

Deaths among People with Hepatitis C in New York City, 2000 – 2011

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Summary: Analysis indicates that HCV-infected adults were at increased risk of dying prematurely, particularly from liver disease, HIV/AIDS, and drug use. Improved testing and treatment is needed to reduce premature death from HCV-related causes.

Abstract

Background: Infection with hepatitis C virus (HCV) increases the risk of death from liver and non-liver related diseases. Co-infection with HIV further increases this risk.

Methods: Surveillance data (2000-2010) and mortality data (2000 – 2011) maintained by the New York City Department of Health and Mental Hygiene (DOHMH) were deterministically cross-matched. Factors associated with and causes of death among HCV-infected adult decedents were analyzed.

Results: Between 2000 and 2011, 13,307 HCV mono-infected adults died, and 5,475 adults co-infected with HCV/HIV died. Decedents with HCV mono-infection were more likely to have died of liver cancer (OR=9.2), drug-related causes (OR=4.3), and cirrhosis (OR=3.7) as compared with persons with neither infection. HCV/HIV co-infected decedents were more likely to have died of liver cancer (OR=2.2) and drug-related causes (OR=3.1) as compared with persons with neither infection. Among co-infected decedents, 53.6% of deaths were attributed to HIV/AIDS; and 94% of deaths occurred prematurely, before age 65. Among persons with HCV who died, over half died within three years of a hepatitis C report to DOHMH.

Conclusion: HCV-infected adults were at increased risk of dying and of dying prematurely, particularly from conditions associated with HCV, such as HIV/AIDS or drug use. The short interval between HCV report and death suggests a need for earlier testing and improved treatment.

Background

An estimated 3.4 to 4.9 million people are living with chronic hepatitis C virus (HCV) infection in the United States (US) [1]. HCV-diagnosed persons have annual all-cause medical costs that are nearly twice that of persons without HCV [2], with total costs ranging from \$4.3 to \$8.2 billion in 2011[3]. Studies suggest that HCV infection leads to premature death [4-7]. Persons born between 1945 and 1965 have the highest prevalence of HCV [8], and approximately 75% of HCV-related deaths between 1999 and 2007 occurred among persons in this birth cohort, over 20 years after initial infection [6]. The number of deaths attributed to HCV has increased in recent years as this cohort ages, surpassing deaths from HIV nationally [6]. Without greater efforts to test and treat, the number of deaths per year is predicted to reach 36,100 between 2030 and 2035 [9], however, recent developments have increased the potential to address this disease. A point-of-care antibody test, reflex RNA testing and improved antiviral treatments for HCV have become available, and treatment is expected to continue to improve [10-13]. These developments mean that people with HCV can be more easily diagnosed and cured, potentially reducing premature deaths.

Among persons chronically infected with HCV, at least 20% develop cirrhosis within 20 years, and, of those, 20% develop hepatocellular carcinoma [14]; both conditions are associated with premature death [7]. Because HIV and HCV are blood-borne viruses that share transmission routes, co-infection is common [15]. HIV accelerates progression of liver fibrosis in people with HCV infection and increases the risk of death [16, 17]. Premature death among HCV-infected persons is also attributed to substance use, particularly injection drug use (IDU) [5, 18]. An estimated 146,500 New York City (NYC) residents have chronic HCV, making it one of the most heavily impacted areas in the country [19]. Though no formal estimates exist, it is assumed

that many are undiagnosed, and only a small proportion are successfully treated each year [2, 4]. Mortality in persons with HCV in NYC has not been studied at a population level.

The aims of this study were to determine the impact of HCV on mortality in NYC and to understand causes of death in people with HCV. These findings can contribute to improving public health activities targeted to the HCV-infected and HCV/HIV co-infected populations, and contribute to an increased awareness among providers of improved diagnosis and treatment for HCV.

Methods

Data Matching

In 2010, the NYC Department of Health and Mental Hygiene (DOHMH) implemented CDC's Program Collaboration and Service Integration (PCSI) initiative to increase data integration and describe the interaction between infectious diseases in NYC [20]. As part of this initiative, a deterministic cross-match of disease surveillance registries was conducted, including reports of HCV, hepatitis B (HBV), HIV, tuberculosis (TB) and sexually transmitted diseases (STDs) from 2000-2010, and vital statistics mortality data from 2000-2011, the methods of which have been described elsewhere [21]. The final de-identified analytic dataset included all deaths reported in NYC between 2000 - 2011, all persons reported with HCV before December 31, 2010 and alive as of January 1, 2000, and all persons reported with HIV before December 31, 2010 and alive as of January 1, 2000. This project was determined by the NYC DOHMH Institutional Review Board to be an epidemiologic investigation not subject to institutional board review.

Analytic Population

For this analysis, HCV cases were restricted to those persons whose first positive antibody test or positive RNA test was reported to DOHMH between 2000 and 2010. HCV-infected persons reported before 2000 were excluded because of variability in reporting prior to 2000 [19]. For analysis of the proportion of persons who died within three years of HCV report, persons first reported after 2008 were censored. Though many persons in the HCV registry have only a positive antibody result and no RNA result confirming current infection, for the purposes of this analysis, we refer to all HCV-reported persons as HCV-infected. A HCV/HIV co-infected case was defined as a person reported to DOHMH with HCV between 2000 and 2010 who also had an HIV report at any time before the end of 2010. Though the date of first report with HCV or HIV does not necessarily represent the date of diagnosis, it is the only available starting point using surveillance data. In the reference group of individuals with neither infection that died, those with HIV mono-infection were excluded, as were persons with HCV reports prior to 2000.

Cause of Death Categorization

DOHMH collects information about all deaths that occur in NYC. Death certificates are completed by clinicians, medical examiners, and funeral directors. More than 93% are submitted electronically through the Electronic Death Registration System (EDRS), in place since 2005. Death certificates include demographic information, cause of death, and date of death. Since 1999, DOHMH has used ICD-10 to classify causes of death. Underlying cause for every death reported between 2000 and 2011 was examined using ICD-10 codes and grouped into nine categories for analysis: cardiovascular-related (I00-I01, I05-I06, I09-I13, I21, I24-I28, I31, I33-

35, I38, I40, I42, I44, I46, I48-I51, I60-I64, I67, I69-I74, I77-I78), non-liver cancer (C01-C02, C06-C11, C14-C21, C25-C26, C32, C34, C38, C41, C43-C46, C48-C57, C60-C62, C64, C67-C68, C71, C73-C74, C76, C78-C85, C88, C90-C93, C95, C97), diabetes/obesity (E10-E11, E14, E66), liver cancer (C22), hepatitis C (B17.1 and B18.2), cirrhosis (K70, K73-K74), HIV/AIDS (B20-B24), drug-related (F11-F19, X40-X44, X60-X64, Y10-Y14, X85), and other, including all other viral hepatitis codes (B15-B19) and all other recorded ICD-10 codes.

Statistical Analysis

To describe causes of death among adults, we restricted analyses to persons who died at age 18 or older. Race/ethnicity and sex were obtained from vital statistics death registry records, as these variables are more complete in the death registry than in the HCV registry. Age at first HCV report was obtained from the HCV registry, and co-infection with HIV was determined via the cross-match of data from the HCV and HIV surveillance registries. Median age at HCV report, at death, and for each cause of death were compared using Wilcoxon median two-sample t-test. We used chi-square to compare differences in the proportion that died prematurely (defined using the common standard as death before the age of 65 [22]) and the proportion who died within three years of HCV report. Age at death, age at each cause of death, and proportion that died prematurely were compared between those with either reported HCV mono-infection or HCV/HIV co-infection and those with neither disease; age at HCV report and the proportion that died prematurely were compared between those with mono-infection and those with co-infection. A separate multivariable logistic regression model was constructed, using a binary outcome variable for each cause of death. A three-level variable for reported infection status (HCV mono-infected, HCV/HIV co-infected, neither infection) was used to determine the associations between cause of death and infection status, with neither infection as the reference group. All

models controlled for age at death, race/ethnicity, sex, and year of death. Lastly, quartiles of age at death were calculated using the distribution of age at death for all HCV reported persons to depict trends in each cause of death by age group. Statistical significance was defined as $p < 0.05$. All analyses were conducted using SAS 9.2., Cary, NC, USA.

Results

Age at death

Between 2000 and 2010, 128,444 people were reported with HCV in NYC, 18,291 (14%) of whom had also been reported with HIV. Of 110,153 persons with HCV mono-infection, 13,307 died between 2000 and 2011, and 8,525 (64.1%) of these died prematurely (**Table 1**, **Table 2**). Of those HCV/HIV co-infected, 5,475 died between 2000 and 2011 and 5,146 (94.0%) were premature. In contrast, of 619,254 adult deaths recorded in NYC with neither disease, 156,499 (25.3%) were premature. Over half of decedents died within three years of HCV report; the difference between the mono-infected and co-infected groups was not statistically significant (**Table 2**).

Persons with HCV mono-infection died at a significantly younger age (median 60.0 years) than those with neither infection (median 78.0 years) (**Table 2**). Persons with HCV/HIV co-infection died at a significantly younger age (median 52.0 years) than the HCV mono-infected and those with neither infection. HCV/HIV co-infected persons were reported with HCV at a significantly younger age (median 48.8 years) than the HCV mono-infected (median 56.9 years).

Causes of death

Of the disease categories examined, persons with neither infection were most likely to die of cardiovascular causes (46.6%) and non-liver cancer (23.7%) (**Table 3**). Decedents with HCV mono-infection died from cardiovascular causes (26.3%), followed by non-liver cancer (16.1%),

hepatitis C (11.6%), liver cancer (8.7%) and drug-related causes (7.6%). The greatest proportion of persons HCV/HIV co-infected died from HIV/AIDS related causes (53.6%) (**Table 3**).

Bivariate analysis indicated that both the HCV mono-infected and co-infected were significantly more likely to die of HCV, liver cancer, cirrhosis, and drug-related causes, and less likely to die of cardiovascular diseases and non-liver cancers than those with neither infection (**Table 3**).

The adjusted odds of death for HCV mono-infected and HCV/HIV co-infected decedents were lower for cardiovascular-related causes, non-liver cancers, and diabetes/obesity in comparison to those with neither infection ($p < .05$ for all comparisons) (**Table 4**); however, this is because these two groups were more likely to die at younger ages of other causes (**Figures 1-3**). HCV mono-infected persons had significantly higher odds of dying of liver cancer (OR=9.2), drug-related causes (OR=4.3), and cirrhosis (OR=3.7) as compared with persons with neither infection ($p < .05$ for all comparisons) (**Table 4**). HCV/HIV co-infected persons had significantly higher odds of dying of liver cancer (OR=2.2) and drug-related causes (OR=3.1) ($p < 0.05$ for all comparisons) than decedents with neither infection. The magnitude of the associations between death due to liver cancer or drug-related causes and HCV mono-infection was higher than the magnitude of the associations between these causes of death and HCV/HIV co-infection.

The age patterns of HCV-related deaths for these eight leading causes followed different trends for persons without HCV or HIV, those with HCV only, and those co-infected with HCV/HIV. Among adults with neither infection, non-liver cancers and cardiovascular causes were the leading causes of death in all age categories; drug-related causes accounted for 16.6% of deaths in the youngest quartile but declined with increasing age (**Figure 1**).

Among HCV mono-infected adults, drug-related causes were the leading cause of death in the youngest quartile, representing almost one-third of deaths (32.9%) (**Figure 2**). In the two

middle age quartiles HCV-related causes (comprised of HCV, liver cancer and cirrhosis) were responsible for over one-third of deaths, surpassing all other causes. Cardiovascular causes were responsible for the greatest proportion of deaths in the oldest quartile (45.7%). The median ages at death for those reported with HCV mono-infection was lower as compared with those with neither disease for all causes, with the exception of drug-related causes (**Table 5**).

Among persons with reported HCV/HIV co-infection, HIV/AIDS related causes were responsible for the greatest proportion of deaths in all age categories, declining from 65.4% in the youngest quartile to 41.2% in the oldest quartile (**Figure 3**). Drug-related causes accounted for 14.2% of the youngest age quartile, declining with age. Cardiovascular causes, non-liver cancers and liver-related causes increased with age, but all represented less than one-third of deaths. The median ages at death for those reported with HCV/HIV co-infection were lower as compared with those with neither disease for all causes, with the exception of drug-related causes and HIV/AIDS (**Table 5**).

Discussion

These findings suggest that there is much work to be done to improve outcomes for people with HCV in NYC. The findings are consistent with prior studies showing that HCV-infected adults are at increased risk of premature death compared with persons without HCV infection, and that the HIV co-infected are at exceptionally high risk of premature death [4-7]. Though HIV co-infected persons were reported with HCV at a younger age, a greater proportion of those who were mono-infected died within three years of HCV report. The large proportion of deaths within three years in the HCV mono-infected group may indicate that, for many, testing for HCV occurs only when they present with symptoms, as HCV is often asymptomatic

until significant liver damage has occurred [4, 14]. This is supported by studies that have found that between 28-75% of persons with HCV in the US do not know they are infected, and many of those who do are not receiving optimal medical management [23, 24].

The leading causes of death overall in both the mono-infected and co-infected groups were extra-hepatic, as previous studies have found [4-6]. Given that advanced liver disease can cause a wide range of systemic problems [25], deaths from extra-hepatic causes may also be related to HCV infection. Among co-infected persons, HCV may play a role in death even when not listed as the underlying cause, as national coding guidelines specify that a person with HIV be listed as dying from HIV/AIDS, regardless of other HCV or chronic infections being present. Co-infected persons died from liver-related causes at younger ages than persons with HCV mono-infection, supporting previous evidence of faster progression of liver disease in persons with HIV [16, 17].

Deaths from drug-related causes were highest in the youngest age quartile, surpassing all other causes of death for the HCV mono-infected group, as has been noted in other studies. [5] HCV treatment programs should incorporate overdose prevention and drug treatment, including buprenorphine prescription, into their programs to prevent premature deaths [26]. Similarly, harm reduction and drug treatment service providers are uniquely positioned to provide services that prevent new HCV infections. This finding also reinforces the need for clinicians to ask about current and past drug use and connect patients to services that have been proven to prevent premature death from drug-related causes.

To decrease mortality for people with HCV and decrease the proportion of people with HCV who die within three years of diagnosis, improvements in testing, care and treatment are needed. The younger age at HCV report in the co-infected group suggests that having an HIV

diagnosis may prompt HCV testing, as is recommended [27] and, therefore, identification of the co-infected persons with HCV occurs slightly earlier, though not early enough to impact mortality. Despite the availability of up-to-date guidelines regarding HCV testing, a national study found that 42% of primary care physicians were unfamiliar with these guidelines; thus, they may be less likely to identify HCV infection their patients [28]. Implementing recommendations to test persons born between 1945 and 1965 [8], offering HCV antibody and RNA testing in primary care settings, using point-of-care antibody testing and RNA reflex testing [10], and integrating HCV testing and treatment in high-risk settings could improve outcomes by identifying individuals with HCV at an earlier stage when steps such as limiting alcohol consumption to reduce risk of cirrhosis can be taken, and when treatment may be more effective [29]. This has been done successfully in methadone programs [30] and correctional settings [31].

With antiviral therapy, it is possible to cure most patients of HCV infection; cure is associated with decreases in all-cause and hepatitis-related mortality [32, 33]. Though barriers to accessing care remain and treatment completion rates are low [34, 35], recent improvements in HCV treatment and more expected in the coming years [11-13] will reduce barriers and more people may be cured. Even in the absence of treatment, earlier diagnosis is crucial, as physicians can promote liver health and prevent liver damage, for example through alcohol reduction counseling and vaccination against hepatitis A and B [29].

There are limitations to our analysis. Using the underlying cause of death recorded on the death certificate to ascribe cause-specific mortality may lead to potential misclassification of cause of death and bias towards some causes of death [36], e.g., HIV/AIDS. In addition, DOHMH vital statistics data only capture deaths occurring in NYC. Deaths that occurred out of

jurisdiction were not captured, potentially underestimating the actual number of deaths. There are two additional limitations related to the use of HCV surveillance data. First, HCV surveillance may capture people who are not currently infected with HCV, because 15-25% of people that are antibody positive are RNA negative, either because of a resolved infection or a false-positive antibody result [1, 37]. Second, we identified some deaths due to HCV and HIV/AIDS that did not match to a HCV or HIV report in DOHMH surveillance registries. We did not add these individuals to the HIV or HCV categories, thus under-counting the infected population and the number of deaths from HIV/AIDS and HCV among persons with these diseases.

This analysis also has several strengths. It was the first population level analysis of cause-specific mortality and HCV in NYC. The number of years of data allowed for a large sample size, which strengthens the findings. Many previous studies of HCV and mortality were limited to specific populations or cohorts [4, 16, 38]. The findings will inform DOHMH activities working with community providers to improve testing and treatment for HCV, and improve outcomes for both HCV mono-infected and HCV/HIV co-infected persons. Further, matching surveillance registries with vital statistics mortality data may be replicable by other health departments to better understand their local patterns HCV mortality.

Identifying HCV infected persons earlier and linking them to comprehensive care and treatment services, and reducing new infections and preventing drug-related deaths through harm reduction is likely to have long and short-term benefits for reducing premature mortality and HCV-associated healthcare costs. The 2011 US Department of Health and Human Services Action Plan for the Prevention, Care and Treatment of Viral Hepatitis and the 2010 Institute of Medicine report both highlight the need to educate providers and communities; improve testing,

care and treatment; improve surveillance and prevent new infections and mortality due to injection drug use [23, 29]. These efforts may reduce the number of infections and improve outcomes for those living with HCV. It is important to continue to track mortality among people with HCV to assess changes in age at death and causes of death, as these important developments in the public health response to HCV unfold.

NOES

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Figure Legends

Figure 1. Causes of death by quartile of age at death for all decedents without a report of HCV or HIV, NYC, 2000-2011

Note: Excludes other category and HIV/AIDS; liver-related includes liver cancer, cirrhosis and HCV.

Figure 2. Causes of death by quartile of age at death for all decedents reported with HCV mono-infection, NYC, 2000-2011.

Note: Excludes other category and HIV/AIDS; liver-related includes liver cancer, cirrhosis and HCV.

Figure 3. Causes of death by quartile of age at death for all decedents reported with HCV/HIV co-infection, NYC, 2000-2011.

Note: Excludes other category; liver-related includes liver cancer, cirrhosis and HCV.

Table 1. Demographic characteristics of decedents, age 18 years and older, without HCV or HIV, HCV mono-infected and HCV/HIV co-infected between 2000-2011, NYC

	Neither infection		HCV mono-infected		HCV/HIV co-infected	
	N	%	N	%	N	%
Total	619,254		13,307		5,475	
Male	291,852	47.1	8,639	64.9	3,885	71.0
Race/ethnicity						
White	337,383	54.5	4,317	32.4	847	15.5
Black	149,439	24.1	4,677	35.1	2,534	46.3
Hispanic	90,456	14.6	3,713	27.9	1,971	36.0
Asian/Pacific Islander	31,831	5.1	365	2.7	17	0.3
Other/unknown	10,145	1.6	235	1.8	106	1.9

Table 2. Median age at first report of HCV, age at death, proportion that died within 3 years of report, and proportion that died prematurely (before the age of 65) comparing decedents without HCV or HIV, HCV mono-infected and HCV/HIV co-infected between 2000-2011, NYC

	Neither infection	HCV mono-infected	HCV/HIV co-infected
N	619,254	13,307	5,475
Age at HCV report			
Median (IQR)	-	56.9 (48.2-65.6)	48.8 (43.7-54.0)
Age at death			
Median (IQR)	78.0 (67-89.1)	60.0 (51.6-68.4)	52.0 (46.8-57.3)
Proportion that died within 3 years of HCV report ^a			
Percent	-	52.6%	51.9%
Proportion died prematurely (<65 years)			
Percent	25.3%	64.1%	94.0%

*Bold denotes statistically significant difference between groups using Wilcoxon median two-sample t-test to compare group medians and chi square to compare proportions

^a Includes individuals reported with HCV between 2000-2008, who contributed at least 3 years

Table 3. Causes of death among adult HCV mono-infected and HCV/HIV co-infected decedents and decedents with neither disease, 2000-2011, NYC

	Neither infection		HCV mono-infected		HCV/HIV co-infected	
	N	%	N	%	N	%
N	619,254		13,307		5,475	
Cardiovascular	288,797	46.6%	3,496	26.3%	568	10.4%
Non-liver cancers	147,016	23.7%	2,141	16.1%	425	7.8%
Other	142,409	23.0%	2,794	21.0%	577	10.5%
Diabetes/obesity	21,102	3.4%	500	3.8%	61	1.1%
Drug-related	8,089	1.3%	1,008	7.6%	517	9.4%
Liver Cancer	5,222	0.8%	1,159	8.7%	138	2.5%
Cirrhosis	5,026	0.8%	645	4.9%	86	1.6%
Hepatitis C	1,344 ^a	0.2%	1,547	11.6%	166	3.0%
HIV/AIDS	249 ^b	0.04%	17 ^b	0.1%	2,937	53.6%

*Bold denotes statistically significant differences using chi-square tests (p<.05)

^a Persons that died of hepatitis C may not have been reported to the NYC DOHMH, or potentially were not captured by the deterministic data match

^b Persons that died of HIV/AIDS may not have been reported to the NYC DOHMH, or potentially were not captured by the deterministic data match

Table 4. Associations* between cause-specific deaths and infection status in NYC, 2000-2011

	HCV mono-infected vs. neither		HCV/HIV co-infected vs. neither	
	OR	95% CI	OR	95% CI
Liver cancer	9.2	8.6, 9.9	2.2	1.9, 2.7
Drug-related	4.3	4.0, 4.6	3.1	2.9, 3.5
Cirrhosis	3.7	3.4, 4.0	0.7	0.6, 1.0
Diabetes/obesity	0.8	0.8, 0.9	0.2	0.2, 0.3
Cardiovascular	0.7	0.7, 0.7	0.3	0.3, 0.4
Non-liver cancer	0.5	0.5, 0.5	0.2	0.2, 0.2

*Logistic regression model adjusted for age at death, race/ethnicity, sex and year of death

Bold denotes statistical significance ($p < .05$).

Table 5. Median age at death by cause, comparing decedents without HCV or HIV, HCV mono-infected and HCV/HIV co-infected, NYC 2000-2011

	Neither infection	HCV mono-infected	HCV/ HIV Co-infected
N	619,254	13,307	5,475
Median (IQR)			
Cardiovascular	82.0 (73.4-90.6)	64.3 (54.6-74.1)	55.0 (50.0-60.0)
Non-liver cancers	72.5 (62.7-82.3)	61.7 (54.2-69.3)	55.2 (50.4-60.1)
Other	77.0 (62.7-91.4)	59.5 (50.6-68.4)	53.3 (48.1-58.6)
Diabetes/obesity	73.9 (63.4-84.4)	61.3 (53.0-69.6)	55.6 (51.7-59.5)
Drug-related	44.0 (36.3-51.7)	49.5 (43.4-55.7)	49.1 (43.8-54.4)
Liver cancer	70.0 (60.1-80.0)	62.2 (55.0-69.5)	56.4 (51.2-61.6)
Cirrhosis	60.0 (50.6-69.4)	57.1 (51.0-63.3)	51.9 (47.8-56.1)
Hepatitis C	57.6 (49.9-65.4)	58.2 (52.1-64.4)	52.9 (48.3-57.6)
HIV/AIDS	48.3 (40.4-56.3)	45.6 (40.1-51.1)	51.0 (46.0-56.1)

*Bold denotes statistically significant differences using Wilcoxon Median Two-Sample Test (p<.05)

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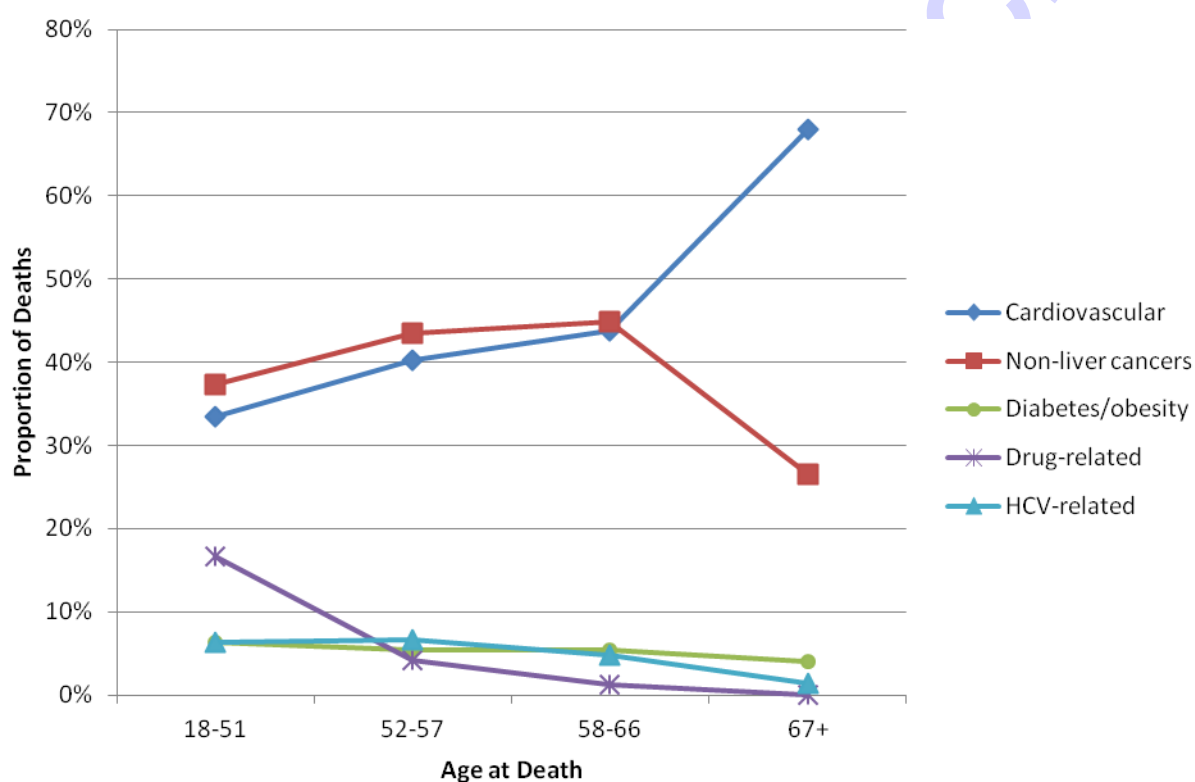
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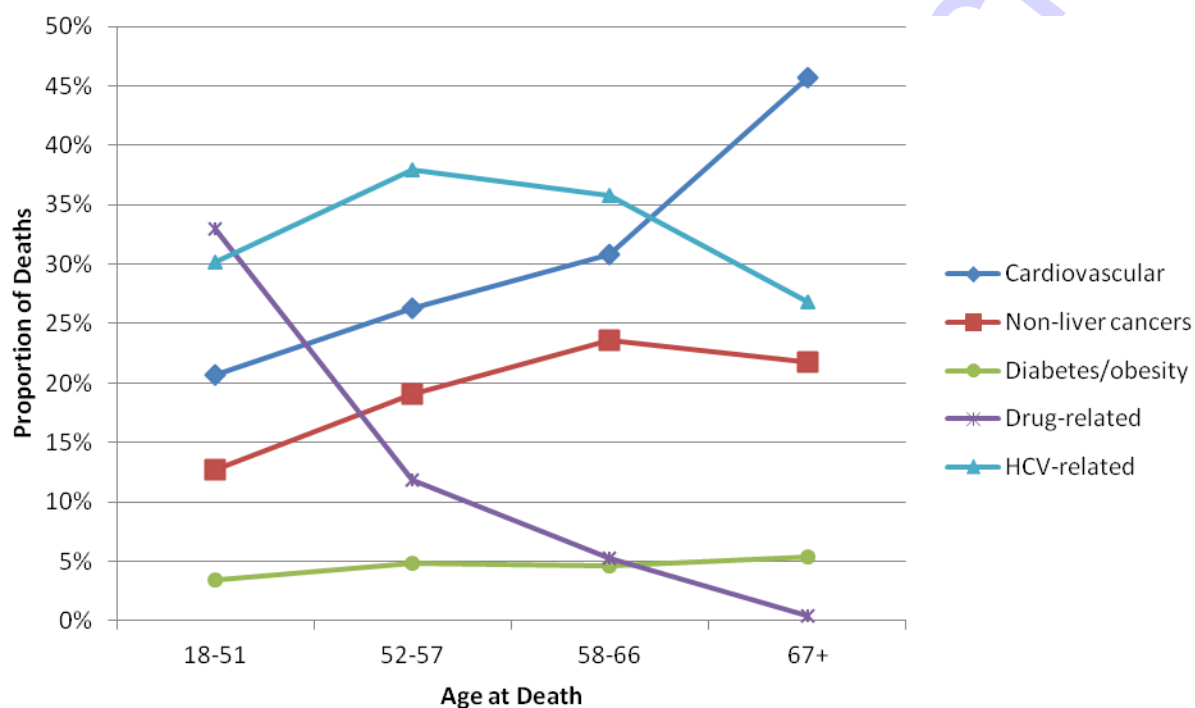
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Figure 1: Causes of death by quartile of age at death for all decedents without a report of HCV or HIV, NYC, 2000-2011



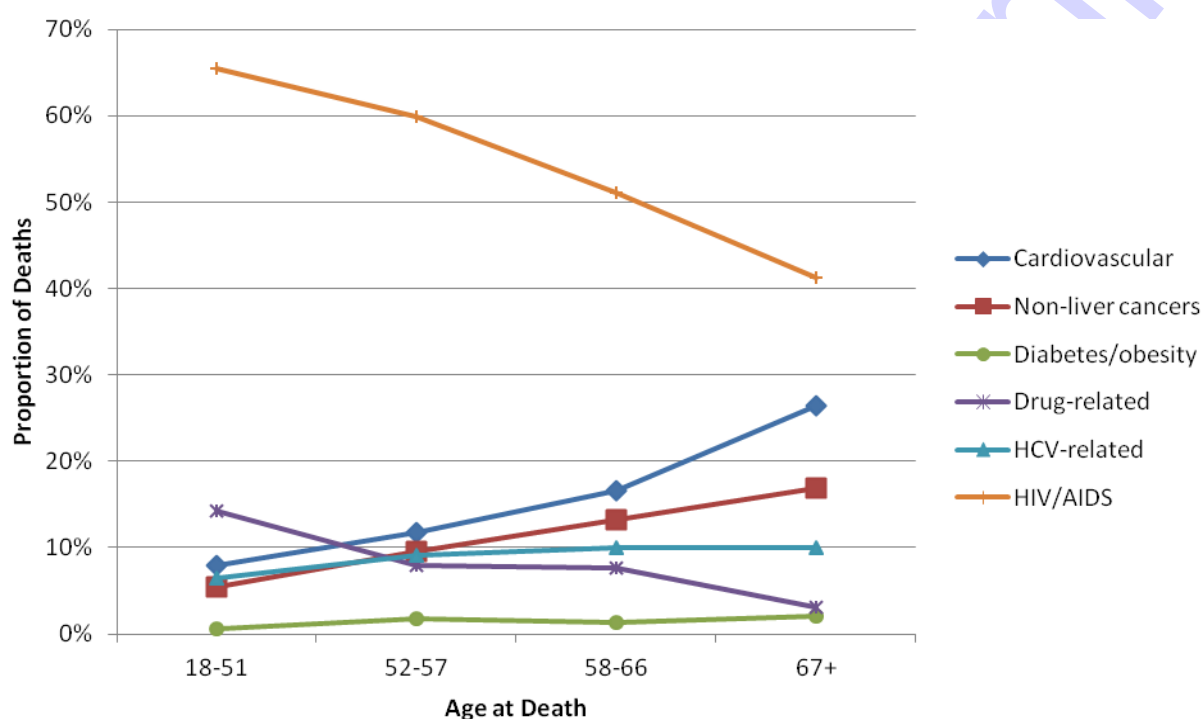
Note: Excludes other category and HIV/AIDS; HCV-related includes liver cancer, cirrhosis and HCV

Figure 2: Causes of death by quartile of age at death for all decedents reported with HCV mono-infection, NYC, 2000-2011



Note: Excludes other category and HIV/AIDS; HCV-related includes liver cancer, cirrhosis and HCV

Figure 3: Causes of death by quartile of age at death for all decedents reported with HCV/HIV co-infection, NYC, 2000-2011



Note: Excludes other category; HCV-related includes liver cancer, cirrhosis and HCV