HHS Public Access

Author manuscript

J Natl Compr Canc Netw. Author manuscript; available in PMC 2023 February 04.

Published in final edited form as:

J Natl Compr Canc Netw. ; 19(3): 285–293. doi:10.6004/jnccn.2020.7616.

Medicare/Medicaid Insurance, Rurality and Black Race Associated with Provision of Hepatocellular Carcinoma Treatment and Survival

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Abstract

Background: Early treatment of hepatocellular carcinoma (HCC) is associated with improved survival but many patients with HCC do not receive therapy. We aimed to examine factors associated with HCC treatment and survival among incident HCC cases in a statewide cancer registry.

Patients and Methods: All HCC cases from 2003–2013 were identified from the North Carolina cancer registry. These cases were linked to insurance claims from Medicare, Medicaid and large private insurers. We examined the association between pre-specified covariates with

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Author contributions:

All authors approved the final version of this manuscript

Sanoff (guarantor): Study concept and design, interpretation of data, drafting and critical revision of manuscript

Moon: Interpretation of data, critical revision of manuscript

Chang: Statistical analysis, study concept and design, interpretation of data, critical revision of manuscript

Lund: Study concept and design, interpretation of data, critical revision of manuscript

Barritt: Study concept and design, interpretation of data, critical revision of manuscript

Hayshi: Study concept and design, interpretation of data, critical revision of manuscript

Stitzenberg: Study concept and design, interpretation of data, critical revision of manuscript

Conflicts of Interest/Disclosures: Dr. Sanoff has received research funding paid to the University of North Carolina from Bayer. Dr. Lund's spouse is an employee of GlaxoSmithKline. Dr. Barritt has received research funding paid to the University of North Carolina from Intercept Pharmaceuticals, Genfit Pharmaceuticals, Bristol Myers Squibb, NuSirt, Target Pharamsolutions. Drs. Moon, Chang, Hayashi, and Stitzenberg report no conflicts.

more advanced HCC stage at diagnosis (i.e. multifocal cancer), visit at a liver transplant center and provision of HCC treatment by multivariate logistic regression. A Cox proportional hazards model was developed to assess the association between these factors and survival.

Results: Of 1,809 patients with HCC, 53% were seen at a transplant center <90 days from diagnosis, with lower odds in blacks [adjusted odds ratio (aOR 0.54, 95% CI 0.39,0.74)], Medicare insurance (aOR 0.35, 95% CI 0.21,0.59), Medicaid insurance (aOR 0.46, 95% CI 0.28,0.77), and rural patients; odds of transplant center visits were higher with pre-diagnosis AFP screening (aOR 1.74, 95% CI 1.35,2.23) and GI care (aOR 1.66, 95% CI 1.27,2.18). Treatment was more likely with pre-diagnosis GI care (aOR 1.68, 95% CI 0.98,2.86) and transplant center visit (aOR 2.42, 95% CI 1.74,3.36). Survival was strongly associated with age, stage, cirrhosis complications, and receipt of HCC treatment. Medicare (aHR 1.58, 95% CI 1.20,2.09) and Medicaid (aHR 1.55, 95% CI 1.17, 2.05) recipients had shorter survival than privately insured patients.

Discussion: In this population based cohort of patients with HCC, Medicare/Medicaid insurance, rural residence and black race were associated with lower provision of HCC treatment and poorer survival. Efforts should be made to improve access to care for these vulnerable populations.

Keywords

Hepatocellular carcinoma; disparities; Medicare; Medicaid; quality of care

Introduction

Hepatocellular carcinoma (HCC) incidence and mortality are on the rise in the United States.[1,2] The prognosis of HCC is poor, in part because potentially curative treatments, including surgical resection, ablation, and transplantation, are feasible in a minority patients with early stage HCC.[3] In the absence of curative therapy, liver-directed locoregional therapies (LRTs) and drug therapy prolong survival, yet up to half of all patients with HCC never receive any cancer-directed therapy.[4–7]

Despite accumulating evidence that provision of timely HCC treatment decreases cancer related mortality,[8] treatment rates remain low and the reasons for non-receipt of therapy in patients with HCC remains unclear. Medical comorbidities, decompensated liver disease and advanced HCC often precludes specific HCC-directed therapies. Other potential factors have been associated with low provision of HCC therapy including older patient age, patient insurance status and care at a low volume center.[9–11] In addition, racial and ethnic disparities in the receipt of HCC treatment and survival have been well documented.[12–16] Lastly, subspecialist consultation has been associated with improved treatment outcomes in the US Veterans Affairs system.[17] This evidence suggests that both patient- and facility-level factors likely influence provision of HCC treatment. However, relatively few data sources allow for the simultaneous investigation of these many potential variables in a population-based sample.

We therefore assessed the potential predictors of advanced cancer, care at a transplant center, provision of treatment and mortality among patients from a population-based state registry linked to insurance claims data.

Materials and Methods

This work was approved by the Biomedical IRB at the University of North Carolina (#12–1828).

Patients

The cohort is comprised of patients diagnosed with HCC between 2003–2013, identified from the North Carolina Central Cancer Registry (NCCCR) by International Classification of Diseases (ICD)-10 C22.0 and histology codes 8170–8175, 8180. These NCCCR cases were linked to claims from Medicare, NC Medicaid, and large private insurers in NC by the UNC Lineberger Cancer Information & Population Health Resource.[18] This subset consisted of patients with continuous healthcare enrollment in any health plan for 12 months preceding and 12 months following diagnosis (or death). Patients participating in a Medicare HMO/advantage plan were excluded as claims are not required to be reported to Medicare.

To evaluate factors associated with treatment and survival, only patients surviving the 90 day exposure window after diagnosis were included in multivariable models, thereby including only patients who may have been eligible for treatment.

Covariates

Patient age, sex, marital status, race, county and zip code of residence, and insurance status at diagnosis were derived from NCCCR demographics file. We used the NCCCR collaborative staging extension variables of number of tumors and presence/absence of vascular invasion to group cancers into clinically meaningful categories (single or multiple, with or without vascular invasion, and extrahepatic disease). Multifocal cancer was defined as the presence of multiple intrahepatic tumors with or without vascular spread, extrahepatic spread, or unstaged HCC. As has been done in previous studies of HCC outcomes using claims data,[5] unstaged HCC was considered together with extrahepatic spread given the similar outcomes among these groups. These categories are similar to the tumor extent component of the Barcelona Clinic Liver Cancer staging system and approximate patients who may qualify for liver transplantation, surgical resection or locoregional therapies.[19,20]

County level economic and healthcare covariates were taken from the Area Health Resource File (AHRF)[21] and the North Carolina Health Professional Data System. Measures were selected to cover domains used in other composite measures of census tract-based socioeconomic status (SES).[22–24] Given the large number of covariates measured across 100 NC counties, we used factor analysis to create representative indices. Factor analysis was conducted separately for health system factors which together had an average variance extracted (AVE) of 58% across counties, and economic factors (see Supplemental Digital Content Table 1 for complete list and factor loadings). For economic variables, two factors combined for an AVE of 83.2% across counties. The first is described as economic disadvantage index as it was dominated by median home value, percent white, and

unemployment rate. The second is described as the rurality index, as it was dominated by rurality and agricultural/ forestry/hunting/mining industries. For each index, the lowest quartile describes the least disadvantaged.

Additional patient level covariates were determined from ICD-9 claims in the 12 months pre-diagnosis. This included non-liver comorbidity using the Klaubunde modification of the Charlson Comorbidity Index (excluding liver disease),[25] psychiatric comorbidity not including substance abuse (e.g. depression, anxiety, bipolar disorder, schizophrenia, post-traumatic stress disorder), liver-related complications (encephalopathy, ascites, varices, hepatorenal syndrome),[26] and underlying cause of liver disease. Because many patients had low healthcare utilization in the year before diagnosis, codes for the cause of liver disease were evaluated from 12 months before to 1 month after diagnosis.

Pre-diagnosis healthcare utilization was determined by visits with a primary care provider or gastroenterology/hepatology provider (GI) in the year before diagnosis (excluding 2 months pre-diagnosis when consultations may reflect referrals for cancer), pre-diagnosis alpha fetoprotein (AFP) screening[27] (guideline recommended every 6 months during this era for patients with cirrhosis and hepatitis virus),[28] and number of unique contacts with the healthcare system (inpatient or outpatient visits). Consultation with HCC-specific subspecialties and at a liver transplant center was measured in the 90 days following diagnosis. Distance from each patient's zip code to the closest liver transplant center was calculated. Treatment was defined as the initial treatment received as previously described,[5] acknowledging that many patients go on to receive multiple therapies.

Analysis

We extracted patient and county level factors for all patients with HCC and linked claims data. We performed univariate analyses on demographic characteristics, insurance status, socioeconomic status, rurality, medical/psychiatric comorbidities, liver disease etiology and complications, and cancer stage at diagnosis, calculating median and interquartile range (IQR) for continuous variables and proportions for categorical variables. We calculated annual rates in subspecialty consultation within 90 days of HCC diagnosis and provision of HCC treatments. We performed multivariable logistic regression to assess variables associated with multifocal cancer at diagnosis, transplant center visit, and provision of HCC treatment. Lastly, we developed a Cox proportional hazards model to assess variables associated with overall survival. All statistical analyses were performed with SAS version 9.4 (SAS, Cary, NC, www.sas.com).

Results

Cohort Description

Our cohort included 1,809 patients with HCC (Table 1, Supplemental Digital Content Figure 1). The majority of patients had single (37%) or multiple (25%) tumors without vascular invasion or extrahepatic spread. A smaller proportion had vascular spread at diagnosis, including 6% and 13% of those with single and multiple lesions, respectively. The median

age was 68 years (IQR 59–76) and patients were predominantly male (73%), white (76%), and insured by Medicare (59%).

Multifocal HCC at Diagnosis

A total of 1,033 (57%) patients had multifocal HCC at presentation. Multifocal cancer at presentation was significantly associated with age, marital status, and sex. Receipt of pre-diagnosis AFP screening [adjusted odds ratio (aOR) of multifocal 0.72, 95% CI 0.58, 0.90] and GI care (aOR 0.77, 95% CI 0.61, 0.96) was associated with a decreased odds of multifocal disease (Table 2).

Visit at a Liver Transplant Center

In the 90 days following diagnosis, 957 (53%) of patients were seen at a liver transplant center for any reason (Table 2, Figure 1). A transplant center visit was significantly less likely among older patients (aOR ≥75 versus <50 years 0.52, 95% CI 0.28, 0.94), black patients (aOR versus whites 0.54, 95% CI 0.39, 0.74), and patients with Medicare (aOR versus private 0.35, 95% CI 0.21, 0.59) and Medicaid (aOR versus private 0.46, 95% CI 0.28, 0.77).

Patients residing a median of 53 miles (aOR 0.46, 95% CI 0.32, 0.66) and a median of 106 miles (aOR 0.27, 95% CI 0.18, 0.41) were less likely to be seen at a transplant center than those living in the closest tertile (median 17 miles). Transplant center visits were also less likely among those living in the most rural counties (aOR versus least rural 0.24, 95% CI 0.14, 0.47). Pre-diagnosis healthcare was also a major determinant of transplant center visit, with an increased odds among those with more pre-diagnosis healthcare utilization (aOR highest versus lowest tertile 2.14, 95% CI 1.57, 2.93), AFP testing (aOR 1.74, 95% CI 1.35, 2.23), and GI care (aOR 1.66, 95% CI 1.27, 2.18).

Provision of HCC Treatment

Of 1,809 HCC patients, 30% died within the 90 day treatment exposure window following diagnosis and were excluded from treatment and survival analyses. These patients were older with greater comorbidity, more advanced cancer, more likely to be divorced, and were less likely to have received pre-diagnosis care. They were significantly less likely to be seen at a transplant center or receive treatment for their HCC.

In the 1,250 patients surviving the 90 day treatment exposure window, 857 (69%) were treated (Table 3). Of these, 478 (56%) has a surgical consultation, 425 (50%) consultation with GI, and 469 (55%) saw a hematologist/oncologist and these rates slowly increased from 2003 to 2013 (Figure 1).

Factors most strongly associated with receipt of HCC treatment included pre-diagnosis AFP screening (aOR 2.61, 95% CI 1.90, 3.60), surgical consultation (aOR 3.40, 95% CI 2.48, 4.67) and visit at a liver transplant center (aOR 2.42, 95% CI 1.74, 3.36) (Table 4). In contrast, advanced age, unmarried status, psychiatric comorbidity, and complications of cirrhosis all significantly reduced the odds of receiving HCC treatment.

Overall Survival

Across the study period, survival increased from a median survival of 6 months (interquartile range (IQR) 2, 21) in 2004–2006 to 8 months (IQR 2, 28) in 2010–2012. In adjusted models accounting for disease severity and treatment, patients diagnosed in 2008 and beyond had significantly better survival than patients diagnosed 2004–2007 [adjusted hazard ratio (aHR) for death 0.75, 95% CI 0.66, 0.85].

In addition to year of diagnosis, cancer stage and receipt of cancer treatment were strongly associated with survival: compared with the 12% of patients who underwent curative surgery, the risk of death was higher among patients treated with ablation (aHR 1.60, 95% CI 1.20, 2.13) and LRT (aHR 2.47, 95% CI 1.90, 3.19). Patients treated with drug therapy (aHR 4.57, 95% CI 3.27, 6.40), radiation (aHR 3.79, 95% CI 2.55, 5.65), and untreated patients (aHR 4.97, 95% CI 3.79, 6.51) all had a higher risk of mortality, although these were not adjusted for factors that may influence treatment selection (e.g. bilirubin) (Table 4).

Survival was better among younger patients and those without comorbidities. Receipt of pre-diagnosis GI care was associated with improved survival compared to patients who saw neither PCP nor GI in the year before diagnosis, (aHR 0.74, 95% CI 0.58, 0.94). Despite adjusting for age and treatment received, patients with Medicare (aHR 1.58, 95% CI 1.20, 2.09) and Medicaid (aHR 1.55, 95% CI 1.17, 2.05) had significantly worse survival than privately insured patients.

Discussion

In this population-based retrospective cohort study examining the effects of patient characteristics, county level resources, and healthcare utilization on HCC outcomes, we found patient-level sociodemographic factors (older age, black race, unmarried status, insurance) to be key determinants of stage at diagnosis and survival following an HCC diagnosis. These same patient factors were associated with liver transplant center visits and cancer-directed treatment. When further analyzing the root causes, survival was most strongly associated with receipt of cancer-directed treatment. Treatment, in turn, was more likely in patients with pre-diagnosis specialty GI care and screening, and post-diagnosis liver transplant center visits, which are likely a surrogate for receipt of multidisciplinary care. The disparities in outcomes are therefore largely accounted for by lower quality healthcare before and after an HCC diagnosis. In all analyses, Medicaid and Medicare beneficiaries experienced significantly inferior outcomes, including a marked reduction in survival, compared to privately insured HCC patients.

Given that HCC incidence is higher among racial and ethnic minorities and in socioeconomically disadvantaged regions,[29,30] we hypothesized that a lack of access to local healthcare resources and greater SES disadvantage are key contributing factors to the low rates of treatment and disparities in care which have been previously reported. After investigating a wide array of county level determinants of economic health and healthcare availability, the only clear associations between county factors and the quality of HCC care was that patients residing in the most rural counties and counties farthest from a transplant

center were least likely to be seen at a transplant center in the 90 days after diagnosis. No other county-level factors clearly influenced treatment or survival in HCC.

Health insurance was strongly associated with the likelihood of transplant center visit and survival. The association between Medicare insurance and these outcomes could be confounded by age, given that Medicare beneficiaries are usually >65 years old and some patients may be ineligible for liver transplantation based on advanced age. However, recent data suggests an increased proportion of patients older than 65 years with HCC are being listed for transplantation[31] and the negative associations between Medicare insurance and transplant center visit and survival persisted in multivariable models adjusting for age. Patients with Medicare and Medicaid had a 24% and 57% increased risk of death compared to the privately insured; it was 67% higher for the uninsured. The effect of insurance status on survival did not diminish after adjusting for patient age, comorbidity and treatment with a 58% and 55% increase in the risk of death for Medicare and Medicaid patients. The influence of public insurance on outcomes could reflect limitations imposed by Medicare and Medicaid on access to care, however, public insurance in this analysis is also likely a proxy for individual socioeconomic resources given that income limits for NC Medicaid are strict.[32] Regardless of county resources, such individuals likely face additional financial challenges that could compromise access compared with their privately insured counterparts. The marked and persistently inferior outcome among single, divorced, or widowed patients (advanced stage at presentation, less consultative care and treatment) and those with psychiatric comorbidity (lower rates of treatment and inferior survival) also speak to the importance of individual resources (e.g. social support) on the ability of HCC patients to receive the care they need.

This study is strengthened by its large population-based sample and the availability of linked insurance claims, allowing for the simultaneous exploration of patient, treatment and facility factors on outcomes. However, this study must be interpreted in the context of potential limitations. First, the survival analysis is limited to patients who survived the 90 day treatment exposure window following diagnosis. While this restriction was necessary to evaluate the effect of treatment on survival, omitting these sickest patients may have obscured the effect of county economic and healthcare factors on HCC outcomes. Though we generally found that the same factors that were associated with treatment were associated with early mortality (advanced age and stage, greater comorbidity, single/divorced, Medicare and Medicaid, less pre-diagnostic care), one potentially meaningful difference was that patients with early mortality were more likely to live in a county with fewer healthcare services and lower density of GI physicians. Second, the data source did not allow for adjustment for liver disease severity via the Model for End Stage Liver Disease (MELD) or Child-Pugh score, although we did account for pre-diagnosis liver-related complications. Lastly, our data source did not allow us to assess for factors that could have contributed to improved survival over time including improved treatments for underlying liver disease (e.g. direct acting antiviral therapy for hepatitis C virus), expanded access to HCC therapies and clinical trials, and broader adoption of multidisciplinary tumor boards and clinics.

Our findings that an individual’s use of the healthcare system before diagnosis and visits at an expert center early in their cancer course are major driving forces behind treatment

and survival for HCC are critical when thinking of how to improve outcomes of HCC patients—in our state and across the nation. To reduce the rates of very early mortality from HCC, public health efforts must focus on detection of cirrhosis and GI referrals for affected individuals. To improve survival among patients who present earlier in their disease course, efforts must focus on increasing access to subspecialty care and treatment. Our ongoing work will examine patient reported barriers to accessing care following an HCC diagnosis, with a focus on high risk black and rural residents, and Medicare and Medicaid beneficiaries.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Grant Support:

This work was supported by National Cancer Institute, K07CA160722 (HKS) and National Institutes of Health grant T32 DK007634 (AMM). Additional support was provided by the Cancer information & Population Health Resource (CIPHR), UNC Lineberger Comprehensive Cancer Center with funding provided by the University Cancer Research Fund (UCRF) via the State of North Carolina

Abbreviations:

AFP	alpha fetoprotein
aHR	adjusted hazard ratio
aOR	adjusted odds ratio
AVE	average variance extracted
CCI	Charlson Comorbidity Index
GI	gastroenterology
HRF	Area Health Resource File
HCC	hepatocellular carcinoma
ICD	International Classification of Diseases
IQR	interquartile range
LRTs	locoregional therapies
NCCCR	North Carolina Central Cancer Registry
PCP	primary care physician
SES	socioeconomic status
TACE	transarterial chemoemoblization
VA	Veterans Affairs

Y90	yttrium-90

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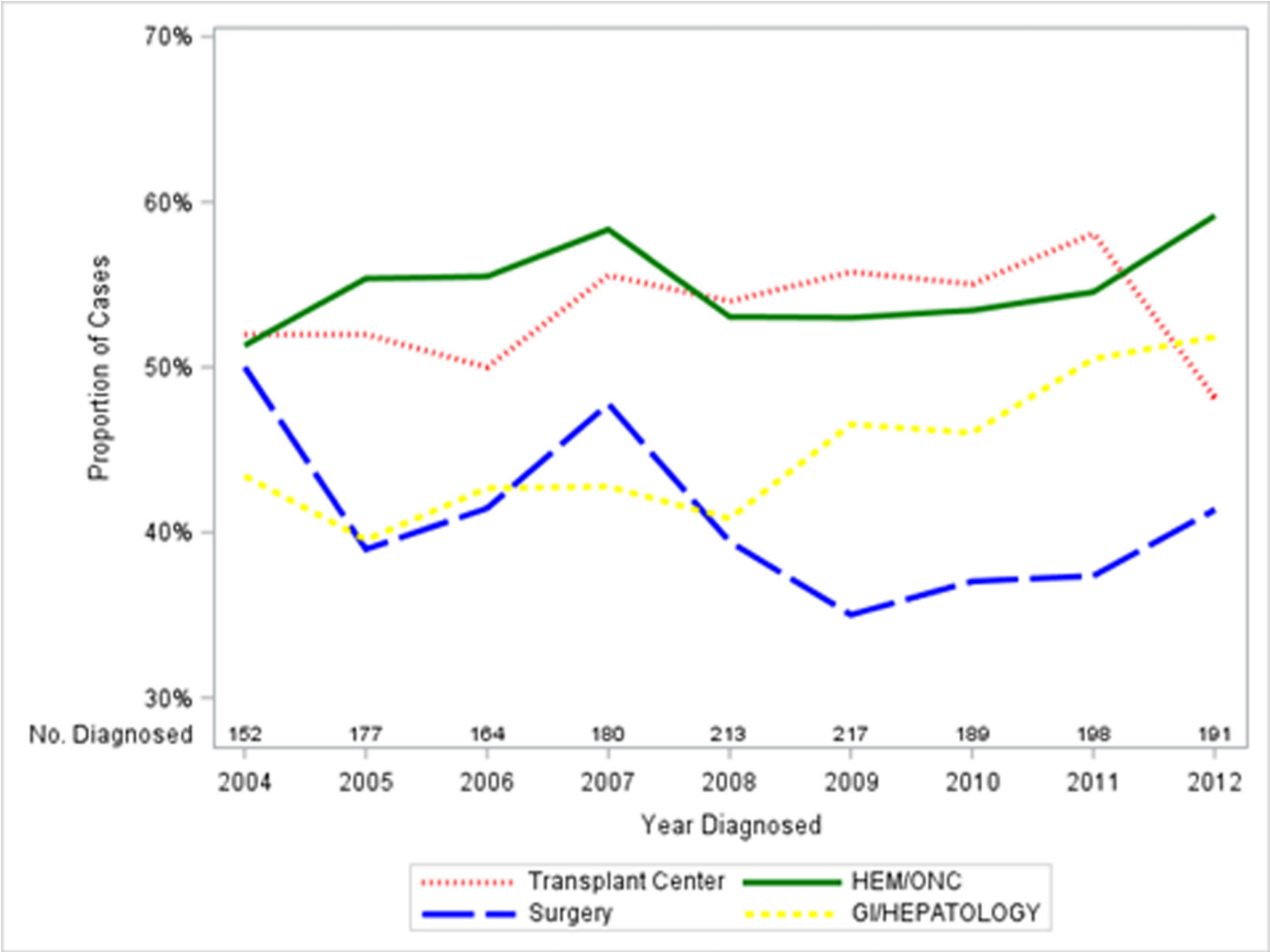

Figure 1: Time trends of subspecialty consultation within 90 days of diagnosis among incident HCC cases diagnosed 2004–2012

The proportion of all HCC cases diagnosed from 2004–2012 with a visit at a transplant center or with a consultation by a surgeon, hematologist/oncologist (HEM/ONC), gastroenterology/hepatology (GI/HEPATOLOGY) within 90 days of diagnosis.

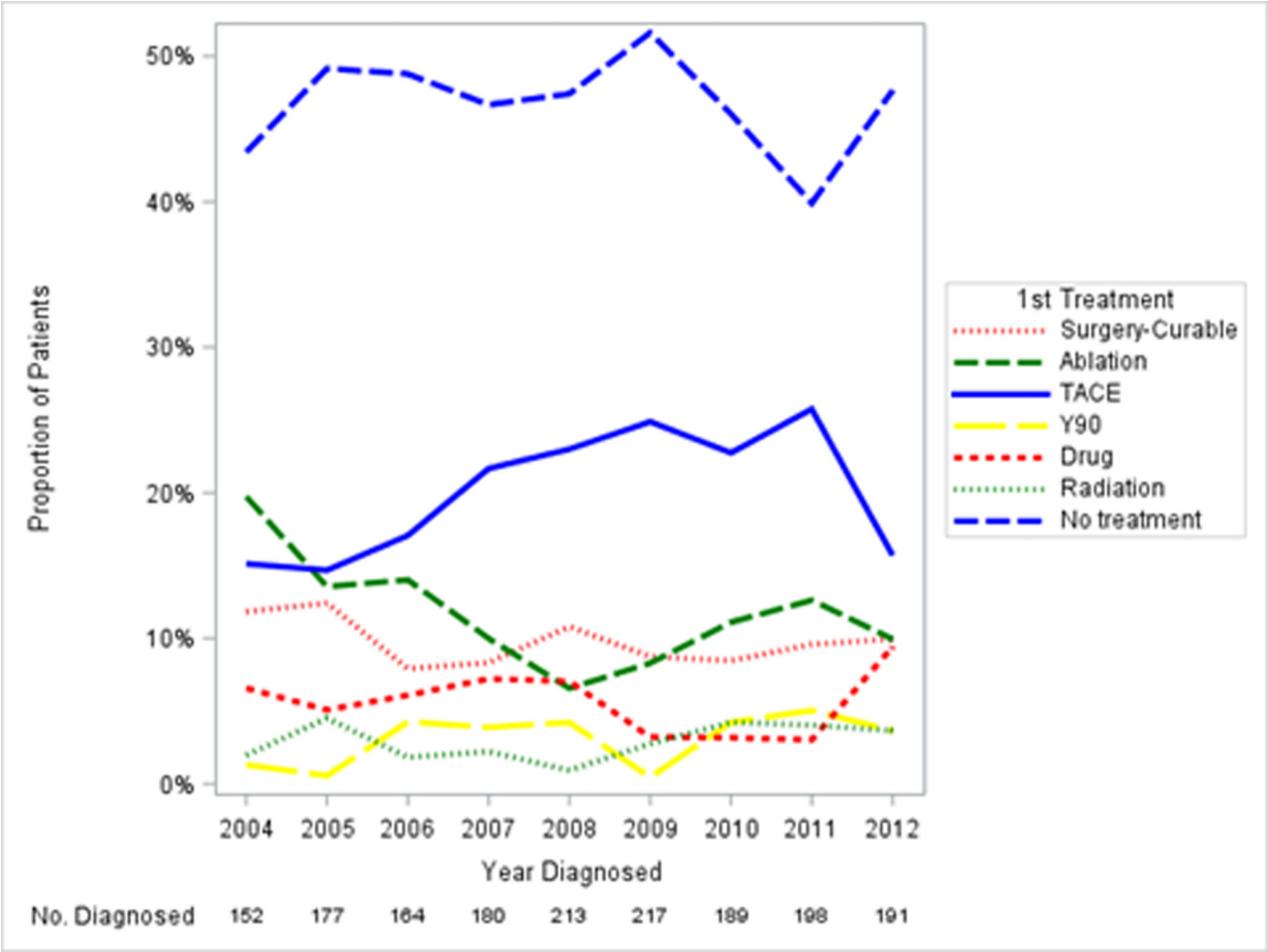

Figure 2: Time trends of type of initial treatment received by year of diagnosis among incident HCC cases diagnosed 2004–2012

The type of first treatment received among patients with HCC diagnosed from 2004–2012. The majority of patients diagnosed with HCC received no treatment for every year during the study period; TACE: transarterial chemoembolization; Y90: yttrium-90

Table 1:

Characteristics of patients with newly-diagnosed HCC

Characteristic	HCC cases n=1,809
Cancer Extent	
Single without vascular invasion	671 (37%)
Single with vascular invasion	105 (6%)
Multiple without vascular invasion	458 (25%)
Multiple with vascular invasion	230 (13%)
Extrahepatic	66 (4%)
Not staged	279 (15%)
Age (median, interquartile range)	68 (59, 76)
<50	110 (6%)
50–64	574 (32%)
65–74	611 (34%)
75+	514 (28%)
Sex	
Male	1,326 (73%)
Female	483 (27%)
Race	
White	1,375 (76%)
Black	368 (20%)
Asian	Combined below†
Native American	Combined below†
Other	66 (4%)
Marital Status	
Married	803 (44%)
Widowed	33 (2%)
Divorced/separated/single	640 (35%)
Other/unknown	333 (18%)
Insurance Payer at Diagnosis	
Private	165 (9%)
Medicare	1,069 (59%)
Medicaid/Dual	575 (32%)
Tricare/VA	NA‡
Other	NA‡
Uninsured	NA‡
Psychiatric Comorbidity	

Characteristic	HCC cases n=1,809
Yes	820 (45%)
No	989 (55%)
Medical Comorbidity (CCI)	
0	657 (36%)
1	526 (29%)
2+	626 (35%)
Liver-related Complications	
0	1,107 (61%)
1+	702 (39%)
Characteristic	**Claims Restricted Cases n=1,809**
Cause of Liver Disease[§]	
Hepatitis B virus	96 (5%)
Hepatitis C virus	538 (30%)
Alcohol	306 (17%)
Other cause of cirrhosis	371 (21%)
County Economic Disadvantage Index	
Quartile 1: Least Disadvantaged	352 (19%)
Quartile 2	645 (36%)
Quartile 3	595 (33%)
Quartile 4: Most Disadvantaged	216 (12%)
County Rurality Index	
Quartile 1: Least Rural	953 (53%)
Quartile 2	433 (24%)
Quartile 3	290 (16%)
Quartile 4: Most Rural	132 (7%)
County Healthcare Disadvantage Index	
Quartile 1: Least Disadvantaged	897 (50%)
Quartile 2	389 (22%)
Quartile 3	308 (17%)
Quartile 4: Most Disadvantaged	214 (12%)

VA, Veterans Affairs; CCI, Charlson Comorbidity Index; PCP, primary care physician; GI, gastroenterology; AFP, alpha fetoprotein

[†]To preserve confidentiality cells with <11 individuals were combined.

[‡]Claims not available for these insurers.

[§]Causes of liver disease are not mutually exclusive, will not sum to 100%.

Table 2:

Association of stage at presentation and transplant center visit with patient and area-level factors

Characteristic	All HCC Cases n=1,809	Multifocal Cancer n=1,033	Odds of Multifocal† aOR, 95% CI	Transplant Center Visit n = 957	Odds of Transplant Center Visit† aOR, 95% CI
Cancer Extension					
Single without vascular invasion	671 (37%)	NA	NA	388 (41%)	Ref
Multiple without vascular invasion	458 (25%)	NA	NA	263 (27%)	0.98 (0.74, 1.31)
Single with vascular invasion	105 (6%)	NA	NA	71 (7%)	1.92 (1.16, 3.18)
Multiple with vascular invasion	230 (13%)	NA	NA	116 (12%)	0.83 (0.58, 1.19)
Extrahepatic	66 (4%)	NA	NA	28 (3%)	0.70 (0.39, 1.26)
Not staged	279 (15%)	NA	NA	91 (10%)	0.34 (0.24, 0.49)
Age (median)	68 (59, 76)			66 (57, 73)	
<50	110 (6%)	55 (5%)	Ref	75 (8%)	Ref
50–64	574 (32%)	324 (31%)	1.31 (0.85, 2.00)	354 (37%)	0.81 (0.48, 1.37)
65–74	611 (34%)	365 (35%)	1.91 (1.19, 3.06)	333 (35%)	0.95 (0.54, 1.69)
75+	514 (28%)	289 (28%)	1.64 (1.01, 2.68)	195 (20%)	0.52 (0.28, 0.94)
Sex					
Male	1,326 (73%)	779 (75%)	Ref	715 (75%)	Ref
Female	483 (27%)	254 (25%)	0.74 (0.59, 0.93)	242 (25%)	0.95 (0.73, 1.23)
Race					
White	1,375 (76%)	763 (74%)	Ref	744 (78%)	Ref
Black	368 (20%)	232 (22%)	1.22 (0.93, 1.61)	174 (18%)	0.54 (0.39, 0.74)
Other	66 (4%)	38 (4%)	1.05 (0.62, 1.80)	39 (4%)	0.62 (0.32, 1.20)
Marital Status					
Married	803 (44%)	429 (42%)	Ref	427 (45%)	Ref
Widowed	33 (2%)	21 (2%)	1.54 (0.73, 3.25)	18 (2%)	0.68 (0.29, 1.58)
Divorced/separated/single	640 (35%)	388 (38%)	1.37 (1.08, 1.72)	280 (29%)	0.71 (0.54, 0.92)
Other/unknown	333 (18%)	195 (19%)	1.26 (0.96, 1.65)	232 (24%)	2.12 (1.52, 2.98)
Insurance Payer at Diagnosis					
Private	165 (9%)	87 (8%)	Ref	129 (13%)	Ref
Medicare	1,069 (59%)	604 (58%)	0.89 (0.60, 1.33)	519 (54%)	0.35 (0.21, 0.59)
Medicaid/Dual	575 (32%)	342 (33%)	1.00 (0.68, 1.48)	309 (32%)	0.46 (0.28, 0.77)
Medical Comorbidity (CCI)					
0	657 (36%)	389 (38%)	Ref	377 (39%)	Ref
1	526 (29%)	299 (29%)	0.95 (0.75, 1.22)	283 (30%)	0.80 (0.60, 1.07)
2+	626 (35%)	345 (33%)	0.85 (0.67, 1.09)	297 (31%)	0.63 (0.48, 0.85)

Characteristic	All HCC Cases n=1,809	Multifocal Cancer n=1,033	Odds of Multifocal† aOR, 95% CI	Transplant Center Visit n = 957	Odds of Transplant Center Visit† aOR, 95% CI
Cause of Liver Disease‡					
Hepatitis B virus	96 (5%)	54 (5%)	1.05 (0.67, 1.64)	62 (6%)	1.36 (0.80, 2.33)
Hepatitis C virus	538 (30%)	304 (29%)	1.16 (0.89, 1.52)	360 (38%)	1.72 (1.25, 2.36)
Alcohol	306 (17%)	174 (17%)	1.09 (0.81, 1.48)	187 (20%)	1.09 (0.76, 1.56)
Other cause of cirrhosis	371 (21%)	203 (20%)	1.03 (0.78, 1.36)	208 (22%)	1.35 (0.98, 1.87)
Prediagnosis Healthcare Utilization (median encounters, Q1, Q3)					
Tertile 1: 1 (0, 2)	526 (29%)	326 (32%)	Ref	216 (23%)	Ref
Tertile 2: 5 (3, 6)	657 (36%)	377 (36%)	0.95 (0.74, 1.21)	352 (37%)	1.45 (1.09, 1.94)
Tertile 3: 12 (9, 16)	626 (35%)	330 (32%)	0.86 (0.66, 1.12)	389 (41%)	2.14 (1.57, 2.93)
1 year prediagnosis specialty care					
None	245 (14%)	725 (70%)	Ref	419 (44%)	Ref
PCP only	951 (53%)	§	§	§	§
PCP + GI/hepatology	567 (31%)	308 (30%)	0.77 (0.61, 0.96)	538 (56%)	1.66 (1.27, 2.18)
GI/Hepatology only	46 (3%)	§	§	§	§
1 year prediagnosis AFP Screening					
Yes	779 (43%)	398 (39%)	0.72 (0.58, 0.90)	521 (54%)	1.74 (1.35, 2.23)
No	1,030 (57%)	635 (61%)	Ref	436 (46%)	Ref
Miles to Closest Liver Txp Center (median, Q1, Q3)			NA		
Tertile 1: Median=17.4 (7.3, 25.3)	605 (33%)	346 (34%)		442 (46%)	Ref
Tertile 2: Median=53.(44.2, 60.8)	602 (33%)	354 (34%)		268 (28%)	0.46 (0.32, 0.66)
Tertile 3: Median=106 (90., 133)	600 (33%)	331 (32%)		247 (26%)	0.27 (0.18, 0.41)
County Economic Disadvantage Index					
Quartile 1: Least Disadvantaged	352 (19%)	185 (18%)	Ref	164 (17%)	Ref
Quartile 2	645 (36%)	369 (36%)	1.13 (0.85, 1.51)	427 (45%)	0.96 (0.65, 1.41)
Quartile 3	595 (33%)	337 (33%)	1.06 (0.77, 1.45)	248 (26%)	0.36 (0.24, 0.56)
Quartile 4: Most Disadvantaged	216 (12%)	141 (14%)	1.50 (1.01, 2.23)	118 (12%)	1.76 (1.10, 2.83)
County Rurality Index					
Quartile 1: Least Rural	953 (53%)	550 (53%)	Ref	553 (58%)	Ref
Quartile 2	433 (24%)	240 (23%)	0.87 (0.65, 1.77)	214 (22%)	0.56 (0.39, 0.81)
Quartile 3	290 (16%)	165 (16%)	0.89 (0.65, 1.20)	158 (17%)	1.28 (0.84, 1.96)

Characteristic	All HCC Cases n=1,809	Multifocal Cancer n=1,033	Odds of Multifocal† aOR, 95% CI	Transplant Center Visit n = 957	Odds of Transplant Center Visit† aOR, 95% CI
Quartile 4: Most Rural	132 (7%)	77 (7%)	0.90 (0.58, 1.39)	32 (3%)	0.24 (0.14, 0.47)
County Healthcare Disadvantage Index					
Quartile 1: Least Disadvantaged	853 (47%)	478 (46%)	Ref	469 (49%)	Ref
Quartile 2	441 (24%)	258 (25%)	1.06 (0.81, 1.39)	241 (25%)	0.98 (0.70, 1.37)
Quartile 3	296 (16%)	164 (16%)	1.04 (0.78, 1.38)	151 (16%)	1.01 (070, 1.45)
Quartile 4: Most Disadvantaged	218 (12%)	132 (13%)	1.21 (0.86, 1.71)	96 (10%)	0.73 (0.48, 1.10)

CCI, Charlson Comorbidity Index; PCP, primary care physician; GI, gastroenterology; AFP, alpha fetoprotein

†Model was also adjusted for psychiatric comorbidity, liver comorbidity (complications of cirrhosis), number of hepatologists per 100,000 population, which were not significantly associated with survival with minimal/no trend suggesting possible effect. These variables were omitted to condense the table size.

‡Causes of liver disease are not mutually exclusive, will not sum to 100%.

§Cells combined with cell above for multivariable model, comparing “any GI/hepatology” to referent of “none or PCP only”.

Table 3:

Factors associated with treatment among HCC patients surviving 90 days from diagnosis

	Treated N=857 (69%)	Untreated N=393 (31%)	Odds of Treatment†	
Characteristic	**n (%)**	**n (%)**	**OR, 95% CI**	**aOR, 95% CI**
Initial Treatment				
Curative surgery	149 (12%)	-	-	-
Ablation	186 (15%)	-	-	-
LRT (TACE + TARE)	387 (31%)	-	-	-
Drug Therapy	89 (7%)	-	-	-
Radiation	46 (4%)	-	-	-
Year of Diagnosis				
2004–2005	162 (19%)	78 (20%)	Ref	Ref
2006–2007	160 (19%)	75 (19%)	1.03 (0.70, 1.51)	0.91 (0.58, 1.44)
2008–2009	200 (23%)	101 (26%)	0.95 (0.66, 1.37)	0.86 (0.56, 1.33)
2010–2011	208 (24%)	77 (20%)	1.30 (0.89, 1.89)	1.33 (0.85, 2.07)
2012–2013	127 (15%)	62 (16%)	0.99 (0.66, 1.48)	1.09 (0.65, 1.82)
Age (median)				
<65	382 (45%)	134 (34%)	Ref	Ref
65–74	306 (36%)	112 (28%)	0.96 (0.72, 1.28)	0.64 (0.41, 0.99)
75+	169 (20%)	147 (37%)	0.40 (0.30, 0.54)	0.30 (0.18, 0.49)
Race				
White	661 (77%)	289 (74%)	Ref	Ref
Black	162 (19%)	92 (23%)	0.77 (0.58, 1.03)	0.84 (0.56, 1.24)
Other	34 (4%)	12 (3%)	1.24 (0.63, 2.43)	1.42 (0.64, 3.18)
Marital Status				
Married	415 (48%)	150 (38%)	Ref	Ref
Divorced/separated/ Single	239 (28%)	173 (44%)	0.53 (0.41, 0.69)	0.62 (0.44, 0.88)
Other/unknown	203 (24%)	70 (18%)	0.99 (0.71, 1.38)	0.81 (0.53, 1.22)
Insurance Payer at Diagnosis				
Private	117 (14%)	18 (5%)	Ref	Ref
Medicare	478 (56%)	233 (59%)	0.32 (0.19, 0.53)	0.78 (0.40, 1.50)
Medicaid/Dual	262 (31%)	142 (36%)	0.28 (0.17, 0.49)	0.80 (0.41, 1.54)
Psychiatric comorbidity				
No	488 (57%)	192 (49%)	Ref	Ref
Yes	369 (43%)	201 (51%)	0.72 (0.57, 0.92)	0.64 (0.47, 0.89)
Medical Comorbidity (CCI)				
0	354 (41%)	140 (36%)	Ref	Ref
1	266 (31%)	108 (27%)	0.97 (0.72, 1.31)	0.90 (0.63, 1.30)

Characteristic	Treated N=857 (69%) n (%)	Untreated N=393 (31%) n (%)	Odds of Treatment† OR, 95% CI	aOR, 95% CI
2+	237 (28%)	145 (37%)	0.65 (0.49, 0.86)	0.78 (0.54, 1.12)
Characteristic	**Treated n (%)**	**Untreated n (%)**	**Odds of Treatment† OR, 95% CI**	**aOR, 95% CI**
Liver-related Complications				
0	561 (65%)	250 (64%)	Ref	Ref
1+	296 (35%)	143 (36%)	0.92 (0.72, 1.18)	0.51 (0.35, 0.74)
Cancer Extension				
Single without vascular invasion	375 (44%)	129 (33%)	Ref	Ref
Single with vascular invasion	59 (7%)	28 (7%)	0.72 (0.44, 1.19)	0.69 (0.38, 1.24)
Multiple without vascular invasion	249 (29%)	87 (22%)	0.98 (0.72, 1.35)	1.07 (0.74, 1.54)
Multiple with Vascular invasion	88 (10%)	52 (13%)	0.58 (0.39, 0.87)	0.59 (0.37, 0.94)
Extrahepatic	20 (2%)	15 (4%)	0.46 (0.23, 0.92)	0.43 (0.19, 0.99)
Not staged	66 (8%)	82 (21%)	0.28 (0.19, 0.41)	0.43 (0.28, 0.68)
1 year Prediagnosis Specialty Care				
None	86 (10%)	65 (17%)	Ref	Ref
PCP only	412 (48%)	225 (57%)	1.38 (0.96, 1.99)	1.36 (0.85, 2.17)
GI/Hepatology	359 (42%)	103 (26%)	2.63 (1.78, 3.89)	1.68 (0.98, 2.86)
1 year Prediagnosis AFP Screening				
No	354 (41%)	267 (68%)	Ref	Ref
Yes	503 (59%)	126 (32%)	3.01 (2.34, 3.87)	2.61 (1.90, 3.60)
Surgical Consult in 90 days after diagnosis				
No	379 (44%)	295 (75%)	Ref	Ref
Yes	478 (56%)	98 (25%)	3.80 (2.91, 4.95)	3.40 (2.48, 4.67)
Visit at Liver Transplant Center in 90 days from Diagnosis				
Yes	659 (77%)	183 (47%)	3.54 (2.76, 4.54)	2.42 (1.74, 3.36)
No	198 (23%)	210 (53%)	Ref	Ref
County Economic Disadvantage Index				
Quartile 1: Least Disadvantaged	175 (20%)	66 (17%)	Ref	Ref
Quartile 2	307 (36%)	143 (36%)	0.81 (0.57, 1.14)	0.56 (0.35, 0.87)
Quartile 3	277 (32%)	135 (34%)	0.77 (0.55, 1.10)	0.80 (0.50, 1.30)
Quartile 4: Most Disadvantaged	98 (11%)	49 (12%)	0.75 (0.48, 1.18)	0.79 (0.44, 1.43)
County Rurality Index				
Quartile 1: Least Rural	467 (54%)	203 (52%)	Ref	Ref
Quartile 2	197 (23%)	92 (23%)	0.93 (0.69, 1.25)	0.90 (0.58, 1.39)
Quartile 3	139 (16%)	64 (16%)	0.94 (0.67, 1.32)	0.70 (0.45, 1.11)

Characteristic	Treated N=857 (69%) n (%)	Untreated N=393 (31%) n (%)	Odds of Treatment† OR, 95% CI	aOR, 95% CI
Quartile 4: Most Rural	54 (6%)	34 (9%)	0.69 (0.44, 1.09)	0.70 (0.37, 1.33)

CCI, Charlson Comorbidity Index; PCP, primary care physician; GI, gastroenterology; AFP, alpha fetoprotein

†Model was also adjusted for sex, cause of liver disease, prediagnosis healthcare utilization, post-diagnosis GI and Hematology/Oncology consultation, county health services index, which were not significantly associated with survival with minimal/no trend suggesting possible effect. These variables were omitted to condense the table size.

Table 4:

Factors associated with survival among newly diagnosed cases of HCC

	Cases surviving 90 days n=1,250	Hazard for Mortality†	
Patient Level Characteristic	**n (%)**	**HR,95% CI**	**aHR,95% CI**
Year			
2004–2007	475 (38%)	Ref	Ref
2008–2013	775 (62%)	0.85 (0.75, 0.97)	0.75 (0.66, 0.85)
Age			
<50	93 (7%)	Ref	Ref
50–64	423 (34%)	0.97 (0.76, 1.26)	1.08 (0.83, 1.40)
65–74	418 (33%)	1.32 (1.02, 1.69)	1.34 (1.00, 1.78)
75+	316 (25%)	1.48 (1.15, 1.92)	1.39 (1.03, 1.87)
Race			
White	950 (76%)	Ref	Ref
Black	254 (20%)	1.09 (0.94, 1.27)	1.09 (0.91, 1.30)
Other	46 (4%)	0.92 (0.66, 1.28)	1.40 (0.98, 1.99)
Insurance Payer at Dx			
Private	135 (11%)	Ref	Ref
Medicare	711 (57%)	2.31 (1.82, 2.93)	1.58 (1.20, 2.09)
Medicaid/Dual	404 (32%)	2.50 (1.95, 3.20)	1.55 (1.17, 2.05)
Psychiatric Comorbidity			
No	680 (54%)	Ref	Ref
Yes	570 (46%)	1.16 (1.03, 1.31)	1.15 (1.00, 1.32)
Medical Comorbidity (CCI)			
0	494 (40%)	Ref	Ref
1	374 (30%)	1.18 (1.02, 1.36)	1.14 (0.97, 1.33)
2+	382 (31%)	1.40 (1.21, 1.62)	1.18 (1.00, 1.38)
Liver-related Complications			
0	811 (65%)	Ref	Ref
1+	439 (35%)	1.00 (0.88, 1.14)	1.24 (1.05, 1.45)
Cancer Extension			
Single lesion	591 (47%)	Ref	Ref
Multiple without vascular invasion	336 (27%)	1.51 (1.31, 1.75)	1.41 (1.21, 1.64)
Multiple with Vascular invasion	140 (11%)	2.18 (1.79, 2.66)	1.74 (1.42, 2.14)
Extrahepatic/not staged	183 (15%)	2.05 (1.71, 2.44)	1.39 (1.15, 1.69)
Initial Cancer Directed Treatment			
Curative Surgery	149 (12%)	Ref	Ref
Ablation	186 (15%)	1.50 (1.14, 1.97)	1.60 (1.20, 2.13)

	Cases surviving 90 days n=1,250	Hazard for Mortality†	
Patient Level Characteristic	**n (%)**	**HR,95% CI**	**aHR,95% CI**
LRT (TACE/Y90)	387 (31%)	2.68 (2.11, 3.41)	2.47 (1.90, 3.19)
Drug Therapy (including Sorafenib)	89 (7%)	5.81 (4.28, 7.90)	4.57 (3.27, 6.40)
Radiation	46 (4%)	4.49 (3.10, 6.49)	3.79 (2.55, 5.65)
Never Treated	393 (31%)	5.57 (4.38, 7.09)	4.97 (3.79, 6.51)
1 year Prediagnosis Specialty Care			
None	151 (12%)	Ref	Ref
PCP only	637 (51%)	0.94 (0.78, 1.13)	0.83 (0.67, 1.03)
GI/Hepatology	462 (37%)	0.68 (0.56–0.83)	0.74 (0.58, 0.94)
Hematology/Oncology Consult			
No	562 (45%)	Ref	Ref
Yes	688 (55%)	1.53 (1.36, 1.73)	1.39 (1.21, 1.59)

CCI, Charlson Comorbidity Index; PCP, primary care physician; GI, gastroenterology.

†Model was also adjusted for sex, marital status, cause of liver disease, prediagnosis healthcare utilization, prediagnosis AFP screening, surgical or GI/hepatology consult in 90 days of diagnosis, National Cancer Institute Center or liver transplant center visit in 90 days after diagnosis, and county level economic, rurality, and health services disadvantage indices, which were not significantly associated with survival with minimal/no trend suggesting possible effect. These variables were omitted to condense the table size.