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Hepatocellular Carcinoma and Viral Hepatitis in New York City

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Summary: Viral hepatitis is the most significant contributor to HCC in NYC. Improvement in viral hepatitis screening and treatment, as well as in HCC screening, is needed.

Abstract

Background: Hepatocellular carcinoma (HCC) incidence and mortality are increasing in the United States. Viral hepatitis infection is a primary risk factor for HCC. This study describes the relationship between viral hepatitis and HCC in New York City (NYC).

Methods: Viral hepatitis cases reported to the NYC Department of Health from 1999–2012 were matched to HCC cases diagnosed from 2001–2012 and reported to the New York State Cancer Registry. HCC cases were stratified by presence or absence of viral hepatitis. Demographic characteristics, factors associated with specific causes of death, and survival time were analyzed for all HCC cases.

Results: From 2001–2012, 8,827 NYC residents were diagnosed with HCC; 38.4% had hepatitis C (HCV) infection, 17.9% had hepatitis B (HBV) infection, and 2.2% had both infections. HCC patients were predominantly men (74.8%) and equally white non-Hispanic (28.6%) and Hispanic (28.9%). Those with HBV were primarily Asian/Pacific Islander (63.2%). The median survival time after HCC diagnosis for persons with HBV infection was 22.3 months, compared with 13.1 months for persons with HCV, and 6.9 months for non-infected persons. The five-year survival rate was 37.5% for those with HBV, 20.0% for those with HCV, 29.5% among coinfected individuals, and 16.1% for those with neither infection reported.

Conclusion: In NYC, most persons with HCC have viral hepatitis; the majority of viral hepatitis infections are due to HCV. Survival for persons with HCC differs widely by viral hepatitis status. This study highlights the importance of viral hepatitis prevention and treatment and HCC screening.

Introduction

Liver cancer, including hepatocellular carcinoma (HCC) and intrahepatic bile duct cancer, is an often fatal disease with increasing incidence and mortality in the United States (U.S.). Nationwide, liver cancer incidence increased on average by 4.0% per year and mortality by 2.7% per year between 2003 and 2012 [1]. This increase in incidence is alarming, as the five-year survival rate is estimated to be only 17% [2]. In 2015, liver cancer was the fifth leading cause of cancer-related death in men and the ninth leading cause in women in the U.S. [2] and is predicted to become the third leading cause of cancer-related deaths by 2030 [3].

HCC comprises more than three fourths of liver cancer cases [4]. Risk factors for HCC include hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection with cirrhosis, alcoholic liver disease, and non-alcoholic fatty liver disease (NAFLD) [5]. Viral hepatitis infection is the most common risk factor and may be present in approximately 60% of cases of HCC in the U.S. [6].

HCC screening guidelines exist for persons with HBV, HCV, or cirrhosis from any cause [7,8]. Thus, clinicians can implement recommended risk-reduction strategies (e.g., treatment for viral hepatitis infection, reduction in alcohol consumption, and weight reduction) with these persons and diagnose HCC early, thereby improving survival. When HCC is identified at an early stage, cure is possible through surgical resection, liver transplant, and other treatment modalities [5,8].

As has been true nationally, HCC incidence and mortality are increasing in New York City (NYC) [9]. However, the epidemiology of HCC in NYC, particularly its relationship with viral hepatitis, has not been described in the literature. Approximately 100,000 persons, or 1.2% of the NYC population, have HBV infection [10], while approximately 146,500 persons, or 2.4% of NYC residents 20 years of age and older, have HCV infection [11]. The majority of HBV and HCV infections are asymptomatic for years, thus many individuals are unaware of their infection and will not benefit from antiviral treatment and/or

screening for HCC. The aim of this study was to describe the relationship between HBV, HCV, HCC, and mortality in NYC.

Methods

Data sources: Data were extracted from the New York State Cancer Registry (NYSCR) and the NYC Department of Health and Mental Hygiene (DOHMH) Viral Hepatitis Surveillance Registry. New cancer diagnoses are reported to NYSCR primarily from hospitals or physicians; other reporting sources include autopsy reports and death certificates.

Cancer data: NYSCR staff selected HCC cases in NYC diagnosed from 2001–2012 using the following International Classification of Diseases for Oncology, 3rd Edition histology codes: 8000 (neoplasm, malignant), 8010 (carcinoma, not otherwise specified), 8170-8175 (hepatocarcinoma, fibrolamellar, scirrhous, spindle cell, clear cell, pleomorphic), or 8180 (combined HCC and cholangiocarcinoma) in conjunction with a primary site code of C220 (liver). Additional cancer registry variables included race/ethnicity, sex, age at HCC diagnosis, cancer stage at HCC diagnosis, zip code of residence at time of diagnosis, reporting source, vital status, and underlying cause of death for deceased individuals. Using the Surveillance, Epidemiology, and End Results (SEER) Summary Stage 2000 for cases diagnosed between 2001 and 2003 [12] and the Collaborative Stage derived SEER Summary Stage 2000 for cases diagnosed between 2004 and 2012 [13], cancer stage was reported as local, regional, distant, and unknown. Neighborhood poverty level was calculated as a proxy for socioeconomic status and was defined as the percentage of residents in a zip code with incomes below 100% of the federal poverty level [14]. Zip code poverty level was determined based on U.S. Census 2000 data for cases diagnosed 2000-2004, by the American Community Survey (ACS) 2007-2011 for cases diagnosed 2005-2009, by ACS 2008-2012 for cases diagnosed in 2010, and by ACS 2009-2013 for cases diagnosed 2011-2012. Neighborhood poverty level for each individual was determined based on his or her zip code at the time of HCC diagnosis.

NYSCR routinely links cancer cases with state death certificates and the National Death Index to obtain vital status and related death information. Deaths through 2012 were included in this study. Underlying cause of death was recorded using ICD-10 codes. Cause of death was grouped into seven categories for analysis: HCC, other liver disease, other cancer, cardiovascular disease, HIV/AIDS-associated, substance abuse-related, and all other causes (*see supplementary table 1 for ICD-10 categorization*).

Viral hepatitis data: The study used HBV and HCV cases reported to DOHMH from 1999–2012. Viral hepatitis reporting improved substantially starting in 1999; to include individuals first reported to DOHMH before 1999, they needed to have at least one additional report received in 1999 or later. All cases met the Centers for Disease Control and Prevention/Council of State and Territorial Epidemiologists' case definition for confirmed or probable chronic HBV infection, or for past or present HCV infection [15,16].

Data matching: The match of persons with HCC to viral hepatitis cases was conducted using Link Plus [17], a program routinely used by NYSCR staff employing a probabilistic algorithm to match individuals. Linkage variables included last name, first name, sex, birth date, and social security number. Link Plus matching was supplemented with manual review by NYSCR staff for borderline matches. The final de-identified dataset included all HCC cases diagnosed from 2001–2012 with HBV and HCV infection status. Ten cases where hepatitis infection was diagnosed after death were excluded.

Statistical Analysis: Descriptive analyses included examining the distribution of demographic and other characteristics of persons with HCC by viral hepatitis status (HBV mono-infection, HCV mono-infection, HBV/HCV coinfection, or neither infection). Comparisons of distributions between groups, using the neither infection group as the referent, were made using Wilcoxon 2-sample *t* tests for numeric variables and Chi-square tests for categorical variables, with a significance cut-off of p=0.01 to account for multiple comparisons.

Multivariable logistic regression was used to determine the odds of dying from specific causes of death among persons who died, comparing each viral hepatitis group with those with neither infection. Each cause of death was set as a binary outcome variable compared with all other causes. All models were adjusted for sex, age at HCC diagnosis, year of HCC diagnosis, cancer stage at diagnosis, race/ethnicity, and neighborhood poverty level. Models for death due to HCC or HIV/AIDS-related causes included significant interaction terms of disease stage by age at HCC diagnosis.

Kaplan-Meier survival analysis was used to calculate median survival time and survival probability for those with HCC, stratified by viral hepatitis status and cancer stage at diagnosis. Survival time was calculated from the date of HCC diagnosis to the date of death. Those alive as of December 31, 2012 were censored. The log-rank test with a Bonferroni correction to account for multiple comparisons was used to compare survival functions across groups.

A Cox proportional hazard model was used to quantify the risk of death in each viral hepatitis infection group compared with the neither infection group. The model adjusted for sex, age at HCC diagnosis, year of HCC diagnosis, cancer stage at diagnosis, race/ethnicity, and neighborhood poverty level. Due to an identified violation in the proportional hazards assumption for HCV infection, an interaction term between HCV and time was included in the model; hazard ratios for HCV were calculated separately at various time points. Survival analyses excluded HCC cases that were diagnosed by autopsy or death certificate only.

Statistical analysis was performed using SAS version 9.4 (SAS Institute; Cary, North Carolina). The NYC DOHMH and NYS DOH Institutional Review Boards approved the study.

Results

From 2001–2012, 8,827 NYC residents were diagnosed with HCC, and of those, 5,166 (58.5%) had a report of HBV, HCV, or both (*Table 1*). Most persons with HCC were men (74.8%), particularly among those with HBV mono-infection (85.2%). The median age at HCC diagnosis was 62 years, ranging from

55 years for HBV mono-infected persons to 68 years for non-infected persons. The majority of persons with HBV mono-infection were Asian/Pacific Islanders (63.2%), whereas persons with HCV mono-infection were most frequently Hispanic (35.0%) or black non-Hispanic (30.1%), and those with neither infection were mainly white non-Hispanic (36.5%) or Hispanic (32.0%).

While 41.4% of persons were diagnosed with HCC at a local stage, another 38.0% were diagnosed at a regional or distant stage (*Table 1*). Disease stage was not reported in one fifth of the cases. Persons with neither infection were less often diagnosed with HCC at a local stage and more often diagnosed with an unknown stage than those with any viral hepatitis infection. HCC cases with neither infection were more likely to be diagnosed during the beginning of the study period and via autopsy/death certificates.

A significantly greater proportion of individuals with HBV mono-infection (52%) and HCV mono-infection (56%) lived in neighborhoods with high or very high poverty compared with those with neither infection (47%) *(Table 1)*. When examining all residents with HCC within a given neighborhood poverty level, the proportion with HCV increased with increasing neighborhood poverty. Among persons with HCC living in low-poverty neighborhoods, 32% had HCV mono-infection. This proportion increased to 36% in medium-poverty neighborhoods and to 39% and 46% in high and very high poverty level neighborhoods, respectively (Cochran-Armitage test for trend, $p<0.001$). In contrast, approximately half (52%) of persons with HCC residing in low-poverty neighborhoods had neither infection reported.

HBV mono-infected persons died at the youngest age (median: 57 years) and persons with neither infection died at the oldest age (median: 70 years) (*Table 2*). The groups with viral hepatitis had significantly greater proportions of premature death (death before the age of 65 years [18]) than the non-infected group. HCC was listed as the underlying cause of death for 66.1% of those who died.

Among persons who died, those with HBV mono-infection were more likely to die of HCC than those with neither infection (aOR 1.30, 95% CI 1.04-1.62); the odds of dying from HCC did not differ for those with HCV mono-infection or HBV/HCV coinfection (*Table 3*). Persons with HCV mono-infection had

greater odds of dying of other liver disease compared with non-infected individuals, while non-infected individuals were more likely to die of cardiovascular diseases than those with HBV or HCV mono-infection.

Kaplan-Meier estimates revealed that persons without viral hepatitis had the shortest survival time after HCC diagnosis, while those with HBV mono-infection had the longest survival time (*Figure 1a*). Survival for each group was significantly different from that of almost all other groups (log-rank test, $p<0.001$), except for the HBV/HCV coinfected group compared with the HCV mono-infection group ($p=0.40$). The median survival time after HCC diagnosis was 6.9 months for persons with neither infection, 13.1 months for persons with HCV mono-infection, and 22.3 months for those with HBV mono-infection (*see supplementary table 2*). The probability of survival 60 months after diagnosis varied from 37.5% among those with HBV mono-infection to 16.1% among those with neither infection.

As expected, survival decreased with worsening stage of disease at diagnosis, regardless of infection status. Nevertheless, patients with HBV mono-infection continued to have longer survival than other groups for all disease stages (*Figure 1b-d*). For patients diagnosed with HCC at a local stage, median survival time was 94.5 months for HBV mono-infected individuals but only 28.1 months for HCV mono-infected individuals. Likewise, when diagnosed at a distant stage, median survival time was 3.7months for those with HBV mono-infection but 3.2 months for those with HCV mono-infection (*see supplementary table 2*).

The risk of death for persons with HBV continued to be smaller than for those with neither infection, even after adjusting for numerous covariates (aHR=0.81, 95% CI: 0.73-0.89). At six months after HCC diagnosis, there was no significant difference in the risk of death for HCV mono-infected persons compared with those with neither infection (aHR=0.95, 95% CI: 0.90-1.02). However, the relative hazard of death increased over time and was significantly larger five years after HCC diagnosis (aHR=1.34, 95%

CI 1.20-1.51). The risk of death for those with HBV/HCV coinfection was not significantly different from those with neither infection (*see supplementary Table 3*).

Discussion

Almost 60% of NYC residents with HCC had a viral hepatitis diagnosis; among those, 70% had HCV infection alone or with HBV, consistent with previous findings in the U.S. [6,19]. Of note, 41% of HCC patients were not reported with either HBV or HCV infection, highlighting the importance of other HCC risk factors such as alcohol use and metabolic syndrome [20]. HCC patients with viral hepatitis were more likely to be diagnosed at a local stage and less likely to have an unknown stage, suggesting a higher degree of medical care. However, the proportion of diagnoses at a local stage was less than 50% for all groups, indicating improvements are needed in screening for HCC risk factors and early diagnosis of HCC.

Persons with HCC often lived in neighborhoods with high or very high poverty, particularly among those with HCV mono-infection. Many risk factors for HCC, including HCV and HBV infection, alcoholism, obesity, and metabolic syndrome are also associated with low socioeconomic status [21]. Individuals who reside in neighborhoods with a high poverty rate might also have limited access to healthcare, which could limit access to viral hepatitis screening and treatment and HCC screening [22,23].

The survival probability for those with HCC was low, with a median survival time of only 10.9 months, consistent with previously reported median survival times of 6-20 months [24]. Given that early diagnosis of HCC improves survival and increases the probability of cure [2], these findings highlight the importance of screening and early treatment of HBV and HCV, as well as screening for HCC in persons with HBV or HCV infection or cirrhosis of any etiology [8,25,26].

Unfortunately, HCC screening in the U.S. is not occurring according to recommendations. One study found that among non-cirrhotic patients with chronic HBV, only 6.7% were appropriately screened (one ultrasound every six months) and 33.7% did not receive HCC screening at all [27]. In another study of

those with HCV and cirrhosis, fewer than 50% of patients received HCC surveillance in the first year following cirrhosis diagnosis and only 12% received ongoing surveillance as recommended [28]. In a retrospective study of patients diagnosed with cirrhosis, fewer than 20% of those who developed HCC had received regular screening [29]. To improve its use, HCC screening according to expert recommendations must be facilitated and covered by all health insurances.

HBV mono-infected individuals in this study had better survival than all other groups, a finding that persisted regardless of HCC stage at diagnosis. Even after adjusting for age at diagnosis, stage at diagnosis, and other factors, the hazard of death was lower for those with HBV compared with those with HCV or with neither infection. It is possible that persons with non-HBV HCC risk factors are more likely to have co-occurring advanced liver disease and/or cirrhosis before developing HCC. Unlike with HBV, virtually all cases of HCV-related HCC occur only after cirrhosis develops [30]. Non-viral HCC risk factors, including alcoholic liver disease and NAFLD, also increase the risk for cirrhosis [31]. The presence of cirrhosis has been found to limit HCC treatment options, potentially reducing survival rates [32]. Our study found that decedents with HCV had greater odds of dying from other liver diseases, whereas decedents with HBV had greater odds of dying from HCC.

There are several limitations to this study. First, the number of viral hepatitis cases in the study population might be underestimated due to undiagnosed infections [33], unreported infections, especially early in the study period before routine electronic laboratory reporting, under-matching of the viral hepatitis and cancer databases, and because some patients may have been diagnosed outside of NYC and thus not reported to DOHMH. Such misclassification would overestimate the number of non-infected persons, resulting in a dilution of the associations observed. Misclassification is also an issue when analyzing cause of death because death certificates can be unreliable [34]. This could affect the distributions of specific cause of death observed and emphasizes the need for improved death certificate accuracy. Additionally, many individuals had an unknown tumor stage at diagnosis, which may be relevant if lacking cancer stage information is related to other factors associated with survival. It is unknown

whether patients had other HCC risk factors, were screened for HCC, or received viral hepatitis and/or HCC treatment. Also unknown was patient HIV status, which influences both on the occurrence of HCC and survival among those with HCV infection [35,36]. Despite the above, this study provides a unique perspective on HCC in an urban setting with high viral hepatitis prevalence.

In this study, viral hepatitis was the largest contributor to HCC in NYC. Though important for those with HBV and cirrhosis from any cause, screening for HCC has its limitations. There is limited evidence for its use in persons with non-infectious risk factors (e.g. obesity, metabolic syndrome), a reduced ability of ultrasound to detect early stage HCC or detect HCC in obese patients, and logistical difficulties for providers in implementing screening procedures as recommended [37,38]. Therefore, efforts targeted at preventing and treating HBV and HCV infections and preventing and managing obesity, excess alcohol use, and metabolic syndrome will be key to reducing the morbidity and mortality associated with HCC. In particular, highly effective and curative HCV treatments may reduce liver damage and subsequent HCC in HCV-infected persons, and treatment for all those with HCV should be a priority.

To further these efforts, health department activities to increase screening, linkage to care, and treatment for those with HCV, both through outreach and direct service programs, should continue to be supported with city, state, and federal funds. Additionally, advocacy efforts to pressure drug manufacturers to make HCV medications affordable and for health insurers to cover the medications without restriction must continue if access to treatment is to become widespread. While in some ways more difficult, prevention of obesity and metabolic syndrome must also remain a priority. Luckily, extensive attention has been given to the obesity epidemic in the U.S., and DOHMH has been aggressive in implementing system-wide policies to address root causes of obesity in the city. Such policies and other innovative programs will be vital in reducing the burden of HCC.

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Table 1: Descriptive statistics of individuals with hepatocellular carcinoma, by hepatitis infection status, New York City, 2001–2012.

	HBV mono-infection n (%)	**HCV mono-infection n (%)**	**HBV/HCV coinfection n (%)**	**Neither infection n (%)**	**Total n (%)**
N (% of total)	1577 (17.9)	3392 (38.4)	197 (2.2)	3661 (41.5)	8827
Male sex	1344 (**85.2**)	2526 (**74.5**)	163 (**82.7**)	2574 (70.3)	6607 (74.8)
Age at HCC diagnosis, median (IQR)	**55** (46-65)	**61** (55-68)	**57** (50-63)	68 (58-77)	62 (55-72)
Race/ethnicity					
White non-Hispanic	155 (**9.8**)	987 (**29.1**)	53 (**26.9**)	1337 (36.5)	2532 (28.6)
Black non-Hispanic	283 (18.0)	1022 (**30.1**)	44 (22.3)	691 (18.9)	2040 (23.1)
Asian/Pacific Islander non-Hispanic	997 (**63.2**)	178 (**5.3**)	41 (20.8)	440 (12.0)	1656 (18.8)
Hispanic	139 (**8.8**)	1187 (**35.0**)	57 (28.9)	1170 (32.0)	2553 (28.9)
Other/unknown race	3 (0.2)	18 (0.5)	2 (1.0)	23 (0.6)	46 (0.5)
Cancer stage at diagnosis					
Local	704 (**44.6**)	1584 (**46.7**)	97 (**49.2**)	1267 (34.6)	3652 (41.4)
Regional	349 (22.1)	794 (23.4)	38 (19.3)	770 (21.0)	1951 (22.1)
Distant	287 (18.2)	442 (**13.0**)	28 (14.2)	646 (17.7)	1403 (15.9)
Unknown	237 (**15.0**)	572 (**16.9**)	34 (**17.3**)	978 (26.7)	1821 (20.6)
Year of HCC diagnosis					
2001–2004	420 (**26.6**)	593 (**17.5**)	47 (**23.9**)	1380 (37.7)	2440 (27.6)
2005–2008	588 (**37.3**)	1233 (**36.4**)	74 (37.6)	1177 (32.2)	3072 (34.8)
2009–2012	569 (**36.1**)	1566 (**46.2**)	76 (38.6)	1104 (30.2)	3315 (37.6)
Reporting source for HCC diagnosis					

Hospital/Physician reports[a]	1556 (**98.7**)	3314 (**97.7**)	193 (**98.0**)	3471 (94.8)	8534 (96.7)
Autopsy/death certificate only	13 (**0.8**)	62 (**1.8**)	4 (2.0)	166 (4.5)	245 (2.8)
Other[b]	8 (0.5)	16 (0.5)	0 (0)	24 (0.7)	48 (0.5)
Neighborhood poverty level[c]					
Low (<10% below poverty)	211 (**13.4**)	461 (**13.6**)	28 (14.2)	745 (20.4)	1445 (16.4)
Medium (10 to <20%)	552 (35.0)	1037 (**30.6**)	73 (37.1)	1202 (32.8)	2864 (32.5)
High (20 to <30%)	548 (**34.8**)	962 (**28.4**)	50 (25.4)	932 (25.5)	2492 (28.2)
Very high (≥30%)	265 (**16.8**)	931(**27.5**)	46 (23.4)	781 (21.3)	2023 (22.9)

Boldface values denote statistically significant differences in each group compared with non-infected individuals using Wilcoxon two-sample t-test or χ^2 test ($p<0.01$). Percentages may not add up to 100% due to rounding.

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus

[a] Includes reports from hospital inpatient units, hospital outpatient units and surgery centers, and private medical practices/physicians' offices.

[b] Includes radiation treatment centers, medical oncology centers, and laboratory reports.

[c] Three individuals were missing zip code of residence, so zip code-based poverty level could not be determined.

Table 2: Death-related statistics for individuals with hepatocellular carcinoma who died, by hepatitis infection status, New York City, 2001–2012.

	HBV mono-infection (n=932)	**HCV mono-infection (n=2446)**	**HBV/HCV coinfection (n=137)**	**Neither infection (n=2934)**	**Total (n=6449)**
Age at HCC diagnosis, median (IQR)	**55** (47-66)	**61** (55-69)	**56** (50-63)	69 (59-78)	63 (55-74)
Age at death, median (IQR)	**57** (48-66)	**62** (56-70)	**58** (51-65)	70 (60-79)	64 (56-75)
Premature death (<65 years), n (% of deaths)	658 (**70.6**)	1465 (**59.9**)	103 (**75.2**)	1020 (34.8)	3246 (50.3)
Cause of death, n (% of deaths)					
HCC	680 (**73.0**)	1555 (63.6)	87 (63.5)	1940 (66.1)	4262 (66.1)
Other liver disease[a]	63 (6.8)	327 (**13.4**)	19 (**13.9**)	168 (5.7)	577 (9.0)
Other cancer[b]	101 (10.8)	211 (**8.6**)	5 (**3.7**)	396 (13.5)	713 (11.1)
Cardiovascular disease	32 (**3.4**)	102 (**4.2**)	5 (3.7)	241 (8.2)	380 (5.9)
HIV/AIDS-associated	14 (1.5)	69 (**2.8**)	10 (**7.3**)	23 (0.8)	116 (1.8)
Substance abuse	1 (0.1)	15 (0.6)	0 (0)	10 (0.3)	26 (0.4)
Other[c]	41 (4.4)	167 (6.8)	11 (8.0)	156 (5.3)	375 (5.8)

Boldface values denote statistically significant differences in each group compared with non-infected individuals using Wilcoxon two-sample t-test or χ^2 test ($p<0.01$). Percentages may not add up to 100% due to rounding.

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; HCC, hepatocellular carcinoma.

[a] Other liver disease includes alcoholic liver disease, alcoholic cirrhosis, cirrhosis/fibrosis, and liver failure.

[b] Common other cancers include secondary liver cancer, lung cancer, pancreatic cancer, and colon cancer.

[c] Other common listed causes of death include hepatitis B or C (acute or chronic), respiratory disease, and diabetes mellitus.

Table 3: Associations between cause of death among those with hepatocellular carcinoma and reported hepatitis infection status (compared with neither infection), New York City, 2001–2012.

Underlying Cause of Death[a]	HBV mono-infection			HCV mono-infection			HBV/HCV coinfection		
	aOR[b]	95% CI	p-value	aOR[b]	95% CI	p-value	aOR[b]	95 % CI	p-value
HCC	**1.30**	**1.04-1.62**	**0.02**	0.97	0.84-1.11	0.64	0.92	0.61-1.39	0.70
Other liver disease	0.80	0.54-1.21	0.29	**1.83**	**1.45-2.32**	**<0.01**	1.44	0.78-2.66	0.25
Other cancer	0.89	0.65-1.21	0.46	**0.68**	**0.55-0.85**	**<0.01**	**0.28**	**0.10-0.76**	**0.01**
Cardiovascular disease	**0.55**	**0.33-0.91**	**0.02**	**0.65**	**0.48-0.86**	**<0.01**	0.86	0.34-2.18	0.75
HIV/AIDS-associated	2.05	0.91-4.66	0.09	**2.80**	**1.56-5.05**	**<0.01**	**6.21**	**2.46-15.69**	**<0.01**
Substance abuse	0.30	0.04-2.61	0.28	1.19	0.47-3.01	0.71	-	-	-
Other	0.89	0.57-1.39	0.62	1.26	0.95-1.65	0.10	1.74	0.87-3.49	0.12

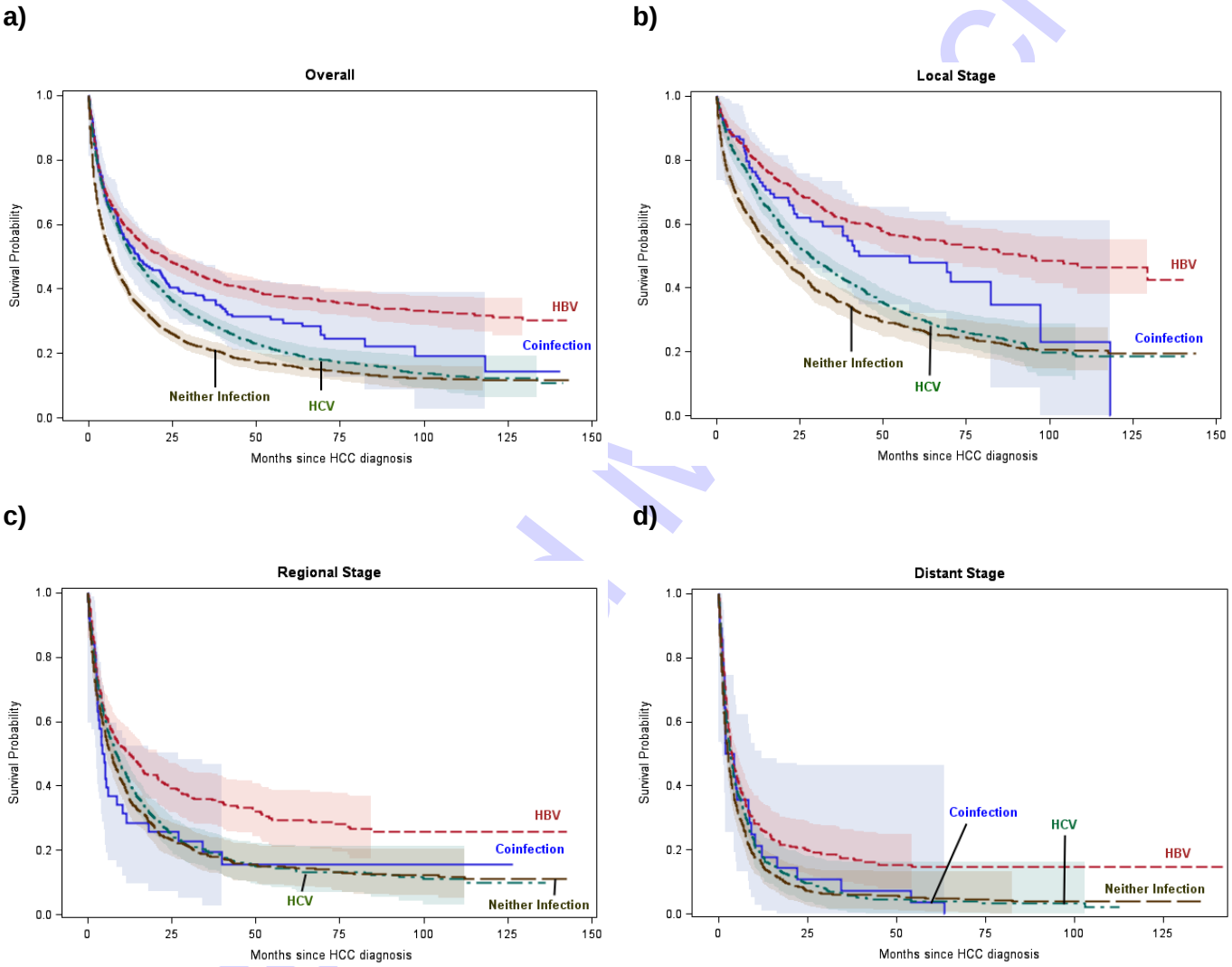
Boldface values denote statistical significance ($p<0.05$).

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; HCC, hepatocellular carcinoma.

[a] Odds ratios calculated comparing the odds of each specific underlying cause of death to all other listed causes.

[b] Logistic regression model adjusted for sex, race, age at HCC diagnosis, year of HCC diagnosis, cancer stage at diagnosis, and neighborhood poverty level. Models for liver cancer and HIV/AIDS-associated causes of death also include an interaction term for stage and age at HCC diagnosis.

Figure 1: Kaplan–Meier survival curves for time since hepatocellular carcinoma diagnosis, by viral hepatitis status (a) and by viral hepatitis status and cancer stage at hepatocellular carcinoma diagnosis (b-d), New York City, 2001––2012. Survival curves include 95% Hall-Wellner confidence bands.



Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; HCC, hepatocellular carcinoma.