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Hepatocellular Carcinoma Surveillance in a Cohort of Chronic Hepatitis C Virus-Infected Patients with Cirrhosis

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Abstract

Background—Six-monthly hepatocellular carcinoma (HCC) screening in cirrhotic patients has been recommended since 2011. HCC prognosis is associated with diagnosis at an early stage. We examined the prevalence and correlates of 6-monthly HCC surveillance in a cohort of HCV-infected cirrhotic patients.

Methods—Data were obtained from the medical records of patients receiving care from four hospitals between January 2011 and December 2016. Frequencies and logistic regression were conducted.

Results—Of 2,933 HCV-infected cirrhotic patients, most were ≥ 60 years old (68.5%), male (62.2%), White (65.8%), and had compensated cirrhosis (74.2%). The median follow-up period was 3.5 years. Among these patients, 10.9% were consistently screened 6 monthly and 21.4% were never screened. Patients with a longer history of cirrhosis (AOR = 0.86, 95% CI = 0.80–0.93)

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were less likely to be screened 6 monthly while decompensated cirrhotic patients (AOR = 1.39, 95% CI = 1.06–1.81) and cirrhotic patients between 18 and 44 years (AOR = 2.01, 95% CI = 1.07–3.74) were more likely to be screened 6 monthly compared to compensated cirrhotic patients and patients 60 years and older respectively. There were no significant differences by race, gender, or insurance type.

Conclusion—The prevalence of consistent HCC surveillance remains low despite formalized recommendations. One in five patients was never surveilled. Patients with a longer history of cirrhosis were less likely to be surveilled consistently despite their greater HCC risk. Improving providers' knowledge about current HCC surveillance guidelines, educating patients about the benefits of consistent HCC surveillance, and systemic interventions like clinical reminders and standing HCC surveillance protocols can improve guideline-concordant surveillance in clinical practice.

Keywords

Hepatocellular carcinoma surveillance; Chronic HCV infection; Hepatitis C virus; Hepatocellular carcinoma; Cirrhosis

Introduction

Hepatocellular carcinoma (HCC) is the most common primary cancer of the liver [1]. HCV infection increases the risk for HCC severalfold [2] and is a major cause of HCC in the USA [3]. Cirrhosis is a common complication of chronic HCV infection (CHC) and is the most important risk factor for HCC [4]. The prognosis for patients with HCC depends on tumor stage at diagnosis with effective treatment only available for patients diagnosed at an early stage [5]. Most HCC is diagnosed at an advanced stage [6]; therefore, consistent HCC surveillance is important to improving survival.

The 2011 guideline from the American Association for the Study of Liver Diseases (AASLD) recommends 6-monthly HCC surveillance by abdominal ultrasound with or without alpha-fetoprotein (AFP) in CHC patients with cirrhosis [7]. HCC surveillance is associated with early HCC detection, timely treatment, and improved survival compared to those who do not receive surveillance [8, 9]. Patients with HCC that are detected at an early stage can achieve a 5-year survival rate of greater than 60% with transplant or resection while patients with advanced stage HCC have a 5-year survival rate of less than 5% [10, 11].

Despite AASLD recommendations, HCC surveillance is not always performed [12]. Prevalence of HCC surveillance among cirrhotic patients in the USA ranges from 10 to 50% [13–17]. A systematic review of nine HCC surveillance studies showed a pooled surveillance rate of 18% [12]; however, several of the studies in this review were conducted prior to the implementation of the 2011 guidelines and therefore, only estimated annual HCC surveillance. Furthermore, few studies have evaluated HCC surveillance among HCV-infected cirrhotic patients [13] with most studies examining HCC surveillance among cirrhotic patients with multiple etiologies [12, 15, 17]. Using electronic medical records (EMR) data from four large integrated health systems, we conducted a retrospective cohort

data analysis of HCV-infected cirrhotic patients to determine the prevalence and correlates of 6-monthly HCC surveillance.

Methods

Data Source

Data for this study were obtained from the Chronic Hepatitis Cohort Study (CHeCS), an ongoing prospective, multicenter cohort study that draws patients from four large integrated health systems. CHeCS participants include patients aged 18 years and older who used any health service at any of the following health systems (Geisinger Health System, Danville, PA; Henry Ford Health System, Detroit, MI; Kaiser Permanente-Hawaii, Honolulu, HI; and Kaiser Permanente-Northwest, Portland, OR) on or after January 1, 2006. Data on demographics, medical encounters, hepatitis treatment, laboratory, radiology, and biopsy results were abstracted following a standardized procedure. The Institutional Review Board at each participating site reviewed and approved the study protocol.

Participants included in this study were 18 years and older, with a cirrhotic CHC diagnosis, and received care between January 1, 2011 and December 31, 2016. The follow-up period began at the latter of January 1, 2011 or first date of cirrhosis and was right censored at December 31, 2016, the date that patient left care at any of the sites or date of patient death. In order to ensure sufficient follow-up time, we excluded patients with less than 12 months of follow-up at any of the four study sites. HCC patients and patients infected with hepatitis B virus infection or HIV were also excluded. Demographic data were obtained at baseline and type of cirrhosis was obtained during follow-up.

A CHC diagnosis was based on a positive HCV RNA test or two or more HCV ICD-9 codes (070.44, 070.54, 070.70, 070.71, 070.41, or 070.51) separated by six or more months. The ICD-9-based measure showed good sensitivity and specificity for determining confirmed CHC and has been validated in a previous study of this cohort [18]. Patients who met at least one of the following definitions were considered cirrhotic: (1) a liver biopsy result consistent with Metavir F4, (2) a FIB-4 ≥ 5.88 (excluding values during acute hospitalization), or (3) ICD-9 or procedure codes consistent with a diagnosis of cirrhosis (571.2 or 571.5) or decompensated cirrhosis (hepatorenal syndrome—572.4; hepatic encephalopathy—572.2; portal hypertension—572.3 or portal decompression procedures—37140, 37160, 37180, 37181, 37182, 37183; esophageal varices, their complications and related procedures—42.91, 44.91, 96.06, 456.0, 456.2, 43,204, 43,205, 43,243, 43,244, 43,400, 43,401; ascites and related procedures—789.5, 589.59, 49,080, 49,081, 54.91). These measures of ascertaining cirrhosis have previously been validated and identified a higher proportion of cirrhotic patients than with only ICD-9 codes in this cohort [19]. Cirrhotic patients were categorized as decompensated if the patient had a de-compensation code at any time.

Data obtained for this analysis included patient demographics (sex, age, race/ethnicity, type of insurance), clinical data (HCV genotype, type of cirrhosis (decompensated/compensated), HCC surveillance), study site, and length of cirrhosis history/diagnosis (years since cirrhosis diagnosis/follow-up period). HCC surveillance was defined as receiving an abdominal imaging test such as an ultrasound, computed tomography (CT), or magnetic resonance

imaging (MRI) scans. Though abdominal ultrasound is recommended, other hepatic imaging modalities like CT and MRI scans are also used in clinical practice [4, 20]. Current procedural terminology codes were used to identify abdominal ultrasound, CT, and MRI imaging codes. HCC surveillance (abdominal ultrasound, CT, or MRI) was categorized as follows: at least screened 6 monthly (≥ 1 abdominal imaging test every 6 months during the follow-up period); not screened 6 monthly (≥ 1 abdominal imaging test during the follow-up period but not every 6 months), and never screened (never had any abdominal imaging test during the follow-up period). In order to determine the correlates of consistent HCC surveillance and because performing irregular HCC screening tests are of little clinical significance [13], HCC surveillance was further classified as consistent HCC surveillance (≥ 1 abdominal imaging test every 6 months during the follow-up period) and inconsistent HCC surveillance (never screened or not screened 6 monthly during the follow-up period).

Statistical Analysis

Descriptive statistics were calculated to describe the demographic and clinical characteristics of the study sample. Frequency of HCC surveillance (at least screened 6 monthly, not screened 6 monthly, and never screened) and differences by demographic and clinical variables were also calculated. Bivariate and multivariable logistic regression were done to identify factors associated with consistent HCC surveillance and unadjusted odds ratios (UOR) and adjusted odds ratios (AOR) with corresponding 95% confidence intervals (CI) were estimated. The multivariable model included clinically important variables identified in the research literature and significant variables ($p < 0.05$) in the bivariate analyses. The study site was included as a covariate in the multivariable model. Statistical significance was set at 0.05 and all analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC).

Results

Table 1 shows the distribution of demographic and clinical characteristics of all study participants ($N = 2933$). The majority were ≥ 60 years old (68.5%), male (62.2%), White (65.8%), had private insurance (43.9%) or Medicaid insurance (43.7%), had compensated cirrhosis (74.2%), and had geno-type 1 HCV infection (77.7%). All patients were followed up for a median of 3.5 years which provided approximately 10,000 person-years of observation. During the follow-up period, 10.9% of patients were screened at least 6 monthly (median follow-up = 3.0 years), 67.7% were not screened 6 monthly (median follow-up = 3.9 years), and 21.4% were never screened (median follow-up = 2.8 years). Compared to HCV-infected cirrhotic patients who were not screened 6 monthly or never screened, the majority of patients screened at least 6 monthly were between 18 and 44 (17.4%), females (11.3%), Asian/other/unknown race (12.1%), had Medicare insurance (12.2%), had decompensated cirrhosis (13.1%), had genotype 3 (13.9%), or mixed genotype (12.7%) HCV infection.

Differences in consistent HCC surveillance (at least 6-monthly screening during the follow-up period) and inconsistent HCC surveillance (not screened 6 monthly or never screened during the follow-up period) were examined. Table 2 shows the UOR with corresponding 95% CI. In bivariate logistic regression, cirrhotic patients between 18 and 44 years (UOR =

1.85, 95% CI = 1.06–3.24) were more likely to receive consistent HCC surveillance compared to patients 60 years and older. Patients with decompensated cirrhosis (UOR = 1.33, 95% CI = 1.03–1.71) were more likely to receive consistent HCC surveillance compared to those with compensated cirrhosis. Patients with a longer history of cirrhosis were less likely to receive consistent HCC surveillance (UOR = 0.87, 95% CI = 0.81–0.94). Participants recruited from the Portland site (UOR = 2.01, 95% CI = 1.39–2.89) and the Detroit site (UOR = 1.47, 95% CI = 1.04–2.09) were more likely to be screened for HCC consistently. There were no significant differences by sex, race, insurance type, or HCV genotype in the bivariate model.

The multivariable logistic regression model included age, sex, race, type of insurance, type of cirrhosis, history of cirrhosis, period of cirrhosis diagnosis, and study site included as a covariate (Table 3). In the multivariable model, patients between 18 and 44 (AOR = 2.01, 95% CI = 1.07–3.74) were more likely to receive consistent HCC surveillance than patients 60 years and older. Decompensated cirrhotic patients (AOR = 1.39, 95% CI = 1.06–1.81) were more likely to receive consistent HCC surveillance than compensated cirrhotic patients while cirrhotic patients with a longer history of cirrhosis were less likely to receive consistent HCC surveillance (AOR = 0.86, 95% CI = 0.80–0.93). Receipt of consistent HCC surveillance did not significantly differ by sex, race, or insurance type.

Conclusion

The proportion of HCV-infected, cirrhotic patients receiving guideline-concordant HCC surveillance in this study is low. Despite AASLD recommendations, approximately 11% of cirrhotic patients received 6-monthly HCC surveillance while 21% were never screened. This estimate is similar to the estimates reported in other studies [12–16, 21, 22]. A meta-analysis demonstrated that less than 20% of cirrhotic patients in the USA undergo surveillance [12]. Two studies of HCV-infected cirrhotic patients each reported that 12% and 22% of their patients received annual HCC surveillance [13, 16]. A study of Medicaid patients and Veterans Affairs patients showed that 26% and 12% of their study population received annual HCC surveillance respectively [14, 15].

Various provider- and patient-level factors can account for the low prevalence of patients who received consistent HCC surveillance. Healthcare providers may be unaware of current HCC surveillance recommendations, appropriate HCC surveillance tests, or may underestimate the utility of HCC surveillance [23, 24]. A study showed that about a quarter of primary care providers who provide care to cirrhotic patients were unaware of the HCC surveillance recommendations while more than half incorrectly believed that liver aminotransferases and AFP alone were appropriate HCC screening tests [23, 24]. Similarly, about two-thirds of providers reported performing annual HCC surveillance instead of biannual surveillance as current guidelines recommend [23]. The medical specialty of the healthcare provider is another factor that can influence the receipt of HCC surveillance. Liver specialists are more likely to conduct routine HCC surveillance than primary care providers [14, 15, 22]. However, because of the small number of liver specialists in the country, the majority of cirrhotic patients receive care from primary care providers who are less likely to be aware of and adhere to specialty guidelines [25]. Patient-related factors such

as non-adherence to providers' recommendations can account for low HCC surveillance [26]. Other patient-related factors include being unaware of the benefits of consistent HCC surveillance, poor health literacy, costs of screening, poverty, and transportation and scheduling difficulties that might impact patients adherence to their providers' 6-monthly screening recommendation [26–28].

Consistent HCC surveillance in this study varied by type of cirrhosis, length of cirrhosis history/diagnosis, and age. Patients with decompensated cirrhosis were more likely to receive consistent surveillance than those with compensated cirrhosis in this study regardless of screening interval. Decompensated cirrhotic patients have more advanced liver disease, are clinically sicker than compensated cirrhotic patients, and are more frequently managed by liver specialists which can account for increased surveillance [29, 30]. They are also more likely to evaluated for liver transplantation or listed for liver transplantation, and consequently, may be more likely to receive consistent HCC surveillance [31]. Conversely, many compensated cirrhotic patients who are asymptomatic remain at high risk for developing HCC and also warrant consistent surveillance [12].

Patients with a longer history of cirrhosis were less likely to receive consistent HCC surveillance. Providers may be more likely to extend screening intervals for some cirrhotic patients, especially if the patient has been cirrhotic for a long time and previous screening results have been non-remarkable. Furthermore, some providers might incorrectly assume that there is a reduced benefit in ongoing consistent HCC surveillance in patients who have been cirrhotic for longer periods compared to recently diagnose cirrhotic patients [9, 23]. Providers may also be reluctant to screen long-term cirrhotic patients every 6 months because of screening costs, especially if previous tests do not show any pathological abnormality [9, 23]. Regardless, this finding is worrisome given that patients with a longer duration of cirrhosis are more likely to develop HCC and require consistent surveillance. Younger patients in this study were more likely to receive consistent HCC surveillance than older patients. Older patients usually have more comorbidities than younger patients and the presence of comorbidities can negatively affect the receipt of consistent surveillance [13].

While other studies have shown disparities in HCC surveillance, there were no racial, gender, or insurance disparities in this study [12–15, 21, 32]. Previous research has shown that Whites are more likely to receive consistent HCC surveillance than Blacks and other racial minority groups [13, 14, 21]. The research on gender differences is mixed with some studies showing females are more likely to receive surveillance [14, 15] while others have shown that males are more likely to receive surveillance [28]. Insurance status has also been shown to impact HCC surveillance with lack of insurance associated with inconsistent surveillance [32]. The majority of these studies examined annual HCC surveillance and not 6-monthly surveillance. Hence, it is possible that the low prevalence of patients receiving consistent 6-monthly surveillance may have underpowered our analysis to detect any significant socio-demographic differences in this study.

Interventions to increase consistent HCC surveillance among cirrhotic patients may improve guideline-concordant practice. Provider recommendation is one of the strongest predictors of the receipt of HCC surveillance [27]; hence, provider-targeted interventions are essential.

Improving provider awareness and education about HCC surveillance recommendations and its benefits, especially among primary care providers who see most cirrhotic patients, can increase the dissemination and adherence to HCC surveillance guidelines.

Systemic interventions such as EMR reminders and standing HCC surveillance protocols can increase surveillance [32–34]. These measures can be built into existing clinical workflow algorithms to enable the identification of cirrhotic patients and order recommended screening tests. HCC surveillance increased by 51% in primary care sites with EMR reminders compared to sites without [33]. Another study that examined the effectiveness of a protocol with automatic HCC surveillance reminders demonstrated a higher prevalence of patients who received screening tests for HCC surveillance compared to those who were not in the protocol [32]. Clinical practices that cannot offer consistent HCC surveillance should have standing surveillance protocols that include referrals to centers where cirrhotic patients can receive screening tests.

Patient involvement is highly correlated with higher HCC surveillance receipt [28]; therefore, improving patient-provider communication should be a target of interventions that aim to increase HCC surveillance among cirrhotic patients. This approach improves health literacy, facilitates personal agency for their health, enables them to understand the benefits of consistent HCC surveillance, and improves adherence to surveillance recommendations [23]. Other patient-focused interventions such as scheduling ultrasound screening on the same day as clinic visits and including social workers in the care of cirrhotic patients with social barriers that hinder clinical visits can also mitigate some patient-related barriers to consistent HCC surveillance [28].

There are limitations to this study. The generalizability of the study findings is limited because study participants were neither randomly selected nor representative of all CHC patients but were selected from four health systems in specific geographic areas of the USA. We also cannot be certain if the abdominal imaging tests were ordered primarily for HCC surveillance or another purpose. The AASLD guideline recommends abdominal ultrasound for HCC surveillance but we included CT and MRI as well because they are sometimes used in clinical practice for screening [4, 20]; however, 93% of these patients had HCC surveillance performed by abdominal ultrasound. The current AASLD guidelines do not recommend surveillance among the small subset of decompensated patients who have the most severe category of Child-Pugh cirrhosis (class C) unless on a transplant waiting list given their low anticipated survival [35]; we did not have data available to identify this subgroup of patients.

Major strengths of this analysis include the large sample size and the long follow-up period. Most published studies examining HCC surveillance have a significantly smaller sample size and have 1–2-year follow-up periods, which might be insufficient to evaluate consistent HCC surveillance [12–16, 21, 22]. While many studies have examined HCC surveillance among cirrhotic patients with multiple etiologies [14, 15, 21, 22], this study focused on HCV-infected cirrhotic patients, the group that accounts for most HCC diagnoses [3, 36]. Lastly, all patients in this sample received clinical care from the same hospital so we were able to access all their surveillance records.

In conclusion, consistent HCC surveillance among cirrhotic HCV-infected patients is low despite existing clinical recommendations. The HCC burden in the USA is high and will likely to continue to increase [37], especially if HCV infection among injection drug users is not urgently addressed [38]. Identifying cirrhotic patients and implementing effective programs to ensure that they receive consistent HCC surveillance is critical to mitigating HCC morbidity and mortality. These findings highlight the need for provider education- and system-level interventions to increase HCC surveillance in cirrhotic patients receiving clinical care.

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Table 1

Frequency of HCC surveillance of HCV-infected cirrhotic patients by demographic and clinical characteristics, $N = 2933$

Variables	Total (column %)	Median follow-up period (years)	At least 6-monthly screening[2] *n* (row %)	Not screened 6-monthly[2] *n* (row %)	Never screened[2] *n* (row %)
	2933		320 (10.9)	1985 (67.7)	628 (21.4)
Median follow-up period (years)		3.5	3.0	3.9	2.8
Age					
18–44	92 (3.1)	3.5	16 (17.4)	51 (55.4)	25 (27.2)
45–59	833 (28.4)	3.2	99 (11.9)	527 (63.3)	207 (24.8)
≥ 60	2008 (68.5)	3.7	205 (10.2)	1407 (70.1)	396 (19.7)
Sex					
Male	1823 (62.2)	3.5	195 (10.7)	1248 (68.5)	380 (20.8)
Female	1110 (37.8)	3.6	125 (11.3)	737 (66.4)	248 (22.3)
Race/ethnicity					
White	1930 (65.8)	3.5	209 (10.8)	1263 (65.4)	458 (23.7)
Black	589 (20.1)	3.7	61 (10.4)	455 (77.2)	73 (12.4)
Asian/other/unknown	414 (14.1)	3.5	50 (12.1)	267 (64.5)	97 (23.4)
Type of insurance					
Private	1287 (43.9)	3.4	130 (10.1)	847 (65.8)	310 (24.1)
Medicaid	1249 (42.6)	3.9	143 (11.4)	898 (71.9)	208 (16.7)
Medicare	288 (9.8)	2.9	35 (12.2)	179 (62.2)	74 (25.7)
Other/unknown	109 (3.7)	3.0	12 (11.0)	61 (56.0)	36 (33.0)
Type of cirrhosis					
Decompensated cirrhosis	758 (25.8)	4.3	99 (13.1)	551 (72.7)	108 (14.2)
Compensated cirrhosis	2175 (74.2)	3.2	221 (10.2)	1434 (65.9)	520 (23.9)
HCV genotype[1]					
Genotype 1	1913 (77.7)	3.6	202 (10.6)	1360 (71.1)	351 (18.3)
Genotype 2	235 (9.5)	3.2	22 (9.4)	148 (63.0)	65 (27.7)
Genotype 3	251 (10.2)	3.6	35 (13.9)	164 (65.3)	52 (20.7)
Genotype other	63 (2.6)	3.5	8 (12.7)	38 (60.3)	17 (27.0)
Study site					
Portland, OR	758 (25.8)	3.2	111 (14.6)	352 (46.4)	295 (38.9)

Variables	Total (column %)	Median follow-up period (years)	At least 6-monthly screening[2] *n* (row %)	Not screened 6-monthly[2] *n* (row %)	Never screened[2] *n* (row %)
Honolulu, HI	282 (9.6)	3.6	16 (5.7)	218 (77.3)	48 (17.0)
Detroit, MI	1322 (45.1)	3.9	148 (11.2)	1003 (75.9)	171 (12.9)
Danville, PA	571 (19.5)	3.5	45 (7.9)	412 (72.2)	114 (20.0)

[1]Other genotype includes genotype 4, 5, or 6 or any combination of HCV genotypes

[2]Received abdominal imaging test such as ultrasound, CT, or MRI

Table 2

Bivariate logistic regression model showing the association between consistent HCC surveillance (at least 6-monthly HCC screening) and variables among HCV-infected cirrhotic patients, *N* = 2933

Variable	Unadjusted odds ratio	95% confidence interval
Age		
18–44	1.85	1.06–3.24
45–59	1.19	0.92–1.53
≥ 60	1.00	1.00
Sex		
Male	0.94	0.74–1.20
Female	1.00	1.00
Race/ethnicity		
Black	0.95	0.70–1.29
Asian/other/unknown	1.13	0.81–1.57
White	1.00	1.00
Type of insurance		
Medicaid	1.15	0.89–1.48
Medicare	1.23	0.83–1.83
Other/unknown	1.10	0.59–2.06
Private	1.00	1.00
Type of cirrhosis		
Decompensated cirrhosis	1.33	1.03–1.71
Compensated cirrhosis	1.00	1.00
Length of cirrhosis history/diagnosis (in years)[1]	0.87	0.81–0.94
Study site		
Portland, OR	2.01	1.39–2.89
Honolulu, HI	0.70	0.39–1.27
Detroit, MI	1.47	1.04–2.09
Danville, PA	1.00	1.00
HCV genotype[2]		
Genotype 1	0.73	0.50–1.07
Genotype 2	0.64	0.36–1.12
Genotype 3	1.00	1.00

[1] Year is a continuous variable

[2] Excludes other genotype (genotype 4, 5, or 6 or any combination of HCV genotypes) because of small sample size

Table 3

Multivariable logistic regression model showing the association between HCC surveillance (at least 6-monthly HCC screening) and variables among HCV-infected cirrhotic patients, $N = 2834$

Variable	Adjusted odds ratio[1]	95% confidence interval
Age		
18–44	2.01	1.07–3.74
45–59	1.26	0.95–1.66
≥ 60	1.00	
Sex		
Male	0.95	0.74–1.21
Female	1.00	
Race/ethnicity		
Black	0.94	0.67–1.32
Asian/Other/Unknown	1.29	0.91–1.82
White	1.00	
Type of insurance		
Medicaid	1.15	0.58–2.30
Medicare	0.98	0.46–2.10
Other/Unknown	0.92	0.47–1.81
Private	1.00	
Type of cirrhosis		
Decompensated Cirrhosis	1.39	1.06–1.81
Compensated Cirrhosis	1.00	
Length of cirrhosis history/diagnosis (in years)[2]	0.86	0.80–0.93
Study site		
Portland, OR	2.07	1.40–3.06
Honolulu, HI	0.76	0.41–1.42
Detroit, MI	1.62	1.08–2.44
Danville, PA	1.00	

[1] Model includes age, sex, race, type of insurance, type of cirrhosis, study site, period of cirrhosis diagnosis, and length of cirrhosis history/diagnosis

[2] Year is a continuous variable