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High Mortality among Patients with Opioid Use Disorder in a Large Healthcare System

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Abstract

Objectives—Elevated mortality has been observed among individuals with opioid use disorder (OUD) treated in addiction specialty clinics or programs. Information about OUD patients in general healthcare settings is needed in light of the current effort to integrate addiction services into primary healthcare systems. This study examined mortality rates, causes of death, and associated risk factors among patients with OUD in a large general healthcare system.

Methods—Mortality data were linked with electronic health records of 2,576 OUD patients cared for in a large university health system from 2006–2014.

Results—There were 465 deaths confirmed (18.1% of the study participants), corresponding to a crude mortality rate of 48.6 per 1000 person-years and standardized mortality ratio of 10.3 (95% CI, 9.4–11.3). Drug overdose and disorder (19.8%), cardiovascular diseases (17.4%), cancer (16.8%), and infectious diseases (13.5%, including 12% hepatitis C virus [HCV]) were the leading causes of death. HCV (HR: 1.99; 95% CI, 1.62– 2.46) and alcohol use disorder (HR: 1.27; 95% CI, 1.05–1.55) were two clinically important indicators of overall mortality risk. Tobacco use disorder (AHR: 2.58; 95% CI, 1.60–4.17) was associated with increased risk of cardiovascular death, HCV infection (AHR: 2.55; 95% CI, 1.52–4.26) with cancer mortality risk, and HCV (AHR: 1.92; 95%CI, 1.03–3.60) and alcohol use disorder (AHR: 5.44; 95% CI, 2.95–10.05) with liver-related mortality risk.

Conclusions—Patients with OUD in a general healthcare system demonstrated alarmingly high morbidity and mortality, which challenges health care systems to find innovative ways to identify and treat patients with substance use disorder.

Keywords

mortality; opioid use disorder; general healthcare system

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Introduction

Opioid use disorder (OUD) has been identified by the U.S. Department of Health & Human Services as a national public health crisis (Macrae & Hyde, 2015; National Heroin Task Force, 2015). In the United States, prescription opioid and heroin overdose deaths reached a record high of more than 28,000 in 2014 (CDC, 2016a). This public health crisis has attracted renewed interest in and attention to better identifying risk factors and implementing strategies that address the recurring opioid epidemic in the United States.

Numerous studies have shown that OUD is associated with elevated morbidity, mortality, and other adverse health and social conditions (Hser et al., 2015). A systematic review and meta-analysis of 58 cohort studies of opioid-dependent individuals found a pooled all-cause crude mortality rate (CMR) of 20.9 per 1000 person-years and a pooled standard mortality ratio (SMR) of 14.7, with overdose being the most common cause of death (Degenhardt et al., 2011). A recent study (Evans et al., 2015) based on 32,322 OUD patients receiving opioid detoxification and maintenance treatment in publicly funded treatment facilities in California from 2006 to 2010 found a fourfold increase in mortality risk compared with the general population; this risk increased to 6.1 when individuals were out of methadone maintenance treatment versus 1.8 when they were in methadone maintenance treatment. Further, the single leading cause of death identified by the study was drug- or alcohol-related (43.6%).

Traditionally, treatment for OUD in the United States has been provided in specialty addiction treatment clinics such as methadone treatment programs, isolated from the primary healthcare system or general medical settings. Recent healthcare reforms related to the passage of the Federal Mental Health Parity and Addiction Equity Act and Affordable Care Act have offered the opportunity to expand services for substance use disorders (SUDs) in primary care. However, studies have shown that most primary care physicians feel they do not have the education, training, resources, or time to diagnose and treat patients with SUDs (Wakeman et al., 2016). Recognition of the role of opioid prescribers and the healthcare system in the opioid overdose epidemic has resulted in increased education and training on opioid prescribing practice, but many physicians do not fully appreciate the mortality risks to their patients. Most clinicians are aware of the elevated mortality among OUD patients, particularly heroin users treated in publicly funded substance use disorder treatment systems; however, information on the rates and causes of mortality among OUD patients in the general healthcare system is lacking. The present study is based on hospital and clinic medical records of patients diagnosed with OUD in a large healthcare system. We calculated the mortality rates among these OUD patients by cause and in relation to the general population in order to investigate risk factors predicting mortality—both by all causes and cause-specific.

Methods

Sample

We identified 2,576 eligible patients age 18 to 64 at their first OUD diagnosis (abuse or dependence using International Classifications of Diseases [ICD]-9th Edition-CM codes

304.0×, 304.7×, or 305.5×) during an inpatient or outpatient visit from 2006 to 2014 from a university health system electronic health record (EHR) system utilizing Epic software. These medical records contain data on patient demographics and clinical diagnoses.

Mortality data, available through the end of 2014 were obtained from the Centers for Disease Control and Prevention (CDC) National Death Index (NDI). NDI data linkage was performed by CDC staff using probabilistic record linkage methods that utilized patients' Social Security number (SSN), full name, birth date, and sex. Among the 2,576 patients, 1,683 patients did not have further encounter data beyond the end of 2014 and their death status was determined by the NDI search; the remaining 893 patients were considered alive as their encounter data went beyond the end of 2014. In May 2016, NDI shared date and cause of death (International Classification of Diseases [ICD-10th revision]) for deaths that occurred as of December 31, 2014. Protocols were approved by the Institutional Review Boards at UCLA and the State of California.

Measures

Causes of death were coded according to the 10th edition of the ICD. Deaths were grouped into the following categories (https://simba.isr.umich.edu/restricted/docs/Mortality/icd_10_recodes.pdf): drug related (overdose—both unintentional and intentional, alcohol/drug disorder), cardiovascular disease, cancer, infectious diseases (HIV/AIDS, hepatitis, other infectious disease), liver disease, external causes (suicide, homicide, motor vehicle accident, etc.), respiratory disease, and all other causes (see Appendix I for details).

Covariates are based on medical records. Sociodemographic variables included: sex, race, age, and health insurance. Clinical variables were defined from diagnoses (ICD-9 codes) for physical health or diseases (e.g., cardiovascular disease, cancer, diabetes), SUDs (e.g., tobacco, alcohol, cannabis), and psychiatric or mental health condition (e.g., bipolar disorder, depressive disorder, anxiety disorder). The lists of ICD-9-CM codes utilized in this study may be obtained upon request from the first author.

Data analysis

Crude mortality rates (CMRs) were calculated by summing person years and numbers of deaths by age and sex and calculating a rate per 1000 person-years. Indirect standardized mortality ratios (SMR) were calculated by dividing observed deaths in the cohort by expected deaths based on U.S. population mortality rates (as provided by the CDC, National Vital Statistics System) by year, sex, and age group. Follow-up duration was determined using first OUD diagnosis to death, or December 31, 2014, for those not dead.

Chi-square or t-tests were used to compare characteristics between living and deceased patients. Cox regression and competing risks regression models were fitted to identify risk factors for all causes of death and to compare the hazard of death from drug-related, cardiovascular, cancer, liver-related, and all other causes of death, respectively. All hypotheses were tested using a significance level of α=0.05. Analyses were conducted using SAS 9.4.

Results

There were 465 confirmed deaths (18.1% of the total sample of 2,576) over a mean of 3.7 person years during the follow-up period. Compared to individuals who remained alive, those who died were older at the first OUD diagnosis (48.4 vs. 39.8), fewer were female (31.6% vs. 41.7%), more were black (11.2% vs. 6.8%), and more had no health insurance and therefore self-paid for their care (87.1% vs. 51.3%; see Table 1). Deceased patients were also more likely to have been diagnosed with other co-occurring SUDs (particularly involving tobacco, alcohol, cannabis, cocaine) and physical health problems (heart, respiratory, HCV, liver disease, cancer, diabetes). However, the deceased patients did not have higher rates of any psychiatric disorder. The mean age of these patients at death was 51.0 (SD=11.0).

Mortality rates for all causes of mortality and selected specific mortality causes are provided in Table 2. The total of 465 deaths over a mean of 3.7 person-years yielded the all-cause CMR of 48.6 per 1,000 person-years (Table 2). The most common cause of death was drug related (92 cases, or 19.8%) including accidental poisoning (78 cases, or 16.8%) or drug overdose, intentional poisoning (1.1%), and alcohol or drug disorder (1.9%; Appendix 1). The next two most common causes were cardiovascular disease (17.4%) and cancer (16.8%), followed by infectious diseases (13.5%, with 12.0% HCV and 0.8% HIV), diseases of the digestive system (12.2%, with 4.9% alcohol-related liver disease), and external causes (6.7%). Cause-specific CMRs are provided in Table 2, with a drug- or substance-related CMR of 9.6 per 1,000 person years.

The overall SMR was 10.3 (95% CI, 9.4–11.3), representing a more than 10-fold higher mortality risk compared to the general population adjusted for sex and age (Table 3). We also provide CMRs and SMRs by key strata. Males had a higher CMR and lower SMR than females. Black and Hispanic OUD patients showed high mortality rates, but they counted for a very small group.

Table 4 presents results on hazard ratios of factors associated with all-cause deaths, and adjusted hazard ratios for selected causes of death. For these OUD patients, HCV (HR: 1.99; 95% CI, 1.62–2.46) and alcohol use disorder (HR: 1.27; 95% CI, 1.05–1.55) are two clinically important indicators of overall mortality risk that were statistically significant. None of the diagnoses examined were predictors of drug-related deaths. Tobacco use disorder (AHR: 2.58; 95% CI, 1.60–4.17) were associated with increased risk of cardiovascular death. HCV infection (AHR: 2.55; 95% CI, 1.52–4.26) was associated with elevated cancer mortality risk. HCV (AHR: 1.92; 95%CI, 1.03–3.60) and alcohol use disorder (AHR: 5.44; 95% CI, 2.95–10.05) both increased the liver-related mortality risk.

Discussion

The present study found extremely high rates of mortality among OUD patients treated in a general medical setting, much higher than those reported among patients treated in a publicly funded substance use disorder treatment system. These study patients had a greater disease burden than those reported in prior literature—they were older when first diagnosed

with OUD, and they showed high rates of comorbid physical and mental health disorders. Still, the mortality indicators of CMR of 48.6 and SMR of 10.3 are alarming and may reflect several past and current issues with current health care delivery systems in identifying and addressing OUD problems. First, SUDs are not routinely screened for in primary care, and most primary care physicians have not received adequate training to diagnose and treat OUD. It is likely that patients seen in this health system became progressively sicker, as their OUD problem was not identified until very late in its course and after physical health complications had already ensued. Second, even after their OUD was recognized, these patients may or may not have received a referral for OUD treatment, increasing the likelihood that their addiction was untreated. Particularly if patients had a serious medical condition such as cancer or end-stage liver disease, their OUD might be viewed as a less pressing problem than their medical condition. Third, oral prescription opioid addiction may be more difficult to identify than heroin addiction if the patient is not spontaneously forthcoming, as there are no physical stigmata like needle tracks or abscesses that readily reveal an injection history.

Based on mortality data provided by the CDC NDI, the present study used ICD-10 codes to identify drug-related deaths. While we cannot specify the type of opioids, it should be noted that some of these overdose deaths may involve fentanyl or carfentanyl mixed with heroin (DEA, 2016). Fentanyl is a synthetic opioid that is much more potent than heroin and carfentanyl is a fentanyl-related compound. The strength of these powerful synthetic opioids, often added to heroin heightens the likelihood of overdose and overdose-related deaths, even among opioid-tolerant users.

No clinically meaningful predictors were identified for drug-related deaths. Nevertheless, HCV and alcohol use disorder were predictors of all-cause deaths. Although treatment regimens for HCV have vastly improved in recent years, considerable barriers to treatment access remain including expensive cost of the medications and restrictions imposed by most health insurance plans. Given the natural course of HCV infection, 20–30% of infected patients will develop cirrhosis within 20–30 years after infection. Of patients with HCV-induced liver cirrhosis, approximately 67–91% will die due to liver disease and 1–8% per year will develop hepatocellular carcinoma (Wirth & Mann, 2016). OUD patients infected with HCV who drink heavily are likely to develop more severe liver injury, progress to cirrhosis, and have increasing risk for liver cancer and mortality.

The study found significant associations between alcohol and liver-related death, tobacco and cardiovascular related death, and cannabis and other causes of death. It is well known that both tobacco and alcohol account for high rates of deaths in the general population (1 in 5 for tobacco [USDHHS, 2014]; 1 in 10 for alcohol [CDC, 2016b]). There is also a growing literature supporting cannabis use is responsible for an increase in morbidity and mortality due to accidents and injury (The National Academies of Science Engineering Medicine, 2017). However, the rates of these disorders in our sample likely represent substantial underdiagnoses, as assessment for substance use disorder is not routine or standardized in primary care clinics. For example, individuals with SUD typically have tobacco use rates above 60% (Lawrence et al., 2009) while it was only 19.6% in our sample. On the other hand, cannabis use disorder rarely comes to clinical attention unless it causes an

exacerbation of psychiatric symptoms. Thus, individuals with more severe cannabis use disorder are likely to be overrepresented in this study and may have greater mortality risk than the broader general population estimates have previously captured. The 10.8% rate in this study suggests that a subset of this sample had a very severe problem with cannabis use that could relate to mortality in ways cannabis use usually does not or that the reports of cannabis use disorder are surrogate markers for some undiagnosed conditions that are associated with mortality. In any event, these findings indicate that the possible relationship between these substance use disorders and mortality warrants further research.

Consistent with existing literature (Evans et al., 2015; Nandi et al., 2014; Wilper et al., 2009), this study revealed that a higher proportion of the deceased OUD patients were black and uninsured. This finding highlights the need for additional focus on disparities in addiction care and treatment outcomes.

The present study is based on patients seen in a single health system serving predominantly white patients living in the Los Angeles area of the United States, which may limit the study's generalizability. Our findings are dependent on the extent, accuracy, and validity of the data available in the EHR dataset. For example, because OUD diagnosis information was obtained from diagnoses assigned in an EHR, we were not able to distinguish if prescription or nonprescription opioids were used or the route of administration. Both mislabeling of people who don't actually have OUD and under-recognition of true OUD could dilute the true OUD patients in the sample. Possibly some of the ICD-9 diagnoses of opioid dependence signifying physiologic dependence that would be expected from prescribed opioid has resulted an increase in the proportion of patients who used opiates for pain and who were therefore medically sicker. On the other hand, routine screening for SUDs is not standardized or mandatory in the health system, leaving room for underdiagnoses and inconsistent documentation of these conditions, particularly in cases of less severe disorders.

Conclusions

The alarmingly high morbidity and mortality among OUD patients revealed in the present study challenge health care systems to find new and innovative ways to expand evidence-based strategies for OUD in a variety of settings. Given the chronic, relapsing nature of OUD and high medical and psychiatric comorbidity, continued care encompassing screening, early intervention, support, and monitoring is essential. In the United States, health care providers outside specialty substance use disorders treatment settings have not traditionally been adequately equipped to identify and address patients' drug addictions. Providing medications, such as buprenorphine, buprenorphine-naloxone,, methadone, and naltrexone, in combination with counseling, behavioral therapies, and monitoring are evidence-based strategies to treat OUD, however the optimal care pathways or implementation of these pharmacotherapies into healthcare setting is currently being studied (Jones et al., 2015; Lasser et al., 2016; Simpatico, 2015). Indeed, expanding access to medication for addiction treatment and training for medical professionals on opioid medication prescribing practices are among initiatives recently issued by former President Obama to address the prescription opioid and heroin epidemic (The White House, 2016). It seems likely that earlier intervention could prevent some of the excess morbidity and

mortality noted in this report and possibly ultimately conserve scarce health care resources. Future research is much needed to better engage the entire spectrum of health care services, with the goal of developing and delivering efficient and effective chronic care management approaches and services for OUD.

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Appendix I

Causes of Death by ICD-10 Codes

Raw category	Subcategory	ICD-10 Codes	N	% of total
Drug or substance related			92	19.8
Poisoning by drugs or substance	Accidental and intent not determined	X40, X41, X42, X44, X45, Y14	78	16.8
	Intentional	X62, X64	5	1.1
Mental and behavioral disease	Drug-related	F10.2, F11.9, F19.1, F19.2	9	1.9
Diseases of circulatory system	Cardiovascular	I05.9, I10, I11.0, I11.9, I12.9, I13.1, I21.9, I24.9, I25.0, I25.1, I25.8, I25.9, I27.9, I33.0, I35.9, I38, I42.0, I42.6, I42.9, I46.9, I51.7, I60.9, I61.9, I62.9, I64, I67.1, I69.8, I71.0, I73.9	81	17.4
Neoplasms			78	16.8
	Malignant neoplasms/cancer	C02.9, C15.9, C18.9, C19, C20, C22.0, C22.9, C25.9, C32.9, C34.9, C41.9, C44.2, C50.9, C51.9, C53.9, C54.1, C55, C62.9, C64, C67.9, C74.9, C78.6, C78.7, C79.8, C80, C85.9, C91.0, C97	77	16.6
	Other	D48.1	1	0.2
Certain infectious and parasitic diseases			63	13.5

Raw category	Subcategory	ICD-10 Codes	N	% of total
	HCV	B18.2	56	12.0
	HBV	B16.9	1	0.2
	HIV-related	B20.3, B23.8	4	0.8
	Other Infections	B25.9, B33.2	2	0.4
Diseases of the digestive system			57	12.2
	Alcohol-related liver disease	K70.0, K70.3, K70.9	23	4.9
	Other liver-related	K72.1, K72.9, K74.6, K76.0, K76.7, K76.9	28	6.0
	Other digestive organ	K27.5, K42.0, K44.9, K55.9, K63.1, K81.0	6	1.3
External causes of mortality			31	6.7
	Unintentional injury	V03.1, V09.2, V43.5, V49.4, V89.2, W13, W18, W19, Y20, Y85.0, Y86	14	3.0
	Suicide	X70, X72, X73, X74, X76, X78, X80	16	3.4
	Undetermined	Y87.2	1	0.2
Disease of the respiratory system	Respiratory	J18.9, J32.2, J43.9, J44.0, J44.8, J44.9, J45.9, J69.0, J84.1, J98.4	20	4.3
Endocrine, nutritional and metabolic diseases			16	3.4
	Diabetes	E10.9, E11.2, E11.9, E14.1, E14.5, E14.7, E14.9	10	2.2
	Obesity	E66.8, E66.9	4	0.8
	Cystic Fibrosis	E84.0, E84.8	2	0.4
Other		D57.1, D69.3, F50.0, G35, G40.9, G41.9, G80.9, G93.5, M321, M359, M726, N18.5, N18.9, N39.0, Q60.5, Q87.4, R99	27	5.8
Total			465	100

Table 1

Demographic Characteristics and Diagnoses (%)

Characteristic	Died n= 465	Did not die n=2,111	TOTAL n=2,576
Sociodemographics			
Female (%) ***	31.6	41.7	39.9
Ethnicity/race (%) ***			
White	75.1	79.2	78.4
Black	11.2	6.8	7.6
Hispanic	2.8	2.9	2.9
Asian	1.1	2.1	1.9
Other/unknown	9.9	9.1	9.2
Age at first OUD diagnosis, Mean (SD) ***	48.4 (11.0)	39.8 (13.3)	41.4 (13.3)
Financial sources (%) ***			
Medicare	4.7	14.3	12.5
MediCal	4.3	11.3	10.1
Commercial health plans	3.9	20.1	17.2
Self-pay/other	87.1	51.3	57.7
Physical health and disease (%)			
Heart disease ***	74.6	48.6	53.3
Respiratory disease ***	66.7	45.9	49.7
Sleep disorder **	12.3	17.5	16.5
Liver disease ***	45.6	14.3	20.0
Cancer ***	28.4	10.9	14.1
Diabetes ***	22.6	11.0	13.1
Sexually Transmitted Disease	0.4	1.2	1.1
HIV	2.4	2.3	2.3
HCV ***	47.5	16.6	22.2
Chronic pain	51.4	53.4	53.1
Other substance use disorders (%)			
Tobacco use disorder *	23.9	18.7	19.6
Alcohol use disorder ***	39.8	22.6	25.7
Cannabis use disorder ***	16.3	9.6	10.8
Amphetamine use disorder	9.7	11.5	11.2
Cocaine use disorder **	17.4	12.3	13.2
Hallucinogen use disorder *	4.3	2.5	2.8
Mental disorders (%) *	60.7	66.3	65.3
Psychotic disorder	11.8	9.9	10.2
Bipolar disorder	9.7	12.9	12.3

Characteristic	Died n= 465	Did not die n=2,111	TOTAL n=2,576
Depression disorder *	40.0	45.7	44.7
Anxiety disorder ***	24.3	34.1	32.3
Other mental disorder	30.1	34.7	33.9

* p<.05,

** p<.01,

*** p<.001

Table 2

All-Cause and Selected Cause-Specific Mortality Rates

Cause of death	N (%) deaths	CMR per 1000 PY (95% CI)
All cause	465 (100)	48.6 (44.2, 53.1)
Drug or substance related	92 (19.8)	9.6 (7.7, 11.6)
Poisoning by drugs or substance	78 (16.8)	8.2 (6.3, 10.0)
Cardiovascular diseases	81 (17.4)	8.5 (6.6, 10.3)
Malignant Neoplasms/Cancer	78 (16.8)	8.2 (6.3, 10.0)
Certain infectious and parasitic diseases	63 (13.5)	6.6 (5.0, 8.2)
HCV	56 (12.0)	5.9 (4.3, 7.4)
Diseases of the digestive system	57 (12.2)	6.0 (4.4, 7.5)
Liver-related	51 (11.0)	5.3 (3.9, 6.8)

Table 3

Crude Mortality Rates and Standardized Mortality Ratios by Key Strata

Strata		Sample size	No. of death	CMR per 1000 PY (95% CI)	SMR (95% CI)
Total[1]		2576	465	48.6 (44.2, 53.0)	10.3 (9.4, 11.3)
Gender[2]					
	Female	1028	147	38.3 (32.1, 44.5)	11.0 (9.2, 12.8)
	Male	1548	318	55.6 (49.5, 61.7)	9.3 (8.2, 10.3)
Race and ethnicity[3]					
	White	2020	349	45.1 (40.4, 49.8)	9.9 (8.9, 10.9)
	Black	196	52	70.3 (51.2, 89.4)	11.8 (8.6, 15.0)
	Hispanic	74	13	63.1 (28.8, 97.4)	11.1 (5.1, 17.2)
	Other	286	51	58.2 (42.2, 74.2)	12.3 (8.9, 15.6)
Age at 1st OUD diagnosis[1]					
	18–30	716	47	15.4 (11.0, 19.9)	13.5 (9.6, 17.4)
	30–40	480	47	23.9 (17.1, 30.7)	10.7 (7.6, 13.7)
	40–50	550	113	53.5 (43.6, 63.3)	10.4 (8.5, 12.3)
	50–64	830	258	105.9 (92.9, 118.8)	9.8 (8.6, 11.0)
Having mental disorder diagnosis[1]					
	Yes	1682	282	44.0 (38.9, 49.2)	9.3 (8.2, 10.4)
	No	894	183	57.9 (49.5, 66.3)	12.4 (10.6, 14.2)
Having other drug diagnosis[1]					
	Yes	1590	324	50.8 (45.3, 56.3)	10.5 (9.4, 11.7)
	No	986	141	44.3 (37.0, 51.6)	10.0 (8.3, 11.6)
Having any chronic pain[1]					
	Yes	1367	239	49.4 (43.2, 55.7)	9.0 (7.8, 10.1)
	No	1209	226	47.8 (41.6, 54.0)	12.3 (10.7, 14.0)

[1]The Standardized Mortality Ratio (SMR) of the total participants is the ratio between the observed number of deaths in the study population and the number of deaths that would be expected, based on the age- and sex-specific rates in the U.S. population in 2013 and the age and sex distribution of the study population. SMRs stratified by age at first diagnosis of OUD, mental disorder diagnosis, other drug diagnosis, and chronic pain are also calculated in this way.

[2]The SMR of each gender is the ratio between the observed deaths of that gender in the study population and the number of deaths that would be expected, based on the age- and sex-specific rates in the U.S. population in 2013 and the age and sex distribution of the study population.

[3]The SMR of each race/ethnicity is the ratio between the observed deaths of that race/ethnicity in the study population and the number of deaths that would be expected, based on the age-, sex-, and race/ethnicity-specific rates in the U.S. population in 2013 and the age, sex, and race/ethnicity distribution of the study population.

Table 4

Cox and Competing Risks Regression Models of All-Cause and Selected Common Causes of Death

	Hazard ratio (95%CI)	Adjusted hazard ratio (95% CI)				
	All causes	Drug-related	Cardiovascular	Cancer	Liver-related	All others
Age	1.05 (1.04, 1.06)	0.99 (0.97, 1.01)	1.07 (1.05, 1.10)	1.07 (1.05, 1.10)	1.08 (1.05, 1.11)	1.04 (1.03, 1.06)
Female	0.87 (0.71, 1.07)	0.53 (0.33, 0.85)	0.84 (0.52, 1.38)	1.00 (0.62, 1.63)	1.24 (0.65, 2.35)	1.05 (0.74, 1.50)
White Race/ethnicity	0.92 (0.75, 1.14)	1.26 (0.72, 2.23)	0.77 (0.47, 1.28)	0.79 (0.49, 1.29)	1.47 (0.76, 2.86)	0.87 (0.61, 1.24)
HCV infection	1.99 (1.62, 2.46)	1.08 (0.62, 1.91)	0.87 (0.51, 1.46)	2.55 (1.52, 4.26)	1.92 (1.03, 3.60)	2.93 (2.06, 4.17)
Chronic pain	0.85 (0.70, 1.03)	0.77 (0.50, 1.18)	1.37 (0.82, 2.29)	0.77 (0.47, 1.26)	0.66 (0.38, 1.14)	1.01 (0.72, 1.42)
Tobacco use disorder	1.00 (0.80, 1.26)	1.21 (0.74, 1.98)	2.58 (1.60, 4.17)	0.98 (0.56, 1.70)	0.46 (0.20, 1.06)	0.67 (0.44, 1.02)
Alcohol use disorder	1.27 (1.05, 1.55)	1.22 (0.78, 1.92)	0.88 (0.54, 1.43)	0.73 (0.44, 1.22)	5.44 (2.95, 10.05)	1.21 (0.87, 1.69)
Cannabis use disorde	1.20 (0.93, 1.55)	0.72 (0.36, 1.45)	0.77 (0.36, 1.65)	0.78 (0.39, 1.55)	1.04 (0.50, 2.14)	1.74 (1.19, 2.54)