage at diagnosis. After identification of HCC, further delays in treatment were relatively uncommon, despite this review occurring amidst a pandemic. Patients who received VA care, were diagnosed in VA, and had VA primary and hepatology care did the best, while patients with outside care had more advanced stage HCC at diagnosis. Though the numbers were low, numerically more patients who were referred inside VA (vs. outside) were listed for transplantation. These data are consistent with

emerging evidence that fragmented care often worsens outcomes.[30,31 32] The inherent delays in care that result from fragmentation were evidenced in this study. Accordingly, the most common reasons identified for treatment delay were coordination of non-VA care and patient preferences.

The VA NGHP and the HCC FAB plan to perform regular evaluations such as this, noting the need for chart review to capture things such as reasons for non-treatment. As HCC treatment continues to evolve, it is important to continue to assess diagnostic stage, treatment modalities, disease control, and survival over time. There were Veterans who had advanced HCC at diagnosis despite regular screening, suggesting the need to explore better methods and modalities for HCC screening. VA investigators (TT and GI) are currently leading a large VA-wide Cooperative Study to assess the role of abbreviated MRI for HCC screening. Other such studies are needed to ensure that we continue to optimize our approaches to care for people already engaged in screening. Recent advances in HCC treatment have been for patients with advanced stage disease, including immune checkpoint inhibitor and angiogenesis inhibitor therapies and targeted radiation therapies.[3] While these have improved survival in late-stage patients, overall 5-year HCC survival rates remain disappointingly low at 20%.[3] This is largely due to the large proportion of patients diagnosed at late stages when curative therapies cannot be employed.[2,33]

Despite the notable strengths, there were also several limitations of this investigation. With all VA studies, extrapolation of findings to non-VA populations is limited by Veteran demographics (mostly male), unique exposures related to service, and higher burden of comorbidities than the general US population. First with any observational study there are several potential biases. For example, survival may be incorrectly attributed to screening programs, when in fact a lead time bias masks the fact that screening does not change the natural history of the disease, only catches it earlier. Second, the 14 VA facilities represented by the HCC FAB are high volume facilities with specialty, multidisciplinary care, and these results may overestimate rates of HCC screening, diagnosis, and treatment and thereby underestimate the magnitude of our findings. Third, the sample size was limited, with the potential to result in type 1 and 2 error, though not dissimilar from other published retrospective chart review studies. We plan to conduct further assessments with larger cohorts after this demonstration project. However, these in depth chart reviews did represent approximately 10% of Veterans with a new diagnosis of HCC in 2021, allowing us to capture granular information about stage at diagnosis and identify important key predictors of HCC diagnosis and care.

In conclusion, this quality improvement project demonstrated the feasibility and value of leveraging a national network of clinicians to conduct timely chart reviews to track HCC care with the potential to improve early detection, intervention, and outcomes. We intend to repeat this quality improvement exercise to provide an ongoing assessment of potential gaps in HCC care and recommendations to bridge these gaps. This study was conducted in the immediate shadow of widespread interruptions in usual healthcare imposed by the COVID-19 pandemic. The sites included in this project represent some of the best resourced VA facilities for specialty care in liver disease, thus measuring best case scenario within this healthcare system that serves the largest population of patients with cirrhosis within the US.

Next steps that were identified from this work include: 1) evaluating other HCC screening modalities; 2) instituting and evaluating population-level approaches to cirrhosis screening; 3) partnering with primary care to improve HCC screening and increase linkage and access to specialty hepatology care within the VA system; 4) putting systems in place to track timeliness and quality of HCC treatment; and 5) ensuring timely access to liver transplant evaluation for eligible patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What You Need to Know

Background.

Large data pulls often do not provide granularity about diagnosis and linkage to treatment for hepatocellular carcinoma (HCC) that is needed to inform system-level improvements in access to and quality of care.

Findings.

A detailed chart review of Veterans with a new diagnosis of HCC in 2021 revealed that keys to early diagnosis, treatment and improved survival, included having been diagnosed with cirrhosis, receiving care within the VA, and receiving HCC surveillance tests.

Implications for patient care.

Diagnosis of cirrhosis and linkage to care and HCC surveillance are critical to outcomes for patients with HCC; VA's national efforts to improve cirrhosis recognition, HCC diagnosis, and care can serve as a model for other healthcare systems as well as quality improvement initiatives.

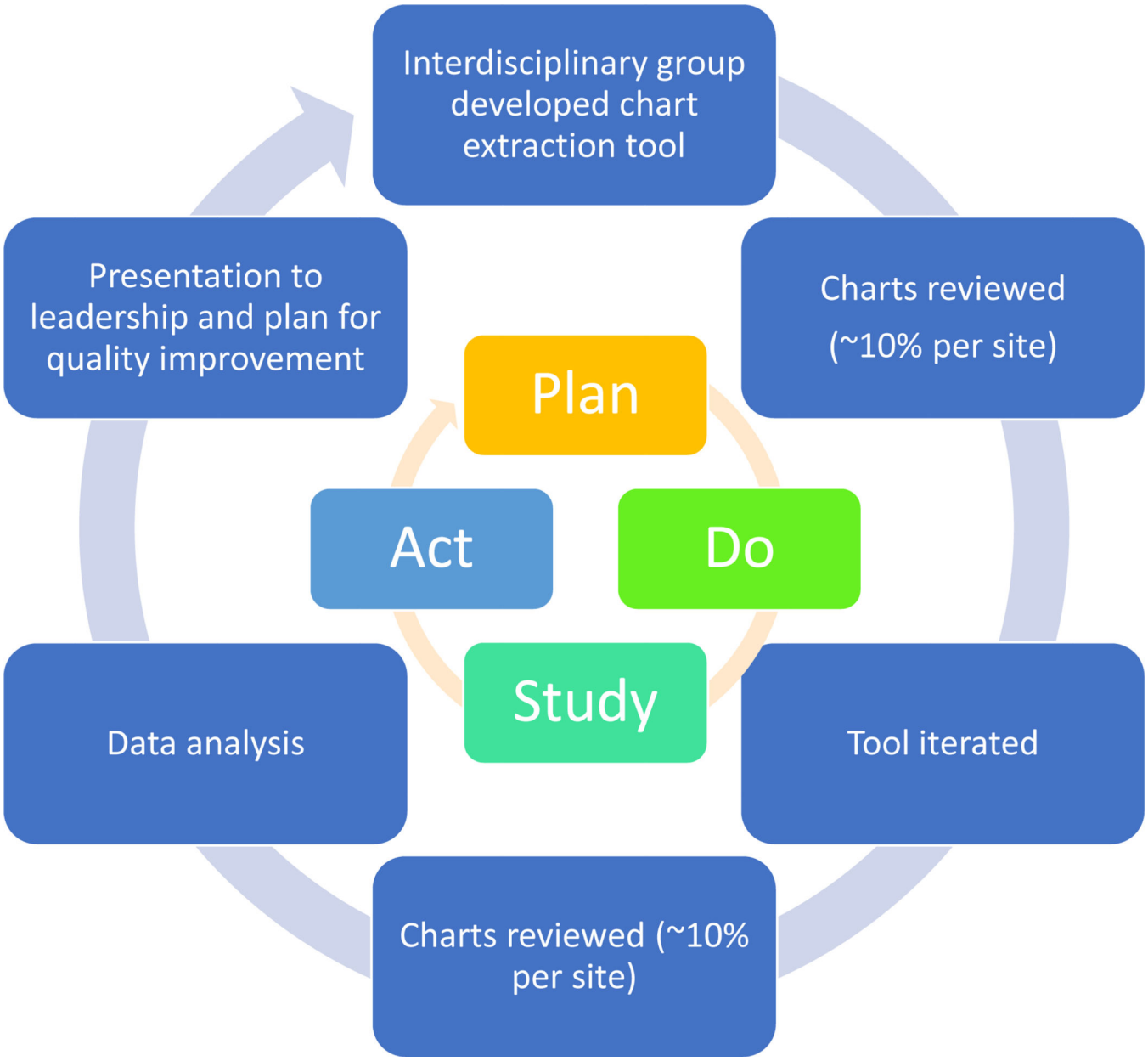

Figure 1.
Process for data monitoring and quality improvement

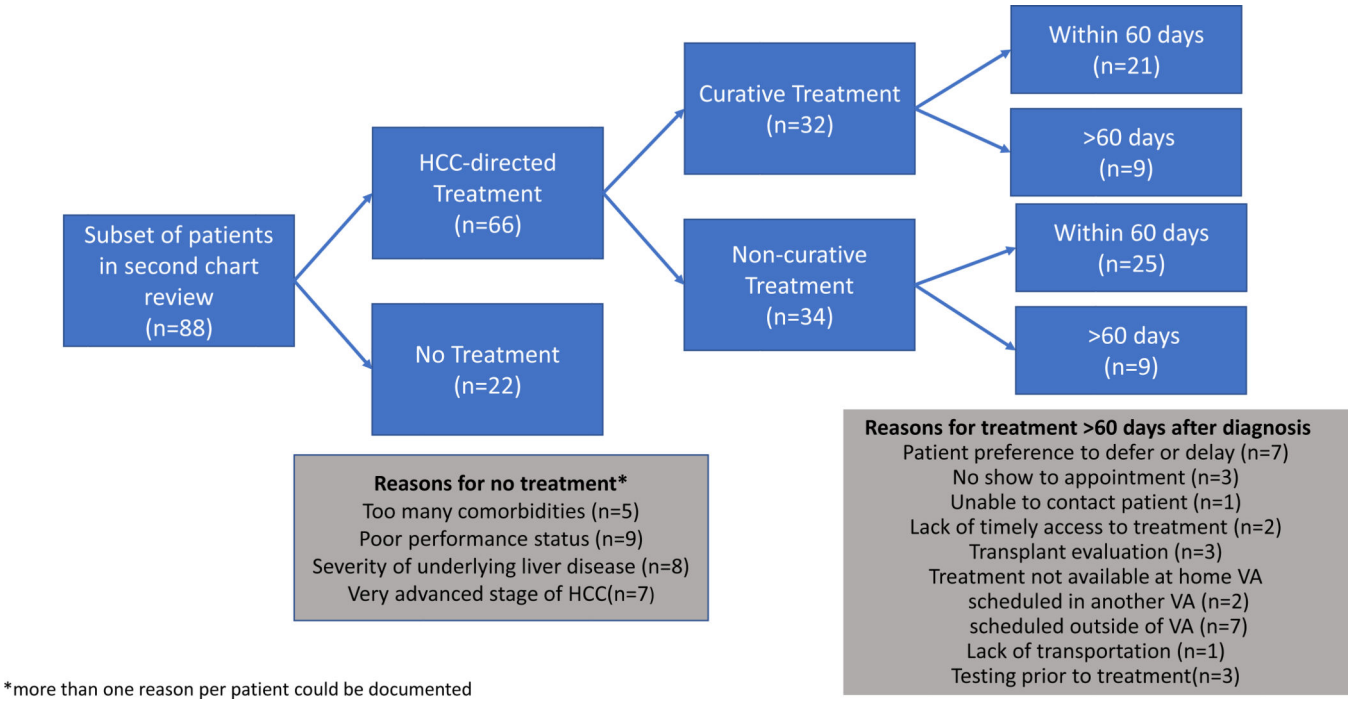

Figure 2.

Reasons for non-treatment and treatment delays in subset of 88 Veterans with further review

Table 1.

Characteristics of cohort of patients diagnosed with HCC in the VA healthcare system in 2021, overall and according to stage at diagnosis and receipt of HCC-directed treatment

	ALL HCC PATIENTS		STAGE AT DIAGNOSIS				HCC-DIRECTED TREATMENTS					
	N=199		T1 or T2 N=107*		Beyond T2 N=90		No HCC-directed treatment† n=52		Non-Curative treatment N=77		Curative treatment N=70	
Characteristics (n, %)	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
SOCIODEMOGRAPHIC AND LIVER DISEASE CHARACTERISTICS												
Age, mean (sd)	71±7		71±7		71±7		72±8		71±6		71±7	
Male, n (%)	196	98%	106	99%	88	98%	52	100%	75	97%	69	99%
Race and ethnicity, n (%)												
Hispanic or Latino	16	8%	8	7%	8	9%	4	8%	6	8%	6	9%
Non-Hispanic Black or African American	61	31%	33	31%	27	30%	14	27%	25	32%	22	31%
Non-Hispanic White	102	51%	58	54%	43	48%	26	50%	38	49%	38	54%
Other (n=5) or missing (n=15)	20	10%	8	7%	12	13%	8	15%	8	10%	4	6%
Charlson Comorbidity Index score, median iqr	2	1,3	2	1,3	2	1,3	2	1,3	2	1,2	2	1,3
Etiology of liver disease												
Cured HCV	93	47%	52	49%	39	43%	19	37%	39	51%	36	51%
Active HCV	32	16%	15	14%	17	19%	13	25%	13	17%	6	9%
ALD	31	16%	18	17%	13	14%	10	19%	11	14%	10	14%
NAFLD	31	16%	16	15%	15	17%	8	15%	10	13%	13	19%
Other***	12	6%	6	6%	6	7%	2	4%	5	6%	5	7%
Cirrhosis status												
No CDW diagnosis	45	23%	22	21%	23	26%	12	23%	19	25%	14	20%
CDW diagnosis before HCC	120	60%	71	66%	47	52%	29	56%	42	55%	49	70%
CDW diagnosis after HCC diagnosis	34	17%	14	13%	20	22%	11	21%	16	21%	7	10%
MELD-Na score at diagnosis, mean (sd)	11±5		11±5		10±5		11±5		11±5		10±5	
MELD-Na												
6 to 10	118	59%	66	62%	52	58%	30	58%	42	55%	46	66%
11 to 20	65	33%	34	32%	31	34%	19	37%	27	35%	19	27%
>20	9	5%	6	6%	3	3%	3	6%	4	5%	2	3%

	ALL HCC PATIENTS		STAGE AT DIAGNOSIS				HCC-DIRECTED TREATMENTS					
	N=199		T1 or T2 N=107*		Beyond T2 N=90		No HCC-directed treatment† n=52		Non-Curative treatment N=77		Curative treatment N=70	
Characteristics (n, %)	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Missing	7	4%	1	1%	4	4%	0	0%	4	5%	3	4%
CTP score at diagnosis, median (IQR)	5	5,7	5	5,6	6	5,8	5	5,7	5	5,7	5	5,6
5–6, or no cirrhosis	139	70%	83	78%	56	62%	34	65%	48	62%	57	81%
7 to 9	46	23%	21	20%	25	28%	15	29%	20	26%	11	16%
≥10	10	5%	2	2%	8	9%	3	6%	6	8%	1	1%
Missing	4	2%	1	1%	1	1%	0	0%	3	4%	1	1%
Alcohol use confirmed at time of diagnosis	56	28%	32	30%	23	26%	16	31%	21	27%	19	27%
HEALTHCARE UTILIZATION												
Facility at which HCC was diagnosed												
VA Facility	179	90%	103	96%	74	82%	45	87%	70	91%	64	91%
Non-VA facility	20	10%	4	4%	16	18%	7	13%	7	9%	6	9%
Pre-diagnosis Primary Care, n (%)												
VA Facility	172	86%	103	96%	68	76%	40	77%	66	86%	66	94%
Non-VA facility	16	8%	4	4%	12	13%	5	10%	8	10%	3	4%
No PCP documented	11	6%	0	0%	10	11%	7	13%	3	4%	1	1%
Pre-diagnosis liver care												
VA Facility	131	66%	83	78%	47	52%	25	48%	51	66%	55	79%
Non-VA facility	15	8%	5	5%	10	11%	5	10%	8	10%	2	3%
No prior liver care documented	53	27%	19	18%	33	37%	22	42%	18	23%	13	19%
HCC SCREENING, DIAGNOSIS and STAGE												
Abdominal imaging that would qualify as HCC screening over 2 years prior to diagnosis												
0–1 imaging tests	47	24%	15	14%	32	36%	21	40%	20	26%	6	9%
2–3 imaging tests	87	44%	45	42%	41	46%	19	37%	35	45%	33	47%
>= 4 imaging tests	65	33%	47	44%	17	19%	12	23%	22	29%	31	44%
HCC Diagnosis Confirmed by:												

	ALL HCC PATIENTS		STAGE AT DIAGNOSIS				HCC-DIRECTED TREATMENTS					
	N=199		T1 or T2 N=107*		Beyond T2 N=90		No HCC-directed treatment† n=52		Non-Curative treatment N=77		Curative treatment N=70	
Characteristics (n, %)	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Radiology (LI-RADS 5 lesion)	137	69%	74	69%	62	69%	32	62%	54	70%	51	73%
Histology	44	22%	23	21%	21	23%	15	29%	14	18%	15	21%
Tumor board	17	9%	10	9%	6	7%	5	10%	9	12%	3	4%
Missing	1	1%	0	0%	1	1%	0	0%	0	0%	1	1%
Liver Tumor Board Review	155	78%	89	83%	64	71%	37	71%	61	79%	57	81%
HCC Stage ††			--	--	--	--						
T1	28	14%					3	6%	7	9%	18	26%
T2	79	40%					9	17%	27	35%	43	61%
Beyond T2	90	45%					40	77%	41	53%	9	13%
Missing	2	1%					0	0%	2	3%	0	0%
Number of HCCs ††												
1	138	69%	89	83%	48	53%	34	65%	47	61%	57	81%
2	36	18%	15	14%	21	23%	9	17%	18	23%	9	13%
3	10	5%	3	3%	8	9%	4	8%	5	6%	1	1%
>3	9	5%	0	0%	8	9%	3	6%	6	8%	0	0%
Missing	6	3%	0	0%	5	6%	2	4%	1	1%	3	4%
Largest lesion size, cm, median (IQR) ††	4	2,6	2	1,3	6	4,6	5	2,6	4	3,6	2	1,3
<2cm	28	14%	28	26%	0	0%	3	6%	4	5%	21	30%
2 to 3	51	26%	43	40%	6	7%	9	17%	12	16%	29	41%
3 to 5	47	24%	28	26%	18	20%	9	17%	24	31%	13	19%
>5 or unable to estimate (with infiltrative HCC)	69	35%	8	7%	61	68%	27	52%	36	47%	6	9%
Missing	4	2%	0	0%	5	6%	4	8%	1	1%	1	1%
Infiltrative HCC, n (%) ††	37	19%	-		37	41%	19	37%	15	19%	4	6%
Vascular Invasion, n (%) ††	36	18%	-		36	40%	16	31%	17	22%	4	6%
Distal metastasis, n(%)††	19	10%	-		19	21%	8	15%	8	10%	3	4%
Any high-risk characteristic (infiltration, vascular invasion, lymph node or distal metastasis)††	61	31%	4	4%	57	63%	25	48%	28	36%	8	11%

	ALL HCC PATIENTS		STAGE AT DIAGNOSIS				HCC-DIRECTED TREATMENTS					
	N=199		T1 or T2 N=107*		Beyond T2 N=90		No HCC-directed treatment† n=52		Non-Curative treatment N=77		Curative treatment N=70	
Characteristics (n, %)	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
AFP at diagnosis, median (IQR)	11	4,167	6	3,22	102	53,625	40	61,943	20	5,368	5	3,14
0–20	109	55%	77	72%	32	36%	21	40%	35	45%	53	76%
>20–100	18	9%	12	11%	6	7%	3	6%	7	9%	8	11%
>100–400	20	10%	11	10%	8	9%	4	8%	11	14%	5	7%
>400	40	20%	5	5%	35	39%	20	38%	17	22%	3	4%
Missing	12	6%	2	2%	9	10%	2	4%	7	9%	3	4%
Functional/ Performance Status ECOG ††												
Unable to determine	33	17%	20	19%	13	14%	9	17%	14	18%	10	14%
0	70	35%	44	41%	26	29%	5	10%	33	43%	32	46%
1	64	32%	36	34%	28	31%	21	40%	18	23%	25	36%
2	10	5%	2	2%	8	9%	4	8%	5	6%	1	1%
3–4	15	8%	2	2%	13	14%	14	27%	4	5%	0	0%
Missing	7	4%	3	3%	2	2%	−1	−2%	3	4%	2	3%
HCC TREATMENT												
Any HCC treatment, n (%)	147	74%	93	87%	50	56%						
First HCC treatment, n (%)												
Ablation	36	18%	34	32%	2	2%						
TACE	36	18%	16	15%	18	20%						
Ablation + TACE	6	3%	5	5%	1	1%						
TARE, SIRT, Y90	25	13%	15	14%	10	11%						
SBRT, external beam radiation	9	5%	6	6%	3	3%						
Surgical resection	17	9%	14	13%	3	3%						
Systemic therapy	16	8%	3	3%	13	14%						
Transplant	2	1%	2	2%	0	0%						
Untreated	52	26%	12	11%	40	44%						
Time (days) from date of diagnosis to date of administration of first HCC-directed treatment												
0 to <30	20	10%	13	12%	7	8%						
30 to <60	38	19%	25	23%	13	14%						

	ALL HCC PATIENTS		STAGE AT DIAGNOSIS				HCC-DIRECTED TREATMENTS					
	N=199		T1 or T2 N=107*		Beyond T2 N=90		No HCC-directed treatment† n=52		Non-Curative treatment N=77		Curative treatment N=70	
Characteristics (n, %)	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
60 to <90	18	9%	13	12%	5	6%						
90 to <120	16	8%	10	9%	4	4%						
>=120	18	9%	15	14%	3	3%						
Untreated	52	45%	31	29%	58	64%						
Missing	37											
Palliative care consultation (%)	66	32%	18	17%	48	53%	27	52%	31	40%	8	11%

† HCC-directed treatment includes all the locoregional treatments, radiation, surgical resection, systemic therapies and liver transplantation; Non-curative treatments include TACE, Y-90, SBRT, systemic therapy; Curative treatments include RFA or RFA+TACE, surgical resection and liver transplantation

* Numbers may not sum to 199 due to missing data

** Non-mutually exclusive categories

*** other etiology includes: 2 with HBV, 1 hereditary hemochromatosis, 2 cryptogenic cirrhosis, 1 pbc, 6 no known underlying liver disease

†† refers to tumor or characteristics at the time of HCC diagnosis

Table 2.

Factors associated with HCC diagnosis at very early (T1) or early (T2) stage among 187 patients diagnosed with HCC in 2021 in the VA Healthcare System

Characteristic	HCC Cases (N)	Diagnosis at stage T1 or T2 (row %)	Odds Ratio for earl diagnosis (95% CI)	Adjusted OR (95% CI)*
All Patients	199	107 (54)	N/A	N/A
Sex				
Female	3	1 (33)	1	1
Male	196	106 (54)	2.49 (.23,54)	5.10 (.44,117)
Age, years				
<65	41	21 (51)	1	1
65–75	110	66 (60)	1.6 (.76,3.38)	1.34 (.59, 3.02)
>75	48	20 (42)	.67 (.28,1.58)	.65 (.24, 1.73)
Race and ethnicity, n (%)				
Non-Hispanic white	102	58 (57)	1	1
Hispanic or Latino	16	8 (50)	.74 (.25, 2.17)	.53 (.16,1.69)
Non-Hispanic Black	61	33 (54)	.91 (.48, 1.73)	.97 (.47,1.99)
Other or Unknown	20	8 (40)	.49 (.18, 1.30)	.51 (.17,1.47)
Charlson Comorbidity Index				
≤2	139	71 (51)	1	1
>2	60	36 (60)	1.42 (.76, 2.69)	.98 (.49,1.98)
Etiology of liver disease				
Cured HCV	93	52 (56)	1	1
Active HCV	32	15 (47)	.71 (.30, 1.63)	1.18 (.47, 2.99)
ALD	31	18 (58)	.88 (.37, 2.14)	1.16 (.44, 3.13)
NASH	31	16 (52)	.75 (.33, 1.73)	.88 (.34, 2.30)
other	12	6 (50)	.71 (.21, 2.43)	1.32 (.32, 5.61)
Cirrhosis status				
No documented pre-HCC diagnosis of cirrhosis	89	36 (40)	1	1
Cirrhosis diagnosis pre-HCC	120	71 (59)	**1.80 (1.02, 3.22)**	1.35 (.68,2.68)
MELD-Na				
≤10	118	66 (56)	1	1
>10	74	40 (54)	.99 (.55, 1.80)	1.14 (.60, 2.20)
CTP score at diagnosis, median (IQR)				
5–6 (or no cirrhosis)	139	83 (60)	1	1
>6	56	23 (41)	**0.47 (.24, .88)**	**0.46 (.23,.90)**
Alcohol use at diagnosis				
No	143	75 (52)	1	1
Yes	56	32 (57)	1.10 (.58, 2.13)	1.02 (.50, 2.11)

Characteristic	HCC Cases (N)	Diagnosis at stage T1 or T2 (row %)	Odds Ratio for earl diagnosis (95% CI)	Adjusted OR (95% CI)*
HCC imaging tests performed over 2 years prior to diagnosis				
0–1	47	15 (32)	1	1
2–3	87	45 (52)	**2.65 (1.25, 5.81)**	**2.60 (1.21,5.78)**
≥4	65	47 (72)	**7.35 (3.16, 18.08)**	**6.34 (2.54, 16.67)**
Performance Status ECOG††				
0 (high performance status)	70	44 (63)	1	1
Unable to determine	33	20 (61)	.83 (.35,1.99)	1.13 (.43, 3.01)
>0 (low performance status)	89	40 (45)	**.49 (.26, .94)**	.72 (.34, 1.49)
Site of HCC diagnosis				
Non-VA facility	20	4 (20)	1	1
VA Facility	179	103 (58)	**5.82 (2.03, 21.01)**	**3.92 (1.21, 15.33)**
Pre-diagnosis Primary Care, n (%)				
Non-VA or no primary care	27	4 (15)	1	1
VA primary care	172	103 (60)	**7.73 (2.78, 27.25)**	**4.81 (1.56,18.19)**
Pre-diagnosis liver care				
Non-VA or no hepatology care	68	5 (7)	1	1
VA hepatology	131	83 (63)	**3.35 (1.79, 6.40)**	1.98 (.92, 4.27)

* aORs are adjusted for CTP score, history of cirrhosis, and screening—except meld which was not adjusted for CTP score

Table 3.

Factors associated with receipt of HCC-directed treatment among 187 patients diagnosed with HCC in 2021 in the VA Healthcare System

	Receipt of non-curative treatments vs. none* **(n=77)**		**Receipt of potentially curative vs. none**** **(n=70)**	
	IRR (95% CI)	**Adjusted IRR (95% CI)**	**IRR (95% CI)**	**Adjusted IRR (95% CI)**
Early stage at diagnosis (vs. beyond T2)	**2.54 (1.14,5.66)**	2.25 (.88,5.70)	**19.33 (7.40,50.45)**	**24.74 (7.60,80.55)**
Age, years (vs. <65)				
65–75	.93 (.35,2.44)	.61 (.20,1.89)	.63 (.43,3.06)	.67 (.21,2.17)
>75	1.15 (.22,1.82)	.67 (.18,2.49)	.48 (.16,1.48)	.42 (.10,1.74)
Race and ethnicity (vs. white)				
Hispanic or Latino	.99 (.25,3.88)	.35 (.07,1.72)	.99 (.25,3.88)	.33 (.07,1.72)
Non-Hispanic Black	1.16 (.49,2.75)	1.07 (.37,3.10)	1.11 (.47,2.64)	1.23 (.37,3.10)
Other or Unknown	.66 (.22,2.00)	.56 (.15,2.14)	.33 (.09,1.22)	.35 (.15,2.14)
Charlson Comorbidity Index	**.70 (.54,.92)**	**.70 (.51,.96)**	.90 (.70,1.16)	.80 (.58,1.11)
Etiology of liver disease (vs. cured HCV)				
Active HCV	.49 (.18,1.30)	.88 (.29,2.72)	**.24 (.08,.76)**	.93 (.17,2.21)
ALD	.54 (.18,1,57)	.86 (.26, 2.86)	.43 (.14,1.32)	.61 (.22,2.81)
NASH	.61 (.20,1.82)	.68 (.18,2.56)	.79 (.28,2.27)	1.29 (.34,4.89)
other	1.21 (.21,6.91)	1.23 (.17,9.15)	1.21 (.21,6.91)	3.21 (.41,25.29)
Cirrhosis diagnosis in VA before HCC	1.09 (.52, 2.26)	.92 (.35,2.37)	**2.32 (1.07,5.05)**	2.09 (.72,6.06)
MELD-Na (>10 vs. <10)	1.15 (.55, 2.43)	2.02 (.75, 5.41)	.70 (.32,1.51)	2.00 (.70,5.71)
CTP score at diagnosis (>7 vs. <7)	.96 (.42,2.19)	1.55 (.59,4,04)	.40 (.18,1.09)	.57 (.20,1.61)
Alcohol use at diagnosis	.90 (.78,1.03)	.94 (.80,1.09)	.92 (.80,1.05)	.97 (.83,1.14)
HCC imaging tests performed over 2 years prior to diagnosis (vs. 0–1)				
2–3	2.15 (.91,5.03)	1.88 (.61,5.78)	**6.59 (2.23,19.43)**	**2.96 (1.20,16.57)**
>=4	2.21 (.82,5.89)	4.45 (.75,11.73)	**10.15 (3.19,32.30)**	**7.03 (1.53,32.26)**
ECOG†† (vs. 0)				
Unable to determine	.24 (.07,.86)	.31 (.08,1.17)	**.24 (.04,.58)**	**.18 (.04,.76)**
>0	.12 (.04,.35)	**.16 (.05,.51)**	**.12 (.04,.35)**	**.20 (.06,.65)**
HCC diagnosed in VA	1.59 (.52,4.85)	1.34 (.31,5.73)	1.74 (.54,5.54)	.51 (.10,2.55)
VA (vs. non) Primary Care	1.63 (.62,4.28)	2.53 (.88,7.26)	**4.14 (1.21,14.14)**	1.71 (.48,6.07)
Pre-diagnosis VA liver care (vs. other or none)	2.32 (1.09,4.91)	1.39 (.52,3.71)	**4.11 (1.82,9.32)**	1.49 (.52,4.22)

Abbreviations: IRR=incidence rate ratio, comparing each category to no treatment in a multinomial regression model.

* Potentially curative treatment includes RFA (+/− TACE), surgical resection and liver transplantation

** Non-curative treatment include chemotherapy, TACE alone, and SBRT

[†]Adjusted IRRs were adjusted for ecog, cirrhosis status, Charlson comorbidity score, number of imaging tests, primary care location, liver care location

Table 4.

Factors associated with all-cause mortality from the time of HCC diagnosis among 187 patients diagnosed with HCC in 2021 in the VA healthcare system with follow-up extending to September, 2022

	Total patients (n)	Died (n, row %)	Hazard Ratio for Death (95% CI)	Adjusted Hazard Ratio for death (95% CI)*
Total	**199**	**82 (41)**	**n/a**	**n/a**
HCC Treatment				
None	52	37 (71)	1	1
Curative treatment	77	15 (19)	**.19 (.10,.35)**	**.46 (.22,.99)**
Non-curative treatment	70	30 (43)	**.38 (.23,.63)**	**.46 (.26,.82)**
Stage at Diagnosis				
>T2	90	59 (66)	1	1
T1 or T2	107	23 (21)	**.22 (.13, .37)**	**.31 (.16,.57)**
Age, yrs				
<65	41	16 (39)	1	1
65–75	110	37 (34)	.73 (.40,1.33)	.90 (.48, 1.69)
>75	48	29 (60)	1.72 (.93,3.20)	1.19 (.60, 2.38)
Race and ethnicity, n (%)				
Non-Hispanic White	102	42 (41)	1	1
Hispanic or Latino	16	7 (44)	1.11 (.50, 2.50)	1.60 (.66, 3.84)
Non-Hispanic Black	61	26 (43)	1.06 (.63, 1.77)	1.33 (.72, 2.46)
Other or Unknown	20	7 (35)	.90 (.38, 2.02)	.44 (.18, 1.07)
Charlson Comorbidity Index				
<2	139	57 (41)	1	1
>2	60	25 (42)	1.01 (.62, 1.64)	1.17 (.66, 2.07)
Etiology of liver disease				
Cured HCV	93	31 (33)	1	1
Active HCV	32	15 (47)	1.41 (.73,2.71)	.80 (.40,1.69)
ALD	31	17 (55)	1.76 (.93,3.34)	1.45 (.75, 2.82)
NASH	31	12 (39)	1.16 (.59,2.27)	.73 (.34, 1.58)
Other	12	7 (58)	**2.46 (1.07,5.63)**	1.94 (.73, 5.16)
Cirrhosis status				
Cirrhosis diagnosis before HCC	120	78 (65)	1	1
No cirrhosis diagnosis before HCC	89	42 (47)	**.59 (.37,.93)**	.86 (.47, 1.57)
MELD-Na				
<=10	118	48 (41)	1	1
>10	74	31 (42)	.96 (.60,1.53)	.71 (.39,1.29)
CTP score				
5–6 (or no cirrhosis)	139	53 (38)	1	1
>6	56	29 (52)	**1.68 (1.05,2.68)**	1.48 (.88,2.51)

	Total patients (n)	Died (n, row %)	Hazard Ratio for Death (95% CI)	Adjusted Hazard Ratio for death (95% CI)*
Total	**199**	**82 (41)**	**n/a**	**n/a**
Alcohol use at diagnosis				
No	143	35 (24)	1	1
Yes	56	21 (38)	1.03 (.95, 1.12)	1.01 (.92,1.11)
Imaging tests prior to diagnosis				
0–1	47	33 (70)	1	1
2–3	87	29 (33)	**.32 (.19, .54)**	.65 (.34, 1.21)
>=4	65	20 (31)	**.29 (.16, .51)**	.83 (.39, 1.79)
Performance Status (ECOG)††				
0 (high performance status)	70	18 (26)	1	1
Unable to determine	33	10 (30)	1.27 (.59, 2.76)	.80 (.35,1.81)
>0 (poor performance status)	89	50 (56)	**2.60 (1.51, 4.48)**	1.26 (.66, 2.41)
Diagnosis Site				
Non-VA facility	20	9 (45)	1	1
VA Facility	179	73 (41)	.75 (.37, 1.50)	1.79 (.85, 3.78)
Primary Care, n (%)				
Non-VA or no primary care	27	22 (81)	1	1
VA primary care	172	60 (35)	**.19 (.11, .33)**	1.71 (.92,3.19)
Pre-diagnosis liver care				
Non-VA or no hepatology care	68	41 (60)	1	1
VA hepatology	131	41 (31)	**.37 (.23, .58)**	.74 (.42, 1.31)

*Adjusted HRs were adjusted for early diagnosis, HCC treatment, ctp, etiology of liver disease, cirrhosis status, liver care, primary care, ecog, imaging tests. Note that gender could not be included since all patients who died were men. Also, due to intercorrelation, VA site of diagnosis was not adjusted for VA pcp or hepatologist.