CLASSIFICATIONS, RE-VISITS, AND MORTALITY FOR OPIOID-RELATED HOSPITALIZATIONS IN PENNSYLVANIA AND THEIR ASSOCIATIONS WITH HCV AND HIV DISCHARGES

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ABSTRACT

The opioid epidemic started in 1990s in the USA. Pennsylvania ranks 9th in the nation in the rate of long-acting pain reliever prescriptions. The objective of this dissertation is to (1) classify opioid-related hospitalizations and discharges of consequences of opioid use: HIV and Hepatitis C virus (HCV) among these classes. By HCV, HIV, and urbanicity, (2) we compared re- hospitalization rates, and (3) compared survival length.

We used hospital discharges from the Pennsylvania Health Care Cost Containment Council and included primary and/or secondary discharge codes for opioid-related visits. Cancer-related visits, patients ages ≤8 years, and out-of-state residents were excluded. Latent class analysis (LCA) was performed using sociodemographics, substances, mental disorders, and pregnancy; logistic regression was used to compare HCV and HIV co-discharges among visits by latent class. We used semi-parametric mixed Poisson regression to compare re-hospitalization rates, and used accelerated failure time models to compare survival length, controlling for demographics, mental disorder, and other substance discharges. For these analyses, discharges after the first opioid-related hospitalization during 2000-2010 (opioid cohort) were used.

LCA used 430,569 visits (202,126 individuals) with opioid-related codes during 2000-2014. Of the 5 latent classes (LCs), the LC Pregnant women, OUD had the highest percentage of HCV co-discharges: 5,273 visits (26.3%); Black, OUD, cocaine had the most visits with HIV: 6,490 (6.9%). Of 136,463 patients in the opioid cohort, there was a median of 4 visits per patient; those who died had a median survival of 92 weeks. Those with HCV had a 1.11 times higher re- hospitalization rate compared to non-HCV visits, and shorter survival lengths starting after age 30 years at index opioid visit. Those with HIV had a 1.38 times higher rate and 0.31 the length of survival.

Although screening for HCV and HIV are not uniform for all opioid-related visits, it is important to specifically target pregnancy visits in high risk groups to be screened/treated for these diseases. This study has public health relevance, as higher re-hospitalization rates and shorter time to death in persons with the diseases indicates that increase in opioid-related hospitalizations, increases health issues due to HCV and HIV.

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PREFACE

Thank you to family, friends, and co-workers at the Epidemiology Data Center, for their support throughout the program.

Thank you to members of my committee: Drs. Krans, Mair, Songer, and Wahed for their input on the project, field, and personal experience: I am very grateful to have the opportunity to work with each and every one.

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1.0 BACKGROUND AND LITERATURE REVIEW

Opioids are a class of drugs that are important for pain relief, consisting of oxycodone (OxyContin®), hydrocodone (Vicodin®), codeine, morphine, and fentanyl[1]. However, there are increasing instances where persons abuse opioids for purposes other than those recommended by clinicians[1].

The absorption of the drug in the body leads to release in dopamine (a neurotransmitter) into the *nucleus accumbens*, which is within the basal forebrain near the hypothalamus[2–4]. This release allows for the feeling of analgesia or even euphoria. Heroin is a type of illegal opioid, and has a slightly different reward systems and addiction or abuse capability compared to the prescription opioid types[2]. Heroin can be metabolized into morphine and is more potent than prescription opioids, leading to more accidental overdoses[5,6]. A metabolite 6-monoacetyl morphine (6MAM) was found to responsible for many sudden deaths from heroin[7].

Despite effectiveness in treating pain symptoms and recent increase in prescriptions for opioids, there are concerns for patients who use opioids for prolonged periods of time. These persons may have opioid tolerance, abnormal pain sensitivity, and hormonal changes[8]. The consequences of long-term use of opioids for non-cancer issues include adverse events such as effects on neuroendocrine function and increased tolerance, leading to opioid addiction and causing clinically significant impairment and distress[9–12]. Prevention of opioid overdoses are crucial and can help prevent downstream morbidity and mortality.

1.1 TYPES OF OPIOID DISCHARGES

Discharge codes from healthcare centers include International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes describing opioid abuse, dependence, and poisonings[13]. These diagnosis codes are used in our current research dataset, and other studies have found the opioid ICD-9-CM codes to have high specificity, despite low sensitivity (around 25%)[14]. Therefore, it is assumed that frequencies of opioid codes in these records are underestimates of true values, yet coding is "sufficiently stable" for surveillance purposes[14]. In an ideal surveillance situation, chart review will be needed to have accurate estimates of the number of emergency department opioid issues. Rowe et al.[14] also hypothesized that healthcare providers may be uncertain of the definition of opioid poisoning and may be inconsistent in coding overdoses.

Other studies categorize opioid-related problems as misuse, abuse, and addiction from research by Butler (description of consensus definition from the National Institute on Drug Abuse, experts on addiction and abuse, and treatment programs) and Sullivan (Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks – ACTTION)[15–17]. *Misuse* refers to opioid use for reasons opposite of prescribed intention, regardless of the presence or absence of harm or adverse effects. *Abuse* is the intentional use of the opioid for a nonmedical purpose, such as euphoria or altering a state of consciousness[17].

Addiction, on the other hand, is the pattern of continued use with experience of, or demonstrated potential for, harm (e.g., impaired control over drug use, compulsive use, continued use despite harm, and craving)[18]. This definition of addiction is not captured in hospital discharges.

1.2 TRENDS OF MORBIDITY AND MORTALITY OF OPIOIDS IN RECENT YEARS

Recent years, starting as early as the late 1990s, have been labeled as an "opioid epidemic" period[19,20]. Among those who seek medical care with pain-related symptoms or diagnoses, the proportion of persons prescribed opioids almost doubled from 2000 to 2010: 11% to 20%, respectively[21]. There has been a steady increase in opioid overdose deaths from 2000-2014. The earlier years in the 2000-2014 were mainly due to prescription opioids, but the increase since 2010 could be related to increased heroin use[22]. In 2014, heroin was involved with 61% of opioid-related deaths, and had 3 times the mortality rate compared to 2010 (1.0 per 100,000 in 2010 to 3.4 per 100,000 in 2014)[23]. There was also an increase in heroin-related deaths in those who used multiple substances[22]. This increase is most apparent in younger adults aged 18-25 years, in women, white, middle-class, living in nonurban areas. Coincidentally, these demographic groups were similar to the corresponding demographics during the prescription opioid rate increase for nonmedical use around 2002[24–26].

In the United States, the age-adjusted mortality deaths from synthetic opioid overdoses (including fentanyl) increased by 72% from 2014 to 2015[27]. Many of the recent fentanyl-related deaths are likely from drugs that were seized and obtained by police (not prescribed by medical professionals)[28,29] and increased supply of illicitly manufactured fentanyl[27,28,30]. Fentanyl is a more potent opioid, which is highly potent with high potential for abuse and dependence[31]. It is important to regulate fentanyl prescription to prevent potential adverse events.

1.3 HETEROGENEITY OF OPIOID ISSUES BY LOCATION AND URBANICITY

The Pennsylvania Health Care Cost Containment Council (PHC4) showed a substantially increased number of inpatient hospitalizations for accidental or purposeful use of pain medicine (225%) and heroin (162%) from 2000-2014. Despite general increases throughout the state of Pennsylvania, rural counties have a larger rate of increase in opioid hospitalizations in than urban counties[32].

Pennsylvania ranks 9th in the nation in prescribing rate of long-acting pain relievers, and above the median for prescription of opioid pain relievers (OPR) and high dose OPR[33]. Per the PHC4 report, rural regions in Pennsylvania (Counties of south-central, north-central, and southern Allegheny) and the rural areas of the Appalachian Mountain region of PA have high hospital burden of opioid abuse and subsequent overdoses and deaths, from overdose of legal and illegal sources of opioids.

The opioid problems have generally, in the past, occurred in low-income, inner-city, minority populations. Most were males and black, according to narcotics registries and decedent data[34]. However, abuse has increased in the suburban and rural areas with a large majority white population. In a nationwide study, the mean age of heroin users seeking treatment was 16 years when they first became opioid abusers in the 1960s. This increased to the early to mid-20s in the 2010 decade (Figure 2), who also lived in less urban (small urban and non-urban) areas compared to those in the 1960s[24].

In Pennsylvania, the increase in number of hospitalizations from 2000-2014 for rural counties increased by 285% and 315% for pain medication and heroin, respectively. The increase in the same time period for urban counties were lower but still substantial, increasing by 208% and 143% for pain medication and heroin[32].

However, evidence shows that the burden of the epidemic is still high in urban areas. In Wisconsin, most of the opioid-related deaths were in urban counties, but rural opioid deaths went from near 0% to 17% of cause-specific deaths in 2003 to 2012[35]. The same trend was emphasized in Paulozzi et al.[33], in a sample of Caucasians in 16 states. The heroin death rates were still highest in large central metro areas. Another study by Paulozzi and Cicero found prescription opioid analgesics deaths were highest in non-metro areas, and specifically in more rural counties areas of West Virginia where pharmaceutical opioid abuse is prevalent in these rural communities[36,37]. It was also shown that epidemic of heroin use in Oregon's urban areas among young males may be related to easy access to prescription opioids from home or the homes of their friends[38].

1.4 TRANSITION FROM PHARMACEUTICAL OPIOIDS TO HEROIN

Those who eventually develop opioid addiction, in part due to limited sources of prescription opioids, may have adopt high-risk behaviors such as injecting prescription opioids and/or heroin[39]. Many persons who inject drugs had previously used prescription opioids for non-medical purposes, especially when compared to those who have not injected[25,40–42]. The National Survey on Drug Use and Health (NSDUH) showed that there was 40 times higher risk of abusing or being dependent on heroin in persons who were had concurrent opioid pain reliever abuse or dependence, when compared to those without prescription opioid abuse or dependence[22]. Many of these persons abuse these drugs are in chronic pain (up to 50%), although some studies found that none of the chronic pain patients abused drugs[43]. In a sample of 2,757 in drug treatment centers in 48 US states, there were 66% who said they abused

prescription opioids prior to treatment[24]. Anecdotal evidence also shows that participants use heroin because the "high" from heroin is greater, ease of inhalation/injection, and the easier access to the drug[24,44]. In addition, rising rates of heroin overdoses may be because of the decreasing cost of heroin and high purity of the drug[45].

The reason for transition to heroin is complicated by several pathways. Persons who are using opioids for medical or non-medical purposes may switch to injecting opioid and/or heroin due to lack of supply of pills, a faster and different sensation by infecting, or due to changes in policy for clinicians prescribing opioids[2]. There are also influences of pressure and/or comfort to use opioids within social networks[46,47]. Despite high rates, there is evidence that there is only a small percentage of nonmedical prescription opioid users who transition to heroin, and previous nonmedical use of opioids are not necessary for starting injection drug use[2,42]. Opioid users who actively acquire prescription opioids compared to those who do not were more frequently white, had more instances of using opioids, and used opioids to achieve a high as opposed to mitigating pain[46]. It is unclear whether there is a difference in demographics and other drug behaviors in heroin user and prescription opioid user populations[48].

Other debated hypotheses include whether the increase in initiation of heroin use are related to prescribing practices of clinicians and OxyContin formulation. As the dangers of prescription opioid abuse were publicized, regulations were released in 2006, accompanied by a subsequent observed rise in heroin use in 2007. Use of heroin increased because it is cheaper and easier to find, despite legal issues[23]. In addition, there was a change in formulation of OxyContin that made it difficult for injection. In several health services, treatment settings, and other surveys there were decreases in OxyContin abuse and continued increase of heroin use after the change in OxyContin ingredients[44,49]. Several states documented the increase in heroin

around the country, but there were no clear evidence that transition to heroin occurred before the policies and whether policies directly increased heroin abuse[23,35,50,51].

1.5 RISK FACTORS FOR OPIOID USE, USE DISORDERS, AND OVERDOSE

Studies have found that factors associated with increased risk for opioid misuse included: history of other substance use disorder(s), younger age, major depression, and use of psychotropic medications[52,53]. Those in chronic pain are also at high risk of misuse, because of initiation via prescription opioids through the healthcare system. Chronic pain has several definitions, but is defined within an International Society for the Study of Pain (IASP) guideline as pain that typically lasts >3 months or past the time of normal tissue healing[54,55]. One study found that avoiding withdrawal was a major reason using opioids (reporting chronic pain as a reason to use opioids)[56]. More studies are required to truly weigh the benefits and harms to long-term opioid therapy among those with chronic, non-cancer pain[57]. There is no agreement on a maximum dose for opioids and it is difficult to assess and generalize quality of life in those in chronic pain. A careful balance must be achieved, as Sehgal et al. emphasized that pain must be mitigated before considering minimizing adverse events due to opioids[57].

Nearly all persons who visit emergency departments in chronic pain who are prescribed short-acting opioids are under suboptimal medication practices, resulting in increased re-visits and healthcare costs[58]. Ekholm et al[59] studied long-term and short-term prescription opioid use among persons with chronic non-cancer pain. Long-term opioid users in pain had 1.72 times higher mortality compared to those non-users without chronic pain. As expected, any use of opioids had higher risks of injuries and poisoning, resulting in hospital inpatient admissions.

Among chronic pain patients, persons who have psychiatric comorbid conditions are at increased risk for opioid misuse[57].

A 2017 study from CDC[60] showed that from a 10-year sample of commercial health plan patients who had at least 1 opioid prescription and ≥6 consecutive months of continuous enrollment, 2.6% of patients continued opioid therapy long-term (1 year or longer) after first use. There was an increase in the probability of long-term opioid use with each additional day of opioids prescribed. The increase in probability of long-term use was greatest after 5 days or 1 months of first opioid therapy, and plateaued after 12 weeks[60].

Despite the use of long-term prescription opioids, there is still debate on the addiction potential of the analgesics. A review by Fishbain et al showed that among those chronic pain patients prescribed opioids, there is a combined estimate, from over 2,500 patients, of 3.27% abusing or addicted to opioids and 11.5% with aberrant drug-related behavior.[61] The development of addiction depends on multiple fronts: the nature of opioid drug itself, in addition to psychological, social, and physiological dispositions for the person taking the drug. Those who are at highest risk for problematic drug-taking have associated qualities of prior history of drug abuse, severe character pathology, and chaotic family relationships. Opioid prescriptions have different benefits and harms for a heterogeneous patient population. Studies before the review in 1996 have shown that addiction among cancer patients after opioid therapy is extremely rare[61]. Persons who have high genetic predispositions for risk of addiction during the course of an opioid prescription is "probably very low"[62].

1.6 OUD AND PSYCHIATRIC DISORDER CO-MORBIDITIES

Opioid Use Disorder (OUD), as defined by the American Psychiatric Association, is the problematic pattern of opioid use leading to clinical impairment. In 2014, there were about 1.9 million Americans who had prescription OUD and 586,000 with heroin use disorder; the combination of these disorders is equivalent to about 0.8% of the population[63]. It is commonly diagnosed in the late teenage years to early 20s, and the risk varies by individual, family, peer, and social environmental factors. Two of the 11 criteria must be fulfilled to be defined as OUD; criteria that range from taking a larger dosage or time period than prescriptions for opioids were intended, to recurrent use that cause hazardous outcomes in person, or cravings, and strong desires to use opioids[11].

Terminology from the Substance Abuse and Mental Health Services Administration (SAMHSA) has changed from abuse and dependence (as seen in hospital records in our analysis) to varying degrees of severity (number of diagnostic criteria) of substance use disorders, which follow coding from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)[63].

There are important co-morbidities for OUD reported in the scientific literature. Several mental disorders, including various personality disorders (obsessive-compulsive, paranoid, schizoid, histrionic, anti-social) were associated with OUD. Schizophrenia, bipolar disorder, and psychosis are associated with higher rates of OUD relapse, among those under treatment for opioid addiction[64]. Of note, those with anti-social personality disorders living in rural areas are more likely to have substance abuse and dependence along with mental disorders[65]. Anti-social personality disorders were more common in those with OUD, opioid abuse, and opioid dependence than in the general population[66].

1.7 MISCLASSIFICATION OF OUD

Diagnosis of OUD may be confused with overlapping symptoms for depressed mood, and may be misconstrued as a mental disorder such as opioid-induced *depressive* disorder. Persons with OUD are less likely to present with symptoms consistent with mental disorder, when compared to other substance abuse disorders. Despite the fact that persons who have psychiatric comorbidities are more likely to receive opioids[57], use of opioids may further compound problems for those with depressive disorder[11]. Depression and/or anxiety are likely to increase the risk of substance use disorders, therefore making it necessary to adjust for mental health disorders when determining the risk of opioid use disorder in those who are prescribed opioids[67].

Co-occurrence of alcohol use and opioid use disorders is common[68]. Persons who have alcohol disorder may also have symptoms that resemble opioid intoxication. Withdrawal from, stimulants for example, may show similar symptoms from those affected by OUD[11].

1.8 SEQUELAE AND MORTALITY IMPLICATIONS OF THE OPIOID EPIDEMIC

1.8.1 Hepatitis C and HIV

Future and/or concurrent issues of the opioid epidemic involve bloodborne infections from injection drug use[69–73]. There is strong evidence that hepatitis C (HCV) and HIV is spread via sharing virus-infected needles and sharing injection paraphernalia, when injecting heroin and other opioids[74].

1.8.2 Studies Examining Prescription Opioids and HCV

Hadland et al.[75] examined a prospective cohort from Vancouver, Canada of recent illicit drug-using youth 14-26 years old during 2005-2011. The authors used the At-Risk Youth Study (ARYS) which depends on *snowball sampling* where recruitment occurs by having the initial participant sample recruit their acquaintances for the study. This was done because of the predominantly transient, homeless population. The investigators performed HCV antibody testing every 6 months during follow-up and found that participants used heroin, cocaine, and/or crystal methamphetamine. Cumulative incidences of HCV seroconversion over time were calculated, and tested heroin and prescription opioid injection interaction. The goal was to directly compare the risk for HCV seroconversion from injection of heroin and other drugs, to injection of prescription opioids.

There were 10.6% of the youth who were HCV-positive at baseline, and of the 512 baseline HCV-negative persons, 56 seroconverted to positive. Heroin (hazard ratio, HR=4.56), cocaine (HR=1.88), and crystal methamphetamine (HR=2.91) were associated with HCV seroconversion. Injection of prescription opioid was not statistically significant (HR=0.94), however there were relatively small numbers (7%) of participants who injected prescription opioids in this analysis.

Another important study by Havens et al. studied Hepatitis C infection and social network correlates among opioid users[70]. They focused on the rural Appalachian region of Kentucky, from the enrolled Social Networks Among Appalachian People (SNAP) study using respondent-driven sampling from 2008-2010. Injection drug users recruited opioid-using persons in their social circle; the analysis only included those who ever injected drug. Antibody screening and follow-up were performed on participants for HCV, HIV, and herpes simplex-2

virus (HSV-2). The analyses accounted for age, sex, race, education, income, employment, drug use, HIV, HSV-2, sexual history, and psychiatric disorders via psychiatric MINI interview (including major depressive disorder, generalized anxiety disorder, post-traumatic stress disorder, and anti-social personality disorder).

They found univariate statistically significant associations for injecting prescription opioids and injecting cocaine, with being HCV seropositive. Persons injecting for 5 or more years had 3 times the odds of being HCV positive. Persons who shared syringes for injection of any drug were 2 times more likely to be HCV positive.

Sacks-Davis et al.[76] analyzed data from HEPatitis COhort, a prospective cohort study of recent injection drug users living in the Island of Montreal, Quebec from 2004-2012. Participants were recruited by word-of-mouth, through community based organizations, and from an existing cohort studying HIV transmission. Follow-up was performed every 6 months and, after March 2011, every 3 months. The determination of prescription opioid injection (POI) was based on a questionnaire, asking mainly about whether they injected opioids other than heroin. HCV infection during follow-up was defined as someone tested positive for antibodies for HCV enzyme immunoassay (EIA) with confirmatory testing via second EIA and recombinant immunoblot assay (RIBA), after a previous anti-HCV negative test. Other covariates included sex, age, housing situation, income, socioeconomic disadvantage, incarceration, cocaine/heroin use, frequency of injecting, needle and equipment sharing, and injection in public.

They performed statistical analyses to determine determinants of POI using models with GEE. Kaplan-Meier survival analyses determined associations, adjusting for residence location, between POI and HCV infection. They found the unadjusted hazard of HCV infection increased around 75% among those using POI. After adjusting for significant covariates, HCV infection

hazard with injecting prescription opioids was greater in urban [3.38 (1.88, 6.07)] vs. suburban [1.26 (0.65, 2.42)] areas. Therefore, when comparing urban against rural areas, urban areas had higher HCV risk and more hospitalizations.

1.8.3 Opioid – HCV Relationship

Despite low risk of acquiring HCV per needle stick, HCV is considered 10 times more infectious than HIV through infected blood[73]. The timing of initiating injection drug use is important, as many of those eventually infected with HCV acquire the virus soon after the first injection, because of less access to syringe exchange programs and suitable treatment[73,77]. Most persons who engage in risky behaviors initiate using legal, prescription opioids, but some start by injecting prescription opioids. The prevalence of HCV is high in injection drug users; country-level prevalence is greater than 20% in almost all countries, and 86% of countries with estimates had HCV prevalence greater than 50%[71].

Defining those who inject drugs may be a good proxy of HIV risk behaviors, which is spread similarly to HCV. Methadone maintenance therapy is effective in preventing HIV disease among IDU, and could also be effective in preventing HCV[78].

There have been increases of acute HCV during the opioid epidemic, with US national rates increasing from 0.3 per 100,000 to 0.7 per 100,000 in 2010 and 2014, respectively. However, the burden of hepatitis C is from the chronically infected persons. The number of HCV-related deaths from certificate data almost doubled from 2003 to 2013[79]. Given these rates, it is possible that we may observe high seroconversion rates among injection drug users, up to above 40 per 100 person-years [80,81].

1.8.4 Opioid-Related Mortality

The direct implication of the large amount of opioid use, as shown for oxycodone and hydrocodone, is higher rates of overdose deaths[82,83]. These include deaths from intentional or accidental overdoses[11]. As expected, one with a non-fatal overdose is at higher risk to die of a future overdose[84]. High-dose opioid use increases the risk for fatal respiratory depression[85,86], which may have contribution from commonly co-prescribed benzodiazepines[87]. Liver disease is one of the most common causes of mortality in the older population with opioid dependence in Australia[88]. Other opioid-related causes of death include acute kidney failure, multiple organ dysfunction syndrome, bowel infarction, hypoxic brain injury, and sepsis[89].

Another important issue with populations of opioid users and those infected with HCV is intentional death. Among opiate users compared to matched general population peers, the excess suicide mortality was around 6-8 times in most studies, and up to 14 times higher suicide rate[90]. The risk is especially higher in persons who are female, depressed, with psychopathology, family dysfunction, and personality disorder(s). In addition, it has been shown that heroin and opioid users have higher risk of attempting suicide[90].

A pragmatic randomized trial, designed to study methadone induction, showed that persons with HCV infection have higher suicidal risk than those without HCV: OR = 13.52, albeit with a wide 95% CI: (1.14, 161.07). The association was adjusted for receiving food assistance and reported number of health problems. The suicidal risk was assessed by a MINI questionnaire which asks about attempted self-harm, death and "suicide ideation"[91].

1.9 RECENT REGULATIONS TO COMBAT THE OPIOID EPIDEMIC

Since rates of opioid prescribing vary widely across the United States, new CDC Guidelines were published in 2016 to address opioid prescriptions among those outside of cancer, palliative, and end of life care[54]. The CDC gave recommendations on when to initiate, continue, or discontinue opioid for chronic pain. They also assessed type of opioid and dosage to be used as well as risks of harm from opioid use (mostly overdose and Opioid Use Disorder).

The burden of opioids is large, and adverse outcomes have been associated with prescribing practices. For example, the Drug Abuse Warning Network estimated that >420,000 emergency department visits were related to the misuse or abuse of narcotic pain relievers in 2011[92]. In addition, a cohort study found that long-term opioid therapy is associated with increased risk for an opioid abuse or dependence ICD-9-CM diagnosis when compared to those with no opioid prescription[93].

1.10 HOSPITAL-BASED OPIOID STUDIES

After performing a literature search using the terms "*opioid" AND "hospital", with or without "inpatient*" there were 9 studies that are relevant to our proposed project. These papers involved analyses from the following datasets: HCUP/NIS, Veterans Health Administration (VA), Washington state Medicaid, Australian Health System, Premier Health Services (sample of 286 acute care hospitals), and Pediatric Health Information System.

Owens et al.[13] used the *Healthcare Cost and Utilization Project (HCUP)* and *National Inpatient Study (NIS)* data to describe opioid "overuse" hospitalizations: opioid dependence,

abuse, poisoning, and adverse effects (excluded codes for heroin, psychodysleptics, and hallucinogens). The data are from sampled hospitals identified by the American Hospital Association as "community hospitals" which exclude rehabilitation and long-term acute care hospitals throughout all US states. This report was published in August 2014.

This is a descriptive report of inpatient stay rates of hospitalizations involving opioid overuse, showing that the crude rate of adult inpatient stays for opioid overuse increased by 153%: from 116.7 cases/100,000 population to 295.6 cases/100,000 population from 1993 to 2012. The percentage of opioid overuse admissions to the hospital from the emergency department increased from 43% to 65% in 1993 to 2005, respectively; and subsequent percentages from 2005-2012 did not have substantial changes. In addition, the average annual opioid hospital rate of stay increased from 1993-2012 was highest in persons 45 years and older (age-specific rates went from 66.6 cases per 100,000 to 338.1 cases per 100,000), as well as in Midwest region hospitals (region-specific rates went from 61.3 cases/100,000 to 320.8 cases/100,000). In 1993, males had a higher rate of opioid overuse-related inpatient visits than females, but the difference in sex-specific rates decreased by 2012.

The study also found that the number of secondary diagnoses, in addition to an opioid overuse over time, increased during 1993-2012. The mean number of secondary diagnoses was only 2.86 in 1993. The number of secondary diagnoses from 2000 and 2012 were 3.77 and 7.93.

Weiss et al.[94] published a statistical brief in June 2017 for opioid-related inpatient and ED visits from *HCUP* data, focusing on estimates by sex and by age group during 2005-2014. This is an update to information provided by Owens et al. By 2014, the opioid-related inpatient stay rates were similar among males and females. However, the similar sex-specific rates were not homogeneous throughout the US; female rates were at least 10% higher in 33 of 45 evaluated

states. Male rates were higher in 11 states, in addition to Washington DC. Males had consistently higher and increasing rates of ED visits.

The highest rates of opioid-related inpatient visits were in the age groups: 25-44 and 45-64. However, cumulative increases of rates of inpatient stays were highest among patients over 65 years old. ED opioid-related visit rates were highest in the 25-44 year old patients.

An additional study, Chandwani et al.[95] also used *HCUP* to study inpatient and ED hospital charges and costs of persons with an opioid ICD-9-CM discharge code (primary or any secondary diagnoses) during 2006-2008. These include dependence, abuse, poisoning by opiates, narcotics (304.0X, 304.7X, 305.5X, 965.00, 965.02, 965.09); the study excluded heroin poisoning. The average age of the persons was about 40 years old among about 347,000 opioid diagnoses.

They estimated nationwide total and average hospital charges (in 2010 US$). The total charges were $9.8, $9.6, and $9.5 billion for 2006, 2007, and 2008. Medicaid-insured visits accounted for the highest total of charges ($3 billion), followed by events covered by Medicare ($2 billion) for each year. The national estimate of per opioid abuse-related event charge was around $19,000 after adjusting for demographic and clinical factors.

Womer et al.[96] studied pediatric and young adult (≤20 years old) inpatients who use opioids in the United States from 2007-2012. They used the *Pediatric Health Information System* and *Premier Perspective Database* from 626 hospitals nationwide (general hospitals and children's hospitals) to study demographics, diagnoses, pharmacy activity, procedures, lab procedures, and other tests. This nationwide study had a total of over 5.6 million hospitalizations. The analysis defined opioid exposure as receiving opioids (including morphine, fentanyl, hydromorphone, methadone, oxycodone, Oxycontin®, nalbuphine, meperidine, and

codeine) during the hospital stay. Complex chronic conditions categories, defined by ICD-9 codes, included cardiovascular, neuromuscular, metabolic, malignancy, neonatal/prematurity, respiratory, renal, gastrointestinal, and hematologic. They estimated the opioid exposure percentage and used linear mixed models to investigate length of opioid use and of hospital stay, by discharge status (alive or dead).

There were 41.2% (about 2.3 million) of all hospital pediatric inpatients in the study who were exposed to opioids, for a mean of 4.6 days. The proportion of opioid exposure among inpatients increased with age and length of stay. There was a higher median length of opioid exposure with death discharge compared to those discharged alive. The lengths also varied widely across hospitals and by discharge statuses; terminal hospitalizations generally had the longest hospitalizations.

The authors concluded that there is a wide range of opioid use by hospital, but it could not be determined whether there was improper opioid use or lack of opioid use. Terminal compared to non-terminal hospitalizations seem to be the reason for the large disparate findings; differences in opioid use across hospital types did not vary as much. There is a need to create a standard to decrease the disparity of opioid use and length of use for pain management.

Mosher et al.[97] studied veterans who had chronic opioid therapy (COT) for acute care visits in all VA Hospitals in the United States, during 2009-2011 (N=122,794). The analysis studied veterans living in community settings, and used ICD-9-CM data from inpatient records as well as outpatient VHA Pharmacy Prescription data. This was a unique study that addresses the use of COT before hospitalization.

Patients were grouped into opioid statuses: no opioids (6 months before hospitalization), occasional use, and chronic use (COT: ≥90-day supply of opioids within 6 months prior to

hospitalization). Of the hospitalized veterans in the analytic sample, 54% had no opioids 6 months prior to the hospitalization; 26% were considered under COT (mostly hydrocodone); the remaining (20%) had occasional opioid therapy. They also defined select co-morbidities of chronic opioid use: 10 conditions based on probable associations or observed high prevalence among the hospitalized veterans.

The persons with COT - compared to those not using opioid chronically - had more COPD, complicated diabetes, PTSD, and mental health disorders. There were more than 50% medical inpatients with at least 1 pre-existing chronic non-cancer pain diagnosis. Univariable associations showed that patients with occasional opioid use or chronic opioid therapy had shorter length of stay, lower rates of non-home discharge, and higher hospital readmission rates after 30 days (also seen in multivariable models) than did patients without any opioid use. Death rates (mortality risk in multivariable models), length of ICU stay did not differ between groups. Most importantly when adjusting for demographics, Charlson Comorbidity Index (CCI), and selected comorbidities, COT was associated with increased risk of death during hospitalizations or within 1 month of the hospitalization. However, the authors acknowledged that COT can be a proxy of poorer health conditions.

Patients with cancer were included in the analysis, but the investigators found that COT was less frequent in persons with cancer than with pain diagnoses not involving cancer.

Herzig et al.[98] studied opioid use in non-surgical admissions to 286 US acute-care hospitals from July 2009- June 2010. Databases are from hospitals who volunteered to participate, and are maintained by *Premier Healthcare Solutions*, Inc. The data contain about 25% of the discharges in the country.

The analysis (about 1.14 million admissions) excluded persons with a length of stay >365 days, and patients from hospitals who had less than 100 admissions during the study period. Patients with surgical procedures were not included because the authors mention that these persons will almost always receive opioid pain medication(s). Opioid exposure was defined as having at least 1 charge for opioid medication during the admission; "severe" opioid-related adverse events were flagged if there was naloxone exposure or opioid-related adverse drug event diagnosis code (per the AHRQ: 965.02, 965.09, E850.1, E850.2, E935.1, E935.2). However, charges on day 1 of the hospitalization were excluded to focus on nosocomial (originating in hospital) events. The study modeled opioid prescription rates using GEE, and summarized relative risk of severe opioid-related adverse event per patient exposed. The main reasons provided for use of the opioids in non-surgical admissions were musculoskeletal injuries, specific and non-specific pain diagnoses, and cancer.

In the analytic sample, patients had a median age of 64 years. Around 51% of the admissions had charges for opioid medications, with 43% of these admissions receiving multiple opioids. Opioid use was more common in females, ages 25-54 compared to older and younger age groups, Caucasians, and those using Medicare/Medicaid. The relative risk of a severe opioid-related adverse event was greater in hospitals with higher opioid prescribing rates. Since pain severity was not available, it is difficult to determine the appropriateness of prescribing opioids and the quality of care. Despite this difficulty, the authors suggest there are opportunities to make opioid prescribing safer among persons of certain characteristics. The risk of opioid adverse events increased as opioid dosage and patient age increases. Older patients who receive high doses could be a target for enhanced education and follow-up. Future studies are needed to identify risk factors for opioid adverse events.

Zedler et al.[99] performed a nested case-control of administrative data from the *Veterans Health Association* from October 2010 to September 2012. The patients eligible for care in the VA Health system are veterans and some employees, family members, and research participants. The objective of the study was to find associated factors with opioid overdose or respiratory/CNS depression deaths among those who are using prescription opioids.

The cases (n=817) were characterized as both: dispensed opioid prescriptions by VHA (drug code), and had claim for serious opioid-related toxicity or overdose (ICD-9-CM code). These serious opioid-related toxicity cases/overdoses included (i) CNS/respiratory adverse effect codes in addition to listed poisoning events or external cause code occurring within 1 day of the adverse effect. Another serious event was (ii) use of mechanical ventilation or critical care in addition to listed poisoning/external cause code.

Ten controls were randomly selected for each case (n=8,170); the control had an opioid dispensed by VHA and did not experience serious opioid-related toxicity or overdose.

Cases were more likely to have poorer health status, and more likely to have other ailments such as depression, hypertension, opioid dependence, substance abuse, viral hepatitis, mental health disorders. The conditional logistic regression showed that the most strongly associated factors for serious opioid-related toxicity/overdose were: opioid dependence, moderate/severe liver disease, skin ulcers, metastatic solid tumor, and pancreatitis. Viral hepatitis was present in 13% of cases compared to 3% of the controls. During this 2-year study period, 19.5% of cases died compared to 3.5% of controls; the case-fatality rate was 2.4%. The maximum prescribed morphine-equivalent dose had 4.1 higher odds of having serious toxicity or overdose compared to opioid users without serious events.

Therefore, they recommend targeting persons at highest risk for serious events by providing naloxone and educational materials to more vulnerable persons (with specific demographics, co-morbid conditions, and medication use). This would help balance the benefits of using opioids and risks of overdoses.

Blanch et al. [100] described trends of prescription opioid use in Australia based on claims from hospitalizations, pharmacy, and accidental poisoning deaths. Australia has universal healthcare, and has 8 types of opioids that are subsidized by the Pharmaceutical Benefit Scheme. The database has information on the number of dispensing episodes and cost. The *ICD-10-CM* hospital records from 1998-2009 were taken from a national database, and was defined as: completion of treatment for an admitted patient due to death, discharge or transfer to another facility. Death certificate data were also defined by ICD-10 and focused on the X42 code (accidental poisoning by and exposure to narcotics and psychodysleptics).

They found that there was a 15-fold increase in number of dispensing episodes, with oxycodone being the major factor identified in the increase. Buprenorphine and fentanyl also had substantial increases in use. In 1998, 65% of opioid hospitalizations were due to heroin, but the proportion decreased gradually until 2009. Non-heroin, opioid-related hospitalizations increased from 605 to 1464 cases (1998 and 2009, respectively).

Fulton-Kehoe et al.[101] examined prescription history of patients before opioid poisonings in the Washington state Medicaid population. They studied adult patients with hospital admission and/or ED visit due to opioid poisoning (965.00 – poisoning by opium, 965.02 – poisoning by methadone, 965.09 – poisoning by other opioids or related narcotics) as well as having at least 1 opioid prescription claim. The analytic sample included persons aged 18-64

years from April 2006-December 2010. Data were from hospitalization discharges, opioid prescription histories, methadone maintenance treatment, and mortality records.

Their statistical analyses included calculation of poisoning rates, descriptive comparisons of methadone and other opioid poisonings, as well as a time-series analysis to compare monthly rates of opioid poisonings (controlling for random and seasonal effects).

In the analytic sample, about 4,000 and 94,000 individuals had at least 1 prescription for a methadone and non-methadone opioid, respectively. During the period of interest there were 2,250 methadone or other opioid poisoning events among 1,809 individuals. Among the non-methadone poisonings only there were 1,452 poisonings among 1,236 individuals during 2006-2010 (264 to 348 poisonings per 100,000 opioid users per year). In the non-methadone poisonings, only 44% of the individuals had chronic opioid use. Methadone poisonings occurred at over 10 times the rate of other prescription opioid rates. In addition, among the analytic sample about 7% with methadone poisoning and 3% with other opioid poisonings had an opioid-related death.

The study also found that less than half of the opioid poisonings occurred in patients with >90 day opioid prescriptions. Many persons (48%) also had opioid prescription in combination with other drugs such as sedatives. Most non-methadone poisonings were among patients prescribed low doses (<80 mg/d MED), contrary to other studies. Although methadone poisonings are a concern, 33% did not have a Medicaid claim for methadone, suggesting that a substantial amount of poisoning were from drug diversion.

1.10.1 Synthesis of Hospital Literature

1.10.1.1 Study Population/Datasets

Of the 9 articles reviewed, there were 7 that examined nationwide US data, 1 that analyzed Australian medical claims, and 1 that studied Washington state Medicaid patients.

Specifically, three articles described trends of opioid discharge rates and costs from HCUP data. Two of the articles used data from the Veterans Health Administration, one article each using Washington state Medicaid data, an Australian government database, a database of pediatric users, and a database that is a sample of the acute care hospitals in the United States.

1.10.1.2 Hospital Records and Hospital Types

There were 8 studies that used ICD (version 9 in US, version 10 in Australia) coding system to identify opioid users, mainly for heroin, opioid dependence, abuse, and poisoning. The other study (Womer) used pharmaceutical records to determine opioid status and length of opioid use (co-morbidities were determined using ICD-9-CM). Six studies used pharmaceutical records to investigate dosage, opioid status during hospitalization, and length of opioid use. Five of the articles had information on patient death.

HCUP studies (Owens, Weiss, and Chandwani) used data from "community hospitals" excluding rehabilitation and long-term acute care hospitals. Womer et al. used general hospitals and children's hospitals to perform analyses. Zedler, Blanche, and Fulton-Kehoe did not describe hospital types used. Mosher et al. used VA hospital data, but used only the acute care visits from the VA. The paper by Herzig analyzed acute care hospitals only, but focused on nosocomial opioid exposures and outcomes during admission.

1.10.1.3 Main Findings

There were few studies that went beyond describing rates, using statistical models to find associations between risk factors and opioid use. Womer et al. found that about 41% of pediatric inpatients were exposed to opioids and the proportion of opioid exposure among inpatients increased with age (among persons ages ≤20 years) and length of stay. Those who died had longer median length of opioid use. Mosher et al. used a VA patient population, and found that chronic opioid therapy prior to hospitalization was associated with increased risk of death. Herzig et al. found that relative risks of a severe opioid-related adverse event suggesting these events are greater in hospitals with higher opioid prescribing rates. Zedler et al. performed a nested case-control study using VA data and found among those dispensed opioids, cases of serious opioid-related toxicity/overdose had poorer health status.

Of the 4 studies involving analyses that went beyond simple statistics, 3 of them used data that spanned only less than 2 years and are not more recent than 2012. This does not allow for much trend analysis, and does not capture a large amount of the heroin use increase after 2010.

1.10.1.4 Risk factors identified

Opioid users had more COPD, complicated diabetes, PTSD, and mental health disorders[97]. Persons who visited VA hospitals who had opioid overdoses more frequently reported traumatic injury, including fractures, dislocation, and contusions[99]. Hospitals that have higher prescribing rates also had higher relative risk of severe opioid-related adverse events[98]. In addition, a nested case-control study found that those with opioid overdoses had poorer health status, and more likely to have discharges for depression, hypertension, opioid dependence, substance abuse, and viral hepatitis[99].

1.10.1.5 Gaps and Strengths of Existing Literature

Overall, there were several quality hospital studies that analyze legal, opioid prescription use, mainly from VHA or from Medicaid. The main advantage of studying these populations is the accuracy of the amount of opioid exposure, compared to most data sources such as patient interviews and surveys. However, a sizable proportion of the recent opioid epidemic involves opioids of illegal sources. The dataset of hospitalization proposed in our study could capture all opioid types, regardless of having an opioid prescription.

Zedler et al. was a quality study evaluating persons who had serious opioid toxicity or overdose among persons with opioid prescriptions. However, it was only over a 2-year period and therefore does not study long-term effects of opioid dependence and abuse. Our proposed study looks at hospitalizations over 15 years in the entire state of Pennsylvania, during 2000-2014. The hospitalizations reported to PHC4 are among persons in the general population, except patients who sought care at VA Hospitals. This will allow us to make recommendations based on a general population, and build upon the published studies based on opioids in US veterans.

1.11 LATENT CLASS ANALYSES FOCUSED ON OPIOID USERS

There have been multiple studies, using latent class analyses for Opioid Use Disorder[11] from the NSDUH[102–104], in a Washington state HMO[53], and a Canadian Cohort study[105].

Castaldelli-Maia et al.[104] used pooled data from NSDUH in 2011-2012 to examine 10 past-year OUD criteria and latent classes of sociodemographic, psychiatric, nonmedical use of prescription opioid (NMUPO). They are representative of persons 12 years and older in the United States.

The investigators used the NSDUH questionnaire for substance use in the last year, as well as lifetime use. Participants were asked questions about their substance use and mental health. They were shown pictures of substances and asked if they used them in the past year, without a doctor's prescription. NMUPO was defined as using prescription opioids for nonmedical reasons more than 120 days in the past year. Those who reported NMUPO were asked questions about tolerance, withdrawal, time spent, physical/psychological, social/interpersonal, and hazardous use. The covariates included were psychiatric (anxiety disorder, major depressive episode, antisocial behavior); sources (doctor shopping, drug dealer, family/friends), and other substance dependence.

The phenotype classes determined by the exploratory factor analysis and LCA were named "non-symptomatic class", "tolerance-time spent class" and "high-moderate symptomatic class". The non-symptomatic class had high probability of having high opioid tolerance (diminished effect of drug) and time spent (spent a lot of time getting drug or recovering from drug use) symptoms. Persons in the non-symptom class also had increasing prevalence of tobacco and/or alcohol dependence. The tolerance-time spent class were more likely to obtain prescription opioids from family and/or friends. High-moderate symptomatic class was more likely to be young adults (ages 18-25 years), persons who procure opioids for nonmedical reasons, and shop doctors to get opioid prescriptions.

Wu et al. used the 2007 version of NSDUH, implementing a factor mixture model which has LCA features, as well as item response theory (IRT). They used the following 11 criteria for OUD. Abuse criteria were (A1) serious problems at home, work, or school; (A2) regular consumption that put the user in physical danger; (A3) repeated use that led to trouble with the law; and (A4) problems with family or friends caused by continued use. Dependence criteria

were (D1) tolerance; (D2) withdrawal; (D3) more frequent use than intended or inability to maintain limits on use; (D4) inability to reduce or stop use; (D5) spending a great deal of time over a period of a month using the drugs or getting over the effects of use; (D6) reduced involvement or participation in important activities because of use; and (D7) continued use despite related problems with emotions, nerves, mental or physical health. They tested the differences in demographics and major depression.

The 11 classes were described among persons with OUD. These were summarized using FMM (accounts for both continuous and categorical factors within a class) as a *severely* affected and a *less severely* affected group. The two groups had statistically significantly different patterns for non-prescribed opioid use, major depression, and use of substance abuse treatment.

Ghandour et al. performed their analyses on 2002-2003 NSDUH data and assessed OUD and a "Severe Mental Illness" (SMI) for the adults in their analytic sample. The goal was to improve upon the DSM-IV criteria, since dependence problems may be more clinical relevant than DSM definitions. They used the definitions for clinical dependence to observe clustering within these definitions. This analysis classified the DSM definition as a variable, categorizing opioid users into Groups: past-year opioid analgesics only (A), past-year opioid analgesics and past-year users of stimulants, sedatives, and tranquilizers (AP), and past-year opioid analgesics/other prescription drugs as well as heroin and/or cocaine (APCH). SMI was determined using a series of 6 questions about psychological distress in at least 1 month, including feeling nervous, hopeless, restless, depressed.

The resulting LCA found classes 1 through 4, ranging from least severe to most severe. Class 1 had the most past-year opioid analgesic users (84%) and had close to 0% probability of having symptoms of opioid dependence. Class 2, 3, and 4 had probabilities of 39%, 85%, and

100% of having opioid dependence symptoms. Belonging to either Group A, AP, or APCH was not significantly different when comparing Class 1 to Class 2. However, being in Groups AP and APCH was significantly higher in Classes 3 and 4, when compared to Class 1. Participants with SMI were more likely to be in the higher classes of severity.

Monga et al.[105] categorized illegal opioid users from the OPICAN cohort in Canada to describe drug use patterns. Participants were recruited using snowball techniques and were administered semi-structured interviews on health, drug use in the last 30 days, crime, and treatment characteristics. HIV and HCV screening tests were also performed using saliva samples. The selected input variables for LCA had prevalence rates >20% were: alcohol, cannabis, cocaine, crack, dilaudid (hydromorphone), heroin, illegal methadone, Tylenol 3 or 4, and benzodiazepines.

Three latent classes were determined to be the best solution. The classes differed by site, but did not differ by sex. Class 3 had the most injection heroin, cocaine use, and highest levels of HIV and HCV, Class 2 used more non-injection drugs: crack and heroin, and Class 1 were mostly persons who used Tylenol 3, benzodiazepines, depression, and self-reported pain.

Banta-Green[53] used Washington state HMO administrative and prescription data and defined chronic opioid use as filling ≥10 opioid prescriptions during the last year, or filling the prescription for at least a 120 day supply and 6 or more opioid prescriptions during the 12 month period. They used factors from DSM-IV opioid abuse, dependence, and misuse, pain, anxiety, and depression. The latent class analysis yielded 3 groups – i) A typical group, which was the majority with persistent and moderate mental health and pain symptoms, ii) Addictive Behaviors group with elevated mental health symptoms and opioid problems, and iii) Pain Dysfunction class with higher pain interference in addition to elevated mental health and opioid problems.

The study found that the Addictive Behaviors and Pain Dysfunction classes had 3 times the prescribed opioid dose of those who in the Typical group.

In a general drug abuse context, Kendler et al.[106] performed a study in Sweden using all persons born during 1950-1993. They used data from hospital discharges, death registry, drug registries, and crime registries to define 6 LCA classes of drug use: 1) low-frequency pure criminal, 2) high-frequency medical criminal, 3) low –frequency pure medical, 4) high-frequency medical, 5) prescription, and 6) death. Each of the latent classes had distinct characteristics. For example, persons in class 2 (high-frequency medical criminal) were predominantly male, lower education level, had alcohol use disorder, and criminal activity. The latent class 5 (prescription) were more often female, low crime, but high percentage of psychiatric illness, and had siblings who did not abuse drugs.

1.12 CONCLUSION

Castaldelli-Maia et al.[104] states that it is important to continue creating more models in different samples of the general population. Our proposed project will study a cohort of those hospitalized in Pennsylvania with a discharge diagnosis of opioid dependence, opioid abuse, or opioid (and heroin) poisoning. These represent Pennsylvania residents who have issues with opioids who had to be hospitalized for either the opioid problem itself or as a secondary diagnosis. These patients have sought care and are likely to be higher-risk opioid users, when compared to someone with OUD. Another important benefit of using these discharge data is that the diagnosis code comes from a clinician, and should have a smaller risk of bias compared to a patient interview.

To our knowledge, no study has looked at a cohort of opioid-hospitalized persons linked with mortality records, representing severe medical care-seeking cases on a large statewide scale over a long period of time. Longitudinal descriptions and analyses are needed to better understand this growing population of persons affected by opioids and viral infections. Therefore, working with the PADOH, we identified an opioid cohort of PA residents in order to investigate individuals' experience over time with regard to encounters with the Hospital in patient system and subsequent mortality. With the high risk of HCV and HIV history in opioid users, and importance of these infections on health as one ages, it is important to compare the differences of survival patterns of persons with HCV or HIV over time. Re-hospitalizations rates and survival length of patients in the opioid cohort are compared by HCV and HIV infection statuses.

2.0 CLASSES OF OPIOID-RELATED HOSPITALIZATIONS IN PENNSYLVANIA AND THEIR ASSOCIATIONS WITH HCV AND HIV

ABSTRACT

***Background*:** The opioid epidemic started in 1990s in the United States. The proportion of persons prescribed opioids almost doubled from 2000 to 2010: 11% to 20%. Pennsylvania ranks 9th in the nation in the rate of long-acting pain reliever prescriptions and 14th for high dose opioid pain relievers. The objective of this study is to describe classes of opioid-related hospitalizations using indicators for opioid use disorder, opioid poisoning, sociodemographic and medical risk factors such as alcohol, tobacco, other drug use, mental disorders, and pregnancy; concurrent HIV and Hepatitis C virus (HCV) discharges were described among these classes.

Methods: We used ICD-9-CM discharge data from the Pennsylvania Health Care Cost Containment Council (PHC4) from 2000-2014. Visits with primary and/or secondary discharge codes for opioid-related hospitalizations (opioid use disorders (OUD), opioid poisoning, and heroin poisoning) were included in the sample. The analysis excluded cancer-related visits, patients 8 years or younger, and out-of-state residents. We performed a latent class analysis (LCA) using sociodemographics (age, sex, race, residence county urbanicity), alcohol, tobacco, other substance use, mental disorders, and pregnancy. Logistic regression was used to compare HCV and HIV co-discharges among visits by latent class (LC).

Results: There were 430,569 opioid-related hospitalizations (202,126 individuals). LCA analysis determined that the most appropriate model had 5 distinct LCs. Based on characteristics by class, they were named: 1) Pregnant women, OUD; 2) Elder women, opioid poisoning; 3) OUD, mental disorder, polydrug; 4) Overdoses, not substance users; and 5) Black, OUD, cocaine. LC3 was the largest class (58.2%), and the number of visits doubled over 2000-2014. The Pregnant women, OUD class had the highest percentage of HCV discharges: 5,273 visits (26.3%); Black, OUD, cocaine had the most HIV discharges: 6,490 (6.9%).

Discussion: There were 5 distinct classes that had different HCV and HIV risks. This study has public health relevance; although screening for HCV and HIV are not uniform for all opioid-related visits, it may be important to recognize groups of persons entering care with characteristics consistent with the LCs. It is important to specifically target pregnancy visits for HCV and other drug users for both HCV and HIV.

2.1 INTRODUCTION

There were 5.1 million Americans using opioid pain relievers for non-medical reasons in the in 2010[20]. Among those who seek medical care with pain-related diagnoses or symptoms, the percent of persons prescribed opioids almost doubled from 2000 to 2010 to around 20%[21]. Earlier years of the epidemic starting in the late 1990s had higher proportions of prescription opioid use, but the burden shifted around 2010 with higher proportions of heroin use[19,22]. Despite effectiveness in treating pain symptoms, there are concerns of opioid tolerance, abnormal pain sensitivity, and hormonal changes for long-term users[8]. This may result in Opioid Use Disorder (OUD), which is defined by the American Psychiatric Association as a problematic

pattern of opioid use leading to clinical significant impairment or distress[6,11]. In addition, opioid overdose or poisoning is a life-threatening emergency that can lead to respiratory depression[6].

Pennsylvania (PA) ranks 9th in the nation in the rate of long-acting pain reliever prescriptions, 21st for prescription of opioid pain relievers (OPR), and 14th for high dose OPR[33]. In PA, urban counties have higher rates of opioid hospitalizations compared to rural counties. However, rural counties of PA (south-central, north-central, and southern Allegheny regions) have recently had greater increases, compared to urban counties[32].

In the early part of the 20th century, the burden of opioid abuse have generally occurred in low-income, inner-city, minority populations. Most cases and deaths were among black males, according to narcotics registries and decedent data[34]. However, abuse in the United States has increased more in the suburban and rural areas with a majority white population, compared to urban areas[24].

Factors associated with increased risk for opioid misuse, defined as use of opioids contrary to its intended or medical recommendation[17], include a history of other substance use disorders, younger age, major depression, and use of psychotropic medications[52,53,68]. Mental disorders, including various personality disorders (obsessive-compulsive, paranoid, schizoid, histrionic, anti-social), are associated with OUD[68]. Furthermore, persons with schizophrenia, bipolar disorder, and psychosis had higher rates of opioid use disorder relapse, among those under treatment for opioid addiction[64]. Persons with other drug abuse and/or dependence also show evidence of increased risk of opioid abuse or misuse[53,107]. For example, persons reporting cannabis use had increased risks of both incident nonmedical prescription opioid use and OUD[107]. Other substances such as benzodiazepines commonly prescribed and used at the same time as opioid poisoning[38,70,101].

The crushed and ground form of prescription opioids, as well as heroin, can injected into the bloodstream via needles[45]. Important sequelae of opioid injectors sharing needles and injection paraphernalia include bloodborne diseases, especially hepatitis C virus (HCV) and HIV[69,70,72–74]. Many acquire these viruses through injections and soon after his/her first injection, due to sharing equipment with more experienced users who are HCV-positive[73]. The prevalence of HCV is high in injection drug users (IDUs)[70,75,76,108]; in most countries HCV prevalence among IDUs is over 50%[71]. Therefore, persons who inject drugs may also be at risk for HIV , which is spread similarly to HCV[73].

Latent class analysis (LCA) is a method to identify class membership, or categories, based on different variable combinations[105]. Due to lack of concrete evidence for causes of opioid hospitalizations, LCA are valuable to define typologies from observed data. Several articles found that opioid users from national surveys fall into 2 to 4 latent classes of increasing severity of disorder or other drug use[102–104]. Monga et al. 2007[105] analyzed Canadian illegal opioid users from a multi-site cohort study and categorized them into 3 classes of varying drug use, where HCV and HIV probabilities were the highest in the heroin and cocaine user group. There were also studies from Washington state patients under HMO health services[53], as well as a Swedish cohort[106] that looked at information on hospital, drug, crime registries, and death records. However, they did not assess HCV or HIV statuses among the latent classes.

The objective of this analysis is to describe the grouping of associated sociodemographic and medical risk factor characteristics including mental disorders, alcohol, tobacco, other substances, and pregnancy among opioid-related hospitalizations. From these groupings, we determined which groups were at highest risk for HCV or HIV discharge.

2.2 METHODS

2.2.1 Data Sources

This analysis uses data from the Pennsylvania Health Care Cost Containment Council (PHC4), a state agency that collects, analyzes, and reports information about health care across the state of Pennsylvania (PA)[32,109]. The PHC4 collects hospital discharge records with International Classification of Diseases, ninth revision, clinical modification (ICD-9-CM) information, in addition to demographic data from hospital records. Our study period of interest included records from 2000 through 2014.

2.2.2 Analytic Sample

The analytic sample included inpatient hospital records with opioid-related primary, first 8 secondary, and/or E-code (external cause of injury) discharges. The 9th to 17th secondary discharges were only available starting in the first quarter of 2011, and were not included in the analyses. The following ICD-9-CM codes were considered opioid-related were categorized: 965.01 and E850.0 (heroin poisoning), 304.00-304.03, 304.70-304.73, 305.50-305.53 (OUD), 965.00, 965.09, and E850.2 (opioid poisoning), and adverse effects in therapeutic opioid use: E935.2. Any record with the aforementioned ICD-9-CM code(s) in the primary and/or first 8 secondary discharge(s) was given an indicator for having that opioid type.

The following visits were excluded from the analysis: 1) records with any cancer discharge in the primary and/or the first 8 secondary diagnosis fields (10.2% of all PHC4 hospitalizations); 2) children ages 8 years or younger (10.3%); and 3) visits from persons who

reside outside of Pennsylvania (4.8%). Cancer visits were excluded because of a 1996 recommendation from the World Health Organization to prescribe opioids to relieve pain in persons with cancer[110]. In addition, children ages 8 years and younger were excluded to eliminate persons with neonatal abstinence syndrome (NAS). Oxycontin was recommended, by the American Academy of Pediatrics, for children 11 years and of age and older who were already receiving and tolerate minimum 20 mg daily opioid dose[111].

2.2.3 Covariates

Demographics including age, sex, race, and urbanicity of the residence county were taken from the patient data in the PHC4. Age was divided into the following groups: 9-14, 15-24, 25-34, 35-44, 45-54, 55-64, 65-74, 75-84, 85+ years. Race was categorized as: White, Black, Asian/Pacific Islander/Native Hawaiian, American Indian/Alaskan Native, Other/Multiple, and Unknown. Residence county urbanicity was determined by using the 2013 NCHS Urban-Rural Classification Scheme[112], using the following categories: Large central metro, Large fringe metro, Medium metro, Small metro, Micropolitan, and Noncore.

All diagnoses were identified by ICD-9-CM codes from primary and/or the first 8 secondary discharges: alcohol history/related reasons, tobacco, marijuana, cocaine, barbiturates, mental disorders (include any of the following: anti-social disorder, anxiety disorder or state, bipolar disorder, major depressive disorder, schizophrenia), as well as pregnancy. The disease outcomes studied in this analysis were hepatitis C virus (HCV) and HIV, and were also identified by ICD-9-CM codes. The specific ICD-9-CM codes used to determine these conditions and diseases are included in the Appendix (Table 12).

2.2.4 Statistical Analyses

We described demographic characteristics, opioid discharge categories, other drugs, mental disorders, pregnancy, HIV, and HCV. The sample excluded cancer, ages 8 and younger and out-of-state residents. The demographics and discharges in the analytic sample of opioid-related records were compared to a sample of other PHC4 hospitalizations (Figure 1 and Table 1). The LCA was performed on the analytic sample of the opioid-related records. Each record was assigned to an independent, exclusive latent class (LC).

The latent classes were defined using variables representing (1) *Demographics:* age group, sex, race, and residence county urbanicity; (2) *Opioids:* heroin poisoning, OUD, and opioid poisoning; (3*) Substance use:* alcohol, tobacco, marijuana, cocaine, and barbiturates; (4) *Mental disorders,* defined as any of the following: anxiety, bipolar disorder, anti-social disorder, major depressive disorder, psychosis, and schizophrenia; and *(5) Pregnancy*.

We fit models with increasing number of classes, from 2 to 11. Selection for the appropriate number of LCs was determined by calculating statistics such as Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), and Chi-squared goodness-of-fit test. Further investigation on LC groupings differences for each model were also used for final model determination.

For separate comparisons of HCV and HIV discharges by latent class, the counts and percentages of HCV or HIV codes were presented by LC. Logistic regression analyses used disease statuses as the outcome and were regressed on the LC variable. Due to multiple comparisons, we used a Bonferroni correction of $\alpha=0.05$ divided by the number of comparisons and reported odds ratios with 95% confidence intervals (CI) with and without the Bonferroni correction.

LCA was performed in R version 3.3.1 (R Foundation for Statistical Computing) using the *poLCA* package, created for polytomous variable latent class analysis. All other statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

This analysis was approved as an exempt, secondary data analysis by the Institutional Review Board at the University of Pittsburgh (IRB#: PRO16020235).

2.3 RESULTS

There were over 28 million observations in the PHC4 dataset from 2000-2014. After excluding records with cancer discharges, persons living out of state, and children 8 years and younger, there were about 21.7 million included hospitalizations. Among these records, 430,569 had an opioid-related discharge at the primary and/or the first 8 secondary discharge(s) (Figure 1). These opioid-related visits were among 202,126 individual patients.

The records from the primary or secondary opioid-related visits from 2000-2014 were mainly male (56%), white (76%), and from large central metro counties (41%) (Table 1). Most of them were in the age range of 25-54 years (68%). The opioid-related hospitalizations from the analytic sample had 85% discharged for OUD, 6% for opioid poisoning, and 2% for heroin poisoning. The selected conditions, such as HCV and mental disorders, had higher percentages among opioid-related hospitalizations compared to hospitalizations that were not opioid-related.

2.3.1 Latent Class Membership

We used LCA to determine that the most appropriate model divided the hospitalizations into 5 distinct classes. The AIC and BIC values were the highest in the 2-class model, and these values decreased as the number of LCs increased (not shown). The Chi-squared goodness-of-fit test statistic had a large decrease comparing the 4-class to the 5-class model.

In the 5-class model, we found that 2 new classes (LC2 and LC4) separated the females in older age groups with opioid poisoning from relatively younger persons with both opioid and heroin overdose indicators. As shown in Table 2, LC2 and LC4 have different probabilities for age group, sex, heroin, OUD, opioid poisoning, alcohol, tobacco, and mental disorders. The Chi-squared value determined that the 5-class model is the best for our sample.

2.3.2 Defining Latent Classes

The determined latent classes (LC) each had specific and defining characteristics, which are presented in Table 2. LC1 "Pregnant women, OUD" is defined with a high probability of pregnancy, younger age groups, with OUD, very low alcohol, mostly white, and in large metro areas. LC2 "Elder women, opioid poisoning" includes records with lower OUD and higher opioid poisoning, and were more likely to be white, women, in the older age groups (~65% probability in the ≥65 year old groups), in counties with small populations, as well as very low probabilities for drug use and mental disorder. LC3 "OUD, mental disorder, polydrug" is defined as records that had 100% probability of OUD, and more likely to be white, males, and higher probabilities of mental disorders, tobacco, marijuana, and barbiturates. LC4 "Overdoses, not substance users" are visits that have a 59% opioid poisoning and 12.5% probabilities with

heroin poisoning, in addition to low marijuana, cocaine, barbiturates probabilities. LC5 “Black, OUD, cocaine” have OUD discharges who were more likely black or multiple race, male, more likely to be in age groups greater than 35 years old, with high probability of cocaine and slightly higher probability of tobacco use.

2.3.3 Latent Class Membership by Year

The latent class allocation was not always constant across the 2000-2014 period (Figure 2). Latent classes 1, 2, and 4 (Pregnant women, OUD; Elder poisoning, opioid poisoning; and Overdoses, not substance users) stayed at consistent proportions. Latent class 5, which is defined by majority Black race and OUD decreased slightly but increased from 2010 to 2014. The largest group was LC3 (OUD, mental, and polydrug), which doubled during the 2000-2014 time period.

2.3.4 Disease Associations

The percentage of any HCV discharge among opioid-only and non-opioid visits was 15.8% and 1.3%, respectively (Table 1). The HCV percentages ranged from 1.0% to 26.3% in the latent classes (Table 3). The highest percentage of HCV discharge was in LC1 “Pregnant women, OUD” (26.3%), followed by LC5 “Black, OUD, cocaine” (22.5%), LC3 “OUD, mental disorder, polydrug” (15.9%).

Odds ratio estimates used LC3 as the comparison group, since it is the largest opioid group (58.2% of the analytic sample). Pairwise tests were performed for HCV discharges among 5 classes and therefore ${}_5C_2 = 10$ comparisons were made; the Bonferroni correction yielded a

critical value of 0.05 / 10 = 0.005. Compared to LC3, the odds ratios for LC1 and LC5 (OR=1.89 and 1.53) showed statistically significantly higher HCV discharge risk; LC2 and LC4 (OR=0.06 and 0.30) had significantly lower HCV discharge risk.

Similarly, the percentage of HIV discharge among opioid-only and non-opioid discharges are 2.4% and 0.6%, respectively (Table 1). HIV percentages ranged from 0.1% to 6.9% in the latent classes (Table 4). The highest percentage of HIV discharge was in LC3 "Black, OUD, cocaine" (6.9%). The remaining latent classes had low prevalence, of 1.3% or less. Compared to LC3, only the odds ratio for LC5 (OR=5.74) showed statistically significantly higher HIV discharge risk; LC1 and LC2 had lower HIV discharge.

2.4 DISCUSSION

The goal of this analysis is to define the clustering of PA opioid hospitalizations from 2000-2014 by sociodemographic characteristics, other substance discharges, mental disorders, and pregnancy. The 430,569 reported opioid-related inpatient visits can be divided into 5 distinct groups: (1) Pregnant women, OUD; (2) Elder women, opioid poisoning; (3) OUD, mental disorder, polydrug; (4) Overdoses, not substance users; and (5) Black, OUD, cocaine. The pregnant women latent class had the highest percentage of HCV on the same visit, while the Black, OUD, cocaine latent class had the highest percentage of HIV.

These primary and/or secondary opioid-related visits reflected 202,126 individuals and there were 82,880 visits in 54,394 individuals with opioid as a primary diagnosis (results in Appendix). There could be biases associated with presenting visits, as some individuals may tend to have more visits than others. LCA performed on the first visit for someone with primary

and secondary discharge yielded similar LCs and characteristic probabilities. The LCA performed on the primary opioid discharge visits yielded slightly different LCs. A six-class model was selected, and unlike the other LCA, did not have a category for pregnancies. This may be because a primary discharge for pregnancy may take precedence over a primary opioid discharge.

There are several existing articles that assess general opioid users, which only included persons with OUD or recreational users[102–104]. Therefore these samples do not necessarily reflect persons with outcomes requiring hospitalization. There are other studies that examine a population of persons hospitalized for opioid that include poisonings and examine risk factors, co-morbidities, and deaths[97,99]. However, compared to these hospital studies our study uses a longer time period (2000-2014), a large non-veteran hospital sample, and includes heroin poisonings.

Although other studies using LCA[102–104] found smaller proportions of persons with abuse and dependence, co-morbid major depression and substance abuse treatment, the analyses were performed on general opioid users representative of the US civilian population. The latent classes determined in these studies had slightly different input variables, with emphasis on sociodemographics and opioid types[103] ; depression, days using opioids[102]; mental disorders, doctor shopping, and how opioid was obtained[104]. However, each study found a latent class with an especially high amount of substance use and/or mental disorder(s).

Our analysis found that OUD discharges are present in almost all (85%) of the opioid hospitalizations. By definition, the Diagnostic and Statistical Manual of Mental Disorders (DSM)-V diagnostic criteria[11] for OUD is wide-ranging, including: taking larger amounts or over a longer period than intended, persistent desire or unsuccessful efforts to control use,

cravings/strong desires, recurrent opioid use resulting in failure to satisfy obligations, tolerance, and withdrawal. It is intuitive to think that persons seeking medical care for opioid will fall into these categories.

The LCs determined from the present analysis showed that there are several distinct groups. LC3 "OUD, mental disorder, polydrug" have posterior probabilities greater than that of the overall, analytic sample of opioid hospitalizations for: OUD, tobacco, mental disorders, marijuana, and barbiturates. They are the largest group in the analytic sample with the number of patients in the category increasing over time. A reason for the increase over time could be the slight growth in psychological distress and major depression in the United States[113,114], increase in opioid poisoning rates from 2006 to 2010[101], as well as the increase in all types drug overdoses over the decade of the 2000s[38].

It would have been expected that persons in LC3 would also have a large percentage with co-listed HCV discharge due to drug use. However, it is possible that young inpatients with drug problems receiving inpatient care may have more urgent problems and may not be screened for HCV. Health education and drug counseling among persons with those characteristics will be necessary to prevent the largest amount of morbidity and mortality due to opioid issues.

Pregnancy is the defining characteristic of the latent class with the highest percentage of those with HCV. Reported HCV rates among pregnant women in the state of Florida have increased from 17 to 125 per 100,000 hospital births in 1998 and 2007[115]. A study by Krans et al.[116] showed 60% HCV positivity among pregnant women with opioid dependence discharges, who delivered infants during 2009-2012. The hypothesized reason for the elevated prevalence is the large number of persons with OUD who share injection drug needles and paraphernalia, which may be infected with HCV. These women might be at higher risk because women, when

compared to men, were more likely to use "dirty" drug-injecting needles[117] and acquiring HCV infection, even after adjusting for demographic and injection patterns[118].

Due to the asymptomatic nature of the disease, many are unaware of their HCV infection[119] and the pregnancy-related visit may be one of few opportunities for screening. The prevalence in our analysis is not as high as the 60% HCV positive reported in Krans et al. This is likely because the US Preventive Services Task Force (USPSTF) does not specifically recommend screening of hepatitis C in pregnant women[120,121]. There may be several HCV-infected women who are not discharged for HCV, but the true prevalence of these women may be closer to 60%.

LC5, defined by Black, OUD with high cocaine use, have the 2nd highest percentage of co-listed HCV discharge and highest percentage of concurrently discharged HIV. Despite decreasing overall rate of HIV diagnoses from 14.2 to 12.3 per 100,000 population in 2010 and 2015, African Americans have the highest rates, when compared to other races[122].

A major strength of this study is use of the LCA in a large dataset of all opioid inpatients in Pennsylvania during a long time period and create categories based on the discharges of observed visits. The long time period allowed us to assess trends during the opioid epidemic. The analysis provided the opportunity to measure the burden of hospitalizations in Pennsylvania among groups of sociodemographic characteristics, mental disorder, other substance use, pregnancy, and HCV and HIV discharge statuses.

This main analysis used PHC4 data on the visit-level, not unique patients. Visit-level results may misrepresent true prevalence due to repeated visits; there could be inflated numbers of those older persons and/or those with more severe conditions. Another limitation is that the

latent class categories by year shows trends, but this assumes that the latent class categorization is the same if LCA models are fit for each year.

An important caveat of interpreting the HCV and HIV analyses are that since the patient is discharged with the viruses and opioid at the same visit, it is not necessarily reflective of the exact time of acquiring the virus. Due to lack of lab results and result dates, it is not certain when the patient tested positive for the viruses. Therefore, the records show those who are discharged with opioid and HCV and/or HIV at the same visit. We can consider it an underestimate of the true prevalence of the viruses.

Since opioid use disorder and opioid addiction are diseases of unknown states, it is important to define and categorize Pennsylvania hospitalizations. These divisions of latent classes can have important implications on informing treatment and prevention strategies for HCV and HIV. Although screening for HCV and HIV are not comprehensive for all opioid-related visits, it may be important to notify persons at pregnancy visits with OUD to be screened and treated.

2.5 FIGURES AND TABLES

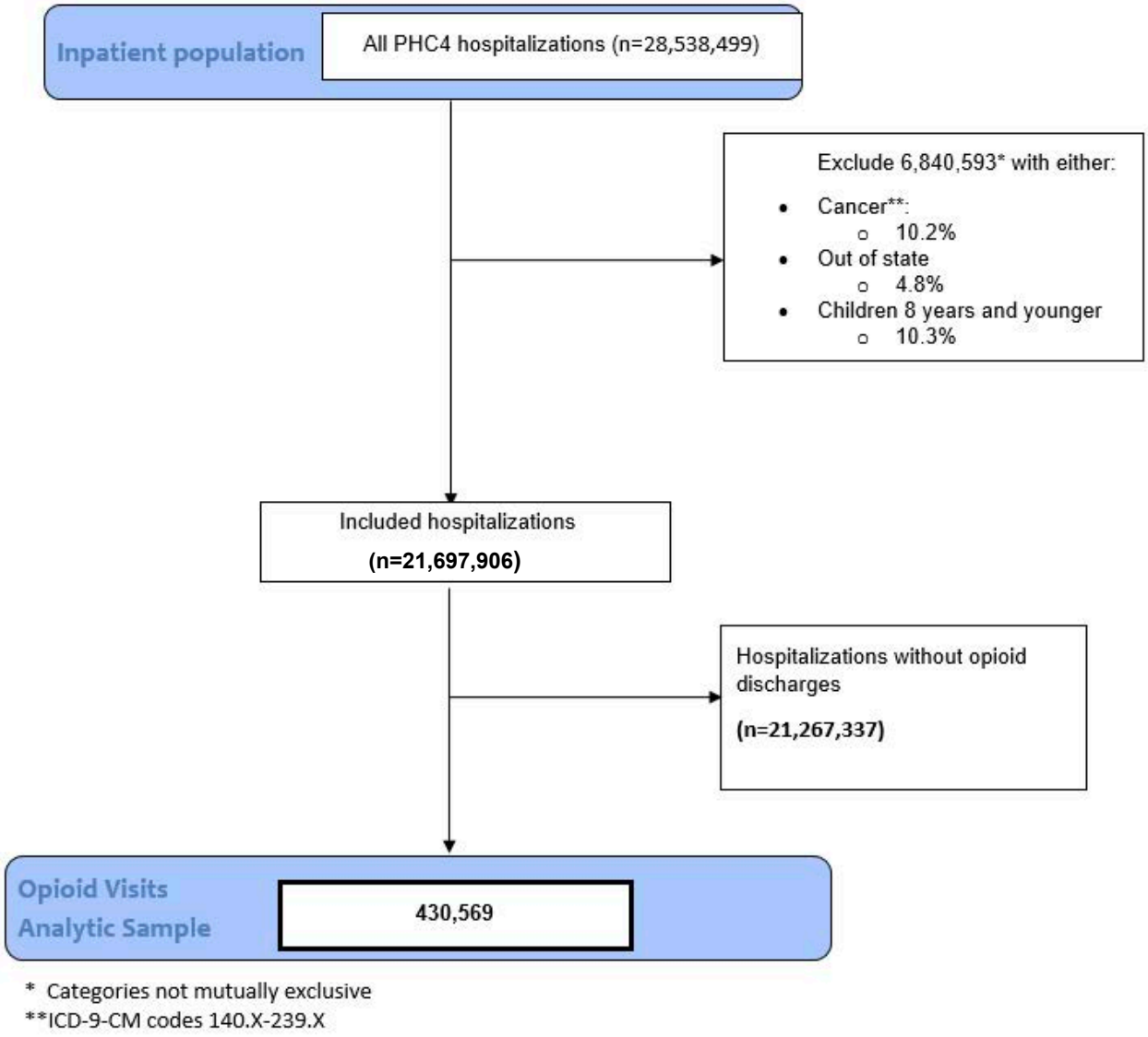

Figure 1. Opioid Visits in PHC4 – 2000-2014

Table 1. Descriptive Characteristics, PHC4 Analytic Sample: 2000-2014

Characteristics	*Opioid only N=430,569*	*Hospitalizations without opioid discharges N=21,267,337*
Age Group		
9-14 yrs	619 (0.1%)	317,992 (1.5%)
15-24 yrs	71,313 (16.6%)	1,629,262 (7.7%)
25-34 yrs	118,592 (27.5%)	2,239,729 (10.5%)
35-44 yrs	93,998 (21.8%)	2,059,539 (9.7%)
45-54 yrs	80,855 (18.8%)	2,580,866 (12.1%)
55-64 yrs	34,857 (8.1%)	2,902,623 (13.7%)
65-74 yrs	14,444 (3.4%)	3,275,617 (15.4%)
75-84 yrs	10,691 (2.5%)	3,922,214 (18.4%)
85+ yrs	5,198 (1.2%)	2,339,316 (11%)
Sex		
Male	242,906 (56.4%)	8,729,392 (41.1%)
Female	187,626 (43.6%)	12,533,924 (58.9%)
Unknown	36 (0.0%)	1,025 (0%)
Pregnancy	20,119 (4.7%)	2,229,389 (10.5%)
Race		
White	329,073 (76.4%)	16,891,665 (79.5%)
Black	57,108 (13.3%)	2,834,980 (13.3%)
Asian/Pac Is/Hawaiian	837 (0.2%)	130,830 (0.6%)
American Ind/AK Native	2,770 (0.6%)	32,166 (0.2%)
Other/Multiple	23,845 (5.5%)	541,282 (2.6%)
Unknown	16,818 (3.9%)	830,085 (3.9%)
Residence County Urbanicity		
Large central metro	177,898 (41.3%)	5,544,607 (26.1%)
Large fringe metro	100,142 (23.3%)	5,955,836 (28%)
Medium metro	98,555 (22.9%)	5,479,663 (25.8%)
Small metro	23,059 (5.4%)	1,713,520 (8.1%)
Micropolitan	23,392 (5.4%)	1,923,615 (9%)
Noncore	7,523 (1.7%)	650,096 (3.1%)
Heroin Poisoning	9,384 (2.2%)	0 (0%)
Any OUD (abuse or dependence)	367,538 (85.4%)	0 (0%)
Opioid Poisoning	25,593 (5.9%)	0 (0%)
Alcohol history/related	36,720 (8.5%)	515,049 (2.4%)

Table 1. Descriptive Characteristics, PHC4 Analytic Sample: 2000-2014, continued

Characteristics	*Opioid only N=430,569*	*Hospitalizations without opioid discharges N=21,267,337*
Tobacco	100,204 (23.3%)	2,449,668 (11.5%)
Any mental disorder	138,176 (32.1%)	2,144,672 (10.1%)
Marijuana	32,709 (7.6%)	207,659 (1.0%)
Cocaine	68,861 (16.0%)	278,664 (1.3%)
Barbiturates	32,027 (7.4%)	35,725 (0.2%)
Amphetamines	1,946 (0.5%)	4,787 (0.0%)
HIV	10,263 (2.4%)	123,190 (0.6%)
HCV	68,143 (15.8%)	271,317 (1.3%)

Table 2. Posterior Probabilities (%) for Class Membership in the 5-Class Model

		Latent classes (percentage of analytic sample, n=430,569)*				
Variable	Outcome	LC1 (4.7%)	LC2 (8.7%)	LC3 (58.2%)	LC4 (6.6%)	LC5 (21.8%)
Age Group	9-14 yrs	0.0	0.9	0.1	0.4	0.0
	15-24 yrs	34.4	0.5	23.0	16.5	4.5
	25-34 yrs	56.3	1.0	33.3	20.2	20.6
	35-44 yrs	9.3	4.5	21.7	22.0	31.0
	45-54 yrs	0.1	9.2	16.3	26.2	29.5
	55-64 yrs	0.0	18.4	4.8	12.3	12.2
	65-74 yrs	0.0	25.6	0.7	2.3	2.1
	75-84 yrs	0.0	26.6	0.1	0.1	0.2
	85+ yrs	0.0	13.3	0.0	0.0	0.0
Sex	Male	0.0	32.1	59.1	49.4	72.6
	Female	100.0	67.9	40.9	50.6	27.4
Pregnancy		94.0	0.0	0.0	0.3	0.0
Race	White	83.4	90.0	91.5	82.0	35.0
	Black	9.2	6.3	1.7	11.7	42.9
	Asian/Pac Is/Hawaiian	0.2	0.3	0.2	0.3	0.2
	American Ind/AK Native	0.1	0.0	1.1	0.0	0.0
	Other/Multiple	1.8	0.9	2.7	2.8	15.0
	Unknown	5.3	2.4	2.8	3.2	6.8
Residence county	Large central metro	40.8	17.2	29.9	22.7	80.9
	Large fringe metro	24.7	28.1	30.0	29.0	4.5
	Medium metro	19.2	32.8	25.0	28.1	13.8
	Small metro	5.6	8.5	6.4	8.8	0.8
	Micropolitan	7.4	10.1	6.5	8.9	0.0
	Noncore	2.2	3.2	2.1	2.6	0.0
Heroin poisoning		0.2	0.0	1.7	12.5	1.5
OUD		95.7	13.5	100.0	6.0	99.2

Table 2. Posterior Probabilities (%) for Class Membership in the 5-Class Model, continued

		Latent classes (percentage of analytic sample, n=430,569)*				
Variable	Level	LC1 (4.7%)	LC2 (8.7%)	LC3 (58.2%)	LC4 (6.6%)	LC5 (21.8%)
Opioid poisoning		0.1	**11.8**	1.2	**59.2**	0.7
Alcohol		1.9	0.3	9.9	9.4	9.6
Tobacco		12.7	5.7	**29.4**	22.1	18.5
Any Mental Disorders		13.4	8.1	**42.7**	29.0	21.9
Marijuana		6.5	0.0	**10.4**	2.7	5.7
Cocaine		12.5	0.0	15.3	3.6	**27.5**
Barbiturates		3.6	0.1	**10.3**	0.9	6.4

→Cells that are **highlighted and bolded** are much higher than the overall sample of opioid hospitalizations

*Names of latent classes
LC1 “Pregnant women, OUD”
LC2 “Elder women, opioid poisoning”
LC3 “OUD, mental disorder, polydrug”
LC4 “Overdoses, not substance users”
LC5 “Black, OUD, cocaine”

Table 3. Hepatitis C by Latent Class

Count Col %		LC1	LC2	LC3	LC4	LC5	Total
Co-listed HCV discharge	No	14,764 73.7%	37,190 99.0%	210,936 84.1%	26,695 94.6%	72,841 77.5%	362,426
	Yes	5,273 26.3%	390 1.0%	39,866 15.9%	1,524 5.4%	21,090 22.5%	68,143
Total		20,037	37,580	250,802	28,219	93,931	430,569

Latent Class	OR estimate	95% Confidence Interval	Bonferroni-adjusted 95% Confidence Interval
1 vs 3	1.89	(1.83, 1.95)	(1.80, 1.98)
2 vs 3	0.06	(0.05, 0.06)	(0.05, 0.06)
4 vs 3	0.30	(0.29, 0.32)	(0.28, 0.33)
5 vs 3	1.53	(1.50, 1.56)	(1.49, 1.57)

Table 4. HIV by Latent Class

Count Col %		LC1	LC2	LC3	LC4	LC5	Total
Co-listed HIV discharge	No	19,877 99.2%	37,528 99.9%	247,602 98.7%	27,858 98.7%	87,441 93.1%	420,306
	Yes	160 0.8%	52 0.1%	3,200 1.3%	361 1.3%	6,490 6.9%	10,263
Total		20,037	37,580	250,802	28,219	93,931	430,569

Latent Class	OR estimate	95% Confidence Interval	Bonferroni-adjusted 95% Confidence Interval
1 vs 3	0.62	(0.53, 0.73)	(0.50, 0.78)
2 vs 3	0.11	(0.08, 0.14)	(0.07, 0.16)
4 vs 3	1.00	(0.90, 1.12)	(0.86, 1.17)
5 vs 3	5.74	(5.50, 6.00)	(5.40, 6.11)

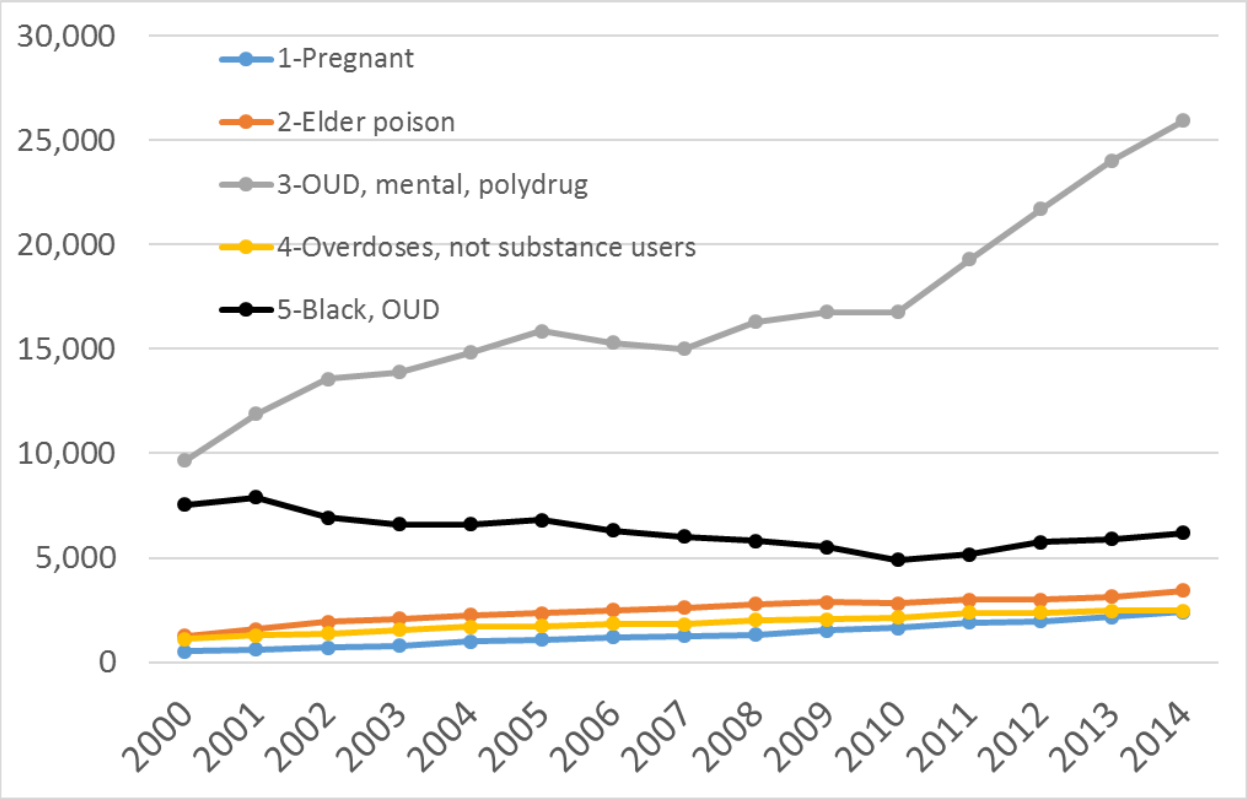

Figure 2. Number of Patients, Trends of Latent Classes by Year, 2000-2014

3.0 RE-HOSPITALIZATION RATES AMONG OPIOID INPATIENTS BY HCV, HIV, AND URBANICITY IN PENNSYLVANIA, 2000-2010

ABSTRACT

Background: Opioid Use Disorder (OUD), is a problematic pattern of opioid use leading to clinical significant impairment and sometimes overdose, who are more likely to have another overdose. Persons injecting opioids have high risk for transmission of Hepatitis C virus (HCV) and HIV, which can develop into comorbid and chronic conditions. The purpose of this analysis is to compare the number of inpatient hospitalizations and rates between persons with and without HCV, HIV discharges and residence county.

Methods: This analysis uses ICD-9-CM discharge information from the Pennsylvania Health Care Cost Containment Council. Codes representing heroin poisoning, opioid poisoning, and OUD were considered opioid-related. Discharges from patients after the first opioid-related hospitalization during 2000-2010 were analyzed. Patients with no record of a re-hospitalization within 2000-2010 were censored at December 31, 2010.

The following demographics were described: age, sex, race, and residence county urbanicity. Additional time-varying covariates included: hospital discharge codes for HCV, HIV, alcohol, tobacco, other illegal drugs (marijuana, cocaine, and/or barbiturates), and mental disorders. Semi-parametric mixed Poisson regression models determined rate multipliers, essentially rate ratios, of re-hospitalization.

Results: The 132,674 individuals (560,480 hospitalizations) in the analytic sample were 55.3% male, had a mean age of 40 years, were 80.5% white race, 90.0% urban residents, had opioid diagnoses: OUD – 99,832 (75.3%), opioid poisoning – 10,883 (8.2%), and heroin poisoning – 2,816 (2.1%). At any time during the cohort, 29,918 (22.6%) patients had a HCV discharge, and 3,741 (2.8%) had HIV discharge.

Patients with HCV was 1.11 (95% confidence interval: 1.10, 1.13) times re-hospitalization rate among persons at mean age of 40 years at the index visit. Those with HIV had a rate multiplier of 1.38 (95% CI: 1.34, 1.42) and urban compared to rural counties was 1.14 (95% CI: 1.12, 1.16).

Discussion: Opioid users with HCV and HIV have higher rates of re-hospitalizations, which is of public health relevance indicating higher morbidity, as well as larger burden to the US healthcare system. Disease screening and avoiding risk behaviors could be beneficial to the patient to decrease the chance of future inpatient stays.

3.1 INTRODUCTION

The opioid epidemic has had a substantial burden in the United States[19,20]. The number of opioid prescriptions has increased in the United States, doubling from 2000 to 2010[21]. In the mid-1990s, it was recommended for healthcare providers to treat pain symptoms in patients with opioids, due to their high effectiveness in treating short-term pain[62]. This resulted in a serious dilemma in the US involving a large group of individuals who become chronic users of opioids.

The issue of tolerance to painkillers and abnormal pain sensitivity may be a direct result for patients who are chronic users of opioids. These persons may progress to Opioid Use

Disorder (OUD), which is defined by the American Psychiatric Association as a problematic pattern of opioid use leading to clinical significant impairment or distress[6,11]. OUDs are also associated with co-morbid psychiatric conditions, including various personality disorders such as obsessive-compulsive, paranoid, schizoid, and anti-social[68]. Furthermore, persons with schizophrenia, bipolar disorder, and psychosis have higher rates of OUD relapse, among those under treatment for opioid addiction[64].

Those with a non-fatal opioid overdose have a higher risk of a future overdose[84]. Zedler et al.[99] studied the national Veterans Affairs (VA) hospital database and found among veterans dispensed opioids, those with overdoses had longer mean length of hospital visit(s), as well as higher percentage of outpatient ED visits, office visits, and number of inpatient hospitalizations. A Washington state study of opioid poisonings analyzed Medicaid claims for opioid prescription, in addition to an emergency department visit or inpatient hospitalization. There were 1,452 opioid poisonings among 1,236 adults. Among these poisonings, 85% had 1 opioid poisoning visit, 9% had 2 opioid poisonings, and 6% had 3 or more opioid poisonings[101]. In addition, Mosher et al. found that veterans accessing VA hospitals during 2009-2011 with chronic opioid therapy had 1.15 times higher odds of being readmitted to a VA hospital[97].

In Pennsylvania, urban areas have higher rates of opioid hospitalizations compared to rural areas. However, rural counties of Pennsylvania (south-central, north-central, and southern Allegheny regions) have recently had greater increases from 2000 to 2014, compared to urban counties[32]. Persons living in urban areas may have better and/or more access hospitals, due to distribution of hospitals in Pennsylvania. Therefore, the clustering of hospitals may contribute to the increased rate of hospitalizations in urban counties. Some patients in rural areas are

concerned about stigma, discrimination, and confidentiality when seeking hospital care because of the smaller population in the surrounding area[123].

Prescription opioid tablets and heroin can be injected into the bloodstream via needles or syringes[45]. Injection needles and their paraphernalia can spread bloodborne diseases such as HIV and Hepatitis C virus (HCV)[69,70,72–74]. The prevalence of HCV is high among injection drug users (IDU)[70,75,76,108]. These viral infections can develop into chronic conditions[124,125], leading to higher morbidity compared to a person without the infection.

Individuals seen in emergency departments or in hospitals are not universally screened for HIV and HCV, and are generally underdiagnosed due to lack of awareness[126,127]. The asymptomatic nature of these diseases, in conjunction with the large rise in opioid use could also have an even larger increase in HCV and/or HIV infections resulting in re-hospitalizations and increased morbidity. To our knowledge, no other studies have analyzed the difference in hospitalization rates for those with co-morbid HCV and/or, HIV, and within urban vs. rural regions in a cohort of patients with at least one opioid-related hospitalization.

The purpose of this analysis is to compare the number of inpatient hospitalizations and rates, in the opioid cohort, between persons with and without HCV discharges, as well as a separate comparison of persons with and without HIV discharges. The rates will also be compared between patients residing in urban and rural counties of Pennsylvania. We will also describe the primary discharge diagnosis in the final visit during the opioid cohort.

3.2 METHODS

3.2.1 Data Source

This analysis uses a dataset of individuals with discharges from inpatient hospitalizations, which are collected by the Pennsylvania Health Care Cost Containment Council (PHC4)[32,109]. The PHC4 collects hospital discharges as International Classification of Diseases, ninth revision, clinical modification (ICD-9-CM) information, in addition to demographic data from hospital patient records. The study population consisted of individuals admitted to a Pennsylvania hospital with a discharge diagnosis of an opioid primary and/or secondary diagnosis in at least one hospitalization between 2000 and 2010 (index visit), as well as any subsequent visits for each patient in that time period. The following ICD-9-CM codes were considered opioid-related: 965.01 and E850.0 (heroin poisoning), 304.00-304.03, 304.70-304.73, 305.50-305.53 (OUD), 965.00, 965.09, and E850.2 (opioid poisoning), and E935.2 (adverse effects in therapeutic opioid use). The study population consisted of linked visits from individuals by a Social Security Number identifier. The index opioid visit for a patient in the cohort was the first presence of any ICD-9-CM opioid code in a primary and/or secondary diagnosis field during 2000-2010. We analyzed a sample including the index opioid visit and all subsequent visits with any discharge(s), until the end of the year 2010. Patients with no record of a re-hospitalization within 2000-2010 were censored at December 31, 2010.

The following groups were excluded from the analysis: (1) persons with cancer discharge at any visit, (2) children ages 8 years or younger, (3) persons who resided outside of PA, and (4) visit transfers between hospitals (if they had 0 or 1 days between hospitalizations, the later hospitalization was excluded). Cancer discharges were excluded from the analysis because of a

1996 recommendation from the World Health Organization to prescribe opioids to relieve pain in persons with cancer[110]. In addition, children ages 8 years and younger were excluded to eliminate persons with neonatal abstinence syndrome (NAS).

3.2.2 Covariates

Demographic characteristics of interest included age, sex, race, and county of residence. Race included the following categories: White, Black, Asian/Pacific Islander/Native Hawaiian, and Other/Multiple. For re-hospitalization rate comparison, urbanicity was defined using the 2006 NCHS Urban-Rural Classification Scheme[112], defined as urban or rural. Urban counties were combined from the categories: Large central metro, Large fringe metro, Medium metro, Small metro; rural counties were combined from Micropolitan and Noncore.

The covariates included the following co-morbidities for opioid use: HCV, HIV, alcohol-related and/or history, tobacco, other illegal drug (marijuana, cocaine, and/or barbiturates), mental disorder (anti-social disorder, anxiety disorder/state, bipolar disorder, major depressive disorder, and/or schizophrenia).

Opioid discharge types were: OUD, opioid poisoning, and heroin poisoning. The specific ICD-9-CM codes used to determine co-morbid conditions and diseases are included in the attached Appendix (Table 12).

3.2.3 Statistical Analyses

Description of variables on the visit-level among patients in the opioid cohort were reported as counts and percentages, including demographic characteristics (age, sex, race, and urbanicity),

opioid discharge type (OUD, opioid poisoning, heroin poisoning), alcohol, tobacco, other illegal drug, mental disorder, HCV, and HIV. In addition, the mean and median number of hospitalizations per patient were summarized; the last visit's primary discharge was also described.

Semi-parametric mixed Poisson regression models were used to analyze re-hospitalization rates. This modeling technique allows for random effects to account for heterogeneity across individuals (with no parametric assumption) and time-varying covariates. The resulting rate multiplier estimates are synonymous with rate ratios of re-hospitalization for the presence of one disease compared to lack of the disease. For example, a multiplier of 2.0 indicates that the disease has twice the rate of re-hospitalization compared to no disease[128]. The semi-parametric mixed Poisson regression models in our present analysis had separate comparisons of covariates: HCV, HIV, and urbanicity, adjusted for the demographic and the other co-morbidity factors listed above. Once patients with these co-morbidities, HCV, and/or HIV were discharged, all following visits were considered positive for those conditions.

Because of the importance of age on hospitalization, separate age interactions with HCV, HIV, and urbanicity were tested. These were included in the regression model if Wald test was statistically significant at $p<0.05$. These analyses were performed in R version 3.3.1 (R Foundation for Statistical Computing) using the *coxph* procedure, in the survival package. All other statistical analyses used SAS 9.4 (SAS Institute, Cary, NC).

3.3 RESULTS

There were 560,480 hospitalizations among 132,674 individuals in the opioid cohort, during 2000-2010. 77.6% of patients had at least one re-hospitalization for any reason. The individuals in the opioid cohort, were 55.3% males, had a mean age of 40 years, were 80.5% white race, and 37.2% lived in Large central metro counties at the index visit (Table 5). In addition, at the index opioid visit 23.4% of persons had a co-diagnosis of another illegal drug use disorder and 24.5% had a mental disorder. 20.2% and 41.2% of the patients had alcohol and tobacco discharge(s). There were the following number of index opioid diagnoses: OUD - 99,832 (75.3%), opioid poisoning – 10,883 (8.2%), and heroin poisoning – 2,816 (2.1%). At any time during the cohort, 29,918 (22.6%) of the visits had a HCV discharge, and 3,741 (2.8%) had a HIV discharge. There were 83,018 patients who had a second visit; at the second visit 36% had an OUD discharge, 1.1% had opioid poisoning, and 0.8% had heroin poisoning (Table 21).

Persons who were discharged with HCV or HIV had higher numbers of hospitalizations (Table 6) compared to patients who never had that discharge. Patients in the cohort living in urban counties, when compared to rural counties, did not have much difference in number of re-hospitalizations.

Mental disorder was the most common primary discharge during the final visit during the 2000-2010 follow-up period for all patients: 44,329 (32.7%) (Table 7). When examining those with HCV discharge, 7.9% of persons had a liver-related primary discharge at the last visit, in addition to 6.6% who were discharged for opioid poisoning. Patients discharged with either primary or secondary HIV discharge during the opioid cohort had, at the last visit during the cohort, high percentages of a HIV primary discharge (15.2%), as well as circulatory (10.9%), and opioid poisoning (4.0%).

In addition, Table 19 shows stratifying percentages of the primary discharge of the last visit by disease and age group (at 35 years old). For those who had HCV discharge during the opioid cohort, the distribution of primary diagnoses was similar, with the exception of pregnancy (20.7%) in the <35-year age group. For those with HIV discharge during the cohort, those in the ≥35 year age group were more likely to have a primary HIV discharge compared to the younger age group (16.2% and 9.7%, respectively), and less likely to have a mental disorder primary discharge (22.3% and 32.4%, respectively).

The semi-parametric mixed Poisson regression models found that the effect of HCV and age interaction was statistically significant. The rate multiplier estimate for HCV was 1.11 (95% CI: 1.10, 1.13), meaning patients with HCV had about 11% more hospital re-hospitalizations among persons at a mean age of 40 years at the index opioid visit (Table 8). For HIV, the rate multiplier was 1.38 (95% CI: 1.34, 1.42). The model examining urbanicity found that patients living in urban counties had 1.14 (95% CI: 1.12, 1.16) times the rate of re-hospitalization than patients living in rural counties.

3.4 DISCUSSION

There were 132,674 patients in the analytic sample; 77.6% of patients had any re-hospitalizations for any reason during this time; there was a median of 4 visits per patient. The rate multiplier of HCV was about 11% higher compared to non-HCV visits, when controlling for other covariates and at mean age of 40 years. HIV had a 38% higher rate compared to non-HIV visits, and urban county residents had a 14% higher rate when compared to rural county residents.

Other studies have shown that patients using or prescribed opioids had higher odds of re-admission, however those analyses were only restricted to VA patients [97,99], or opioid poisoning visits[84,101]. To our knowledge, no other studies analyzed the longitudinal differences in HCV, HIV, and urbanicity in a cohort of non-veteran patients with opioid-related hospitalizations.

As mentioned, HCV and HIV infections increase morbidity of an infected person as the disease's natural course progresses over time. The rate multiplier for HCV was 11%, but HIV had an especially higher hospitalization rate multiplier of 38%. One potential reason HIV has a higher rate multiplier is because the disease can be spread both through bloodborne transmission routes, as well as through bodily fluids, and/or sexual intercourse. Despite low HIV prevalence (2.7%) among the opioid cohort visits, persons with HIV may engage in more high-risk behaviors that warrant hospital stays. For example, HIV can be transmitted in persons with non-injection substance use[129]. Amphetamines, stimulants, cocaine use, and high-risk sexual behaviors (multiple partners, multiple MSM partners, and sex workers) are associated with higher risk for sexually-transmitted HIV[130–132].

HCV and HIV infections may be related to a higher hospitalization rate due to the biological mechanism of the viral infection, or the disease discharge could be a proxy of injection drug use and/or correlated with behaviors that may put one at higher risk for a hospitalization[124,125]. Persons with HCV had a higher percentage of being discharge with liver-related issues at the final visit during the opioid cohort. This is also consistent with how HCV infection progresses to liver complications, such as liver fibrosis and cirrhosis[124].

3.4.1 Limitations

Our sample of hospital discharges only included information from 2000-2010; histories of patients outside of this time period were not available. The present investigation did not have laboratory confirmation of HCV or HIV infection upon admission. It is possible that infection could be from the past or an incident case, or persons without HCV discharge could be HCV-infected. This may limit the accuracy of the risk estimates. Future studies could be done using laboratory data to confirm HCV and HIV disease statuses. In addition, it would be helpful to ask patients about additional risk behaviors to determine the reason for transmission of HCV and/or HIV. For analytic purposes, our study assumes that persons with HCV or HIV will remain infected during a future hospitalization. This may not always be true because newer HCV treatments (sofosbuvir and ledipasvir were approved around 2013-2014) may cause viral loads to become undetectable[121,133,134]. However, during our 2000-2010 analytic sample, existing interferon-based treatments may not have been used because of unpleasant side-effects[135].

3.4.2 Strengths

The individuals reported from PHC4 were linked between hospitalizations, making possible the follow-up of patients over time. The presented statistical approaches are useful to compare rates of HCV, HIV, and urbanicity within the opioid cohort. In particular, it shows if patients with HCV or HIV discharge is a factor in the number of inpatient visits when controlling for other covariates. This further demonstrates the importance of prevention and treatment of bloodborne diseases among inpatients with opioid-related hospitalizations.

3.4.3 Conclusion

Among this cohort of inpatients with a primary or secondary discharge diagnosis of opioid-related hospitalization(s), HCV and HIV play important roles in the increased risk of a future hospitalization. Disease screening and education to avoid risk behaviors among these individuals will be beneficial to the patient to decrease the chance of future inpatient stays.

With increasing rates of opioid hospitalizations, it is important to acknowledge that consequences of the opioid epidemic will also increase. Patients with HCV and HIV have higher rates of re-hospitalizations, which are indicators of morbidity, and an increased burden to the US healthcare system. Preventing these infections should be a top priority for healthcare providers, especially those treating patients affected by the opioid epidemic.

3.5 TABLES AND FIGURES

Table 5. Characteristics of Patients in the Opioid Cohort, 2000-2010

Characteristics	*N=132,674 patients*
Age Group	
9-14 yrs	417 (0.3%)
15-24 yrs	28,160 (21.2%)
25-34 yrs	30,745 (23.2%)
35-44 yrs	28,143 (21.2%)
45-54 yrs	22,081 (16.6%)
55-64 yrs	8,922 (6.7%)
65-74 yrs	5,712 (4.3%)
75-84 yrs	5,622 (4.2%)
85+ yrs	2,872 (2.2%)
Median Age (Q1, Q3)	37 (26, 49)
Mean Age (SD)	40 (17.5)
Sex	
Male	73,387 (55.3%)
Female	59,277 (44.7%)
Race	
White	99,033 (80.5%)
Black	17,467 (14.2%)
Asian/Pac Is/HIian	310 (0.3%)
Other/Multiple	6,286 (5.1%)

Table 5. Characteristics of Patients in the Opioid Cohort, 2000-2010, continued

Characteristics	*N=132,674 patients*
County of Residence Urbanicity	
Large central metro	49,094 (37.2%)
Large fringe metro	31,886 (24.2%)
Medium metro	31,454 (23.8%)
Small metro	5,091 (3.9%)
Micropolitan (rural)	12,227 (9.3%)
Noncore (rural)	2,270 (1.7%)
Alcohol	27,564 (20.2%)*
Tobacco	56,159 (41.2%)*
Any Mental disorder	32,454 (24.5%)
Marijuana, Cocaine, Barbiturates	31,067 (23.4%)
Opioid Discharges	
OUD	99,832 (75.3%)
Opioid Poison	10,883 (8.2%)
Heroin Poison	2,816 (2.1%)
HIV	3,741 (2.8%)*
HCV	29,918 (22.6%)*

***Frequency and percent for persons who had the characteristic at any time during the cohort**

Table 6. Description of Re-Hospitalizations by HCV, HIV, and Urbanicity

Number of Hospitalizations per Patient	*Opioid Cohort* *N=132,674 individuals*	*Hepatitis C discharge at any visit*		*HIV discharge at any visit*		*County of Residence*	
	Total	*Yes*	*No*	*Yes*	*No*	*Urban*	*Rural*
Mean (SD)	6.4 (8.9)	8.3 (10.4)	5.9 (8.4)	10.1 (12.9)	6.3 (8.8)	6.5 (9.1)	6.2 (7.4)
Median (Q1, Q3)	4 (2, 8)	5 (3, 10)	3 (1, 7)	6 (3, 12)	4 (2, 7)	4 (2, 8)	4 (2, 8)

Table 7. Primary Diagnosis at Last Visit during Opioid Cohort, 2000-2010

Primary Discharge	*Overall (n=135,481)*	*HCV (n=25,659)*	*HIV (n=16,841)*
Opioid Dependence	12739 (9.4%)	336 (1.3%)	58 (1.6%)
Opioid Abuse	150 (0.1%)	1104 (4.3%)	186 (5.2%)
Heroin Poisoning	1680 (1.2%)	24 (0.1%)	3 (0.1%)
Opioid Poisoning	2494 (1.8%)	1692 (6.6%)	142 (4.0%)
HIV	545 (0.4%)	332 (1.3%)	545 (15.2%)
HCV	288 (0.2%)	288 (1.1%)	20 (0.6%)
Mental Disorders	44329 (32.7%)	8746 (34.1%)	849 (23.7%)
Injury/Poisoning	12433 (9.2%)	268 (1.0%)	30 (0.8%)
Respiratory	7708 (5.7%)	580 (2.3%)	65 (1.8%)
Pregnancy	7558 (5.6%)	807 (3.2%)	102 (2.9%)
Digestive	7384 (5.5%)	512 (2.0%)	85 (2.4%)
Circulatory	7122 (5.3%)	1558 (6.1%)	390 (10.9%)
Musculoskeletal	6739 (5.0%)	1094 (4.3%)	184 (5.1%)
Symptoms/Signs/Ill-defined	6110 (4.5%)	142 (0.6%)	16 (0.5%)
Skin	4640 (3.4%)	12 (0.1%)	3 (0.1%)
Genitourinary	3649 (2.7%)	1432 (5.6%)	183 (5.1%)
Infectious/Parasitic Diseases	3052 (2.3%)	682 (2.7%)	136 (3.8%)
Endocrine	2443 (1.8%)	462 (1.8%)	65 (1.8%)
Nervous System	2225 (1.6%)	192 (0.8%)	27 (0.8%)
Liver-related**	940 (0.7%)	2023 (7.9%)	51 (1.4%)
Blood Diseases	608 (0.5%)	123 (0.5%)	32 (0.9%)
Endocarditis /Cardiomyopathy*	500 (0.4%)	1157 (4.5%)	143 (4.0%)
Congenital Anomalies	145 (0.1%)	2093 (8.2%)	262 (7.3%)

*ICD-9-CM discharges: 421-425

**ICD-9-CM discharges: 570-573

Table 8. Re-Hospitalization Rate Multipliers for HCV, HIV, and Urbanicity

	Covariate of Interest		
	Hepatitis C discharge at any visit, at mean age	*HIV discharge at any visit*	*County of Residence*
Rate Multiplier (95% CI)	1.11 (1.10, 1.13)	1.38 (1.34, 1.42)	1.14 (1.12, 1.16)

4.0 TIME TO DEATH AMONG OPIOID HOSPITALIZATIONS BY HEPATITIS C, HIV, AND URBANICITY IN PENNSYLVANIA, 2000-2010

ABSTRACT

Background: Opioid prescriptions in the US doubled during 2000-2010, from 10% and 20%. The recent increase in opioid prescriptions is concerning for opioid tolerance, abnormal pain sensitivity, and hormonal changes for long-term users. Rates of opioid deaths are high in the state of Pennsylvania, which in 2015 ranked 5th in the nation for, age-adjusted drug overdose rates (25 deaths per 100,000).

Methods: We analyzed a linked dataset of discharges and mortality during 2000-2010 from (1) the Pennsylvania Health Care Cost Containment Council and (2) the PA Death Registry. The survival analysis included patients with opioid-related primary and/or secondary discharges in at least one inpatient visit. Discharges from patients after the first opioid-related hospitalization during 2000-2010 were analyzed. Cancer cases, children under 8 years old, and non-PA residents were excluded. The covariates for survival analyses included: age, sex, race, alcohol, tobacco, other illegal drugs (marijuana, cocaine, and/or barbiturates), and mental disorder discharges. Kaplan-Meier survival and accelerated failure time (AFT) models were used for descriptive analyses and adjusted survival analyses, respectively, to compare survival between Hepatitis C virus (HCV) and non-HCV discharges, HIV and non-HIV discharges, and urban and rural county residents.

Results: Among the 136,463 individuals in the opioid cohort, 13% died during 2000-2010. The analyzed patients were 55.3% male, median age 37 years, 74.7% white, and 89.0% in urban counties. These persons had 23.4% illegal drug and 24.3% mental disorder discharges at the index opioid visit. Patients had 20.2% and 41.2% alcohol and tobacco discharges during the follow-up period. Among patients ages ≥30 years, persons with HCV had significantly shorter survival compared those never discharged with HCV. Those with HIV had shorter survival (AF=0.31 (95% CI: 0.28, 0.35)). Urban and rural residents had the same survival (AF=1.00).

Discussion: Shorter survival for HCV is consistent with the natural course of disease, where the disease progresses at older ages. Patients with HCV are often chronically infected and unaware of infection status, until the onset of severe liver disease. These findings are of public health relevance because it is important to treat HCV and/or HIV infection before long-term health problems can occur.

4.1 INTRODUCTION

Opioid use has been increasing in the United States, with 5.1 million Americans using pain relievers in 2010[2,19,20,23,45]. The late 1990s started the "opioid epidemic" period and has continued through the decade of the 2010s[20]. Emergency department visits increased 153% from 2004 to 2011. In addition, the rate of prescription drug overdose went from 1.5 to 5.9 deaths per 100,000 persons[2].

In the past, healthcare providers were recommended to treat pain symptoms in patients with opioids, due to their high effectiveness in short-term pain relief[62]. However, the recent increase in opioid prescriptions have increased concerns of opioid tolerance, abnormal pain

sensitivity, and hormonal changes for long-term users[8]. An epidemic and emergency in some areas in the United States, many are suffering from opioid use disorder (OUD) and addiction, and cause clinically significant impairment and distress[9–12].

Persons with OUD[11] have higher risks of death compared to the general population. A study by Hser et al. found in a California university health system that those with OUD had an overall standardized mortality ratio (SMR) of about 10.3, including 19.8% (92 cases) dying from drug-related issues[136]. Among a similar California population, in persons being treated for OUD, SMR was 4.5[137]. Opioid overdoses are also a concern, and can be occur from using oxycodone and hydrocodone[82,83] and heroin. A particularly potent and illicit opioid, heroin that has different addiction or abuse capability compared to the prescription opioid types[2], as well as increased risk in accidental overdoses[5,6].

High-dose opioid use increases the risk for fatal respiratory depression[85,86]; contribution from commonly co-prescribed benzodiazepines may have elevated mortality risk[87]. Other common cause for mortality among opioid users is liver disease among the older population with opioid dependence in Australia[88], acute kidney failure, multiple organ dysfunction syndrome, bowel infarction, hypoxic brain injury, and sepsis[89].

Opioid deaths are of great importance in the state of Pennsylvania, which in 2015 ranked 5th in the nation for drug overdose, age-adjusted death rates (about 25 deaths per 100,000)[27]. This was also shown in a comparison by Paulozzi et al.[138], which reported that the 2006 age-adjusted death rates (mostly from opioid analgesics) in Pennsylvania and New York State was 12.3 and 7.6 per 100,000 persons, respectively. The study hypothesizes that the reason could be better policy regulation of prescription opioids in New York. In addition, the city of

Philadelphia toxicology reports showed that there was a 13-fold increase in drug-related deaths from 2004 to 2006[139].

Before the 1970s, opioid abuse had generally occurred in low-income, inner-city, minority populations. Most abuse and death were among black males, according to narcotics registries and decedent data from New York City before 1970, with Hispanics becoming the group with the highest burden during 1970-1990[34]. However, abuse has recently increased more in the suburban and rural areas (and mainly among Caucasians) compared to urban areas[24].

Bloodborne diseases such as HIV and Hepatitis C virus (HCV) are commonly contracted via shared infected needles and paraphernalia[69,70,72–74]. The prevalence of HCV is high among injection drug users (IDU)[70,75,76,108]; IDUs in most countries have HCV prevalences over 50%[71]. These viral infections can develop into chronic conditions[124,125], leading to morbidity and earlier mortality compared to a person without the infection. Among HCV-infected adults, liver cirrhosis has increased rapidly in the United States[140]; the number of HCV-related deaths from certificate data almost doubled from 11,051 to 19,368 deaths in 2003 and 2013[79]. Hser et al. found that of those with OUD, 12% died of HCV and 0.8% died of HIV; in addition, those with HCV had an adjusted hazard ratio 1.99, when compared to those without HCV[136].

The goal of this analysis is to describe the survival in a cohort of persons who had an opioid-related inpatient visit in a PA hospital during 2000-2010. Our objective is to compare the differences between time to mortality in persons in this cohort, separately, by HCV and HIV discharge statuses, and residence county urbanicity. The quantification of survival time of these groups will provide supporting evidence for hepatitis C and HIV prevention, screening, and treatment of these bloodborne diseases in this large population of opioid users.

4.2 METHODS

4.2.1 Data Sources

This analysis uses a linked dataset of discharges and mortality from (1) the Pennsylvania Health Care Cost Containment Council (PHC4)[32,109] and (2) the PA Death Registry. The PHC4 collects hospital discharge records via International Classification of Diseases, ninth revision, clinical modification (ICD-9-CM) information, in addition to demographic data from hospital records. The data from the PA Death Registry includes cause of death and time to mortality.

4.2.2 Analytic Sample and Cohort

The survival analysis includes patients with opioid-related primary and/or the first 8 secondary discharges in at least one hospitalization. The following ICD-9-CM codes were considered opioid-related: 965.01 and E850.0 (heroin poisoning), 304.00-304.03, 304.70-304.73, 305.50-305.53 (opioid use disorder [OUD]), 965.00, 965.09, and E850.2 (opioid poisoning), and E935.2 (adverse effects in therapeutic opioid use). The underlying causes of death used categories for ICD-10 diagnosis codes.

The following groups were excluded from the analysis: persons with cancer discharge at any visit, children age 8 years or younger, and persons who reside outside of PA. Cancer discharges were excluded from the analysis because of a 1996 recommendation from the World Health Organization to prescribe opioids to relieve pain in persons with cancer[110]. In addition, children ages 8 years and younger were excluded to eliminate persons with neonatal abstinence syndrome. Oxycontin was recommended, by the American Academy of Pediatrics, for children

11 years and of age and older who were already receiving and tolerate minimum 20 mg daily opioid dose[111].

The datasets were linked by a Social Security Number identifier for each unique patient. The index visit for a patient in the cohort was the first presence of any ICD-9-CM opioid code in a primary and/or secondary diagnosis field during 2000-2010.

4.2.3 Covariates

Demographic characteristics of interest included index information for age, sex, and race; residence county urbanicity were taken from the patient data from PHC4. Race included the following categories: White, Black, Asian/Pacific Islander/Native Hawaiian, American Indian/Alaskan Native, Other/multiple, and Unknown. Urbanicity was defined using the 2006 NCHS Urban-Rural Classification Scheme[112] and used the following categories: Large central metro, Large fringe metro, Medium metro, Small metro, Micropolitan, and Noncore.

Co-morbidities for opioid issues included: alcohol-related and/or history, tobacco-related, other illegal drug-related (marijuana, cocaine, and/or barbiturates) discharges. Mental disorder was defined as any of the following: anti-social disorder, anxiety disorder/state, bipolar disorder, major depressive disorder (MDD), and/or schizophrenia. An additional variable categorized the history of opioid discharges during the cohort and had the following categories: OUD only, opioid poisoning only, heroin poisoning only, OUD and overdose, and adverse events due to opioids only. The specific ICD-9-CM codes used to determine co-morbid conditions and diseases are included in the attached Appendix (Table 12).

4.2.4 Statistical Analyses

Description of information from index visit of patients in the opioid cohort were reported as counts and percentages, including demographic characteristics (age, sex, and race), previously mentioned opioid discharge history category(ies), alcohol, tobacco, other illegal drug-related at index visit, and mental disorder at index visit.

The time to mortality was calculated as the time between the beginning of the index opioid visit to the recorded death date in PA Mortality Record. Patients with no record of death within 2000-2010 were censored at December 31, 2010. Time to mortality was summarized as median weeks and first (Q1) and third (Q3) quartiles.

We performed descriptive survival analyses using the Kaplan-Meier method to compare time to death separately by 1) HIV discharge, 2) HCV discharge, and 3) residence county urbanicity. Regression analysis was performed using accelerated failure time (AFT) models, due to violation of proportional hazards between groups. AFT models are parametric models that allow for comparison of the length of survival between groups, instead of comparing hazards in Cox proportional hazards models. The models were adjusted for the covariates: index age, race, sex, illegal drug, mental disorder comorbidities, having alcohol and tobacco at any visit, and history of the type of opioid discharge(s) during the cohort. To test whether the association of time to death with the diseases may have varied at different ages, interaction terms were tested and adjusted in the AFT models if statistically significant at $p<0.05$. Adjusted survival results were reported as acceleration factors (AF), which is the ratio of survival length between having the disease, compared to not having the disease.

Statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC), using PROC LIFETEST for descriptive survival analysis, and PROC LIFEREG for adjusted, parametric survival models.

This analysis was approved as an exempt, secondary data analysis by the Institutional Review Board at the University of Pittsburgh. An honest broker from the PA Department of Health was used to merge the PHC4 and PA Mortality records.

4.3 RESULTS

4.3.1 Demographics and Underlying Death Causes

There was a total of 136,463 individuals in opioid cohort, and 17,722 (13.0%) died at some time during 2000-2010. There were about 9.8% and 9.9% of the cohort who entered in 2009 and 2010, respectively. These patients are more likely censored due to unequal follow-up time compared to persons entering at earlier years. Among the individuals in the opioid cohort, 55.3% were male, median age of 37 years, 74.7% white race, and 37.2% in large central metro counties (Table 9). Of the individuals, 23.4% had any illegal drug and 24.3% had any mental disorder at the index opioid visit. In addition, 20.2% and 41.2% patients in our analytic sample had alcohol and tobacco discharge(s) during the follow-up period. The combinations of opioid discharges were: OUD only (69.6%), opioid poisoning only (6.2%), heroin poisoning only (0.7%), OUD and overdose discharges (7.3%), and opioid adverse events (16.3%). For the diseases that were used for comparisons, 27,122 (19.9%) had a HCV discharge during the cohort, and 3,662 (2.7%) had a HIV discharge during the cohort.

The underlying causes of death are listed in Table 10. The most common cause of death was drug-related, with 23.5% of the deaths in the opioid cohort. Among persons with HCV during the opioid cohort, the most common underlying cause of death was also drug poisoning, and had a substantial percentage dying of liver-related causes (11.1%). The majority of persons with HIV during the cohort had HIV (48.4%) listed as the underlying cause of death.

In addition, when stratifying by <35 and ≥35 year-old age groups, we observed the <35 year-old age group had much higher drug poisoning percentage (59.0%) among the other causes of death, when compared to the ≥35 year-old age group (15.9%) (Table 24). The same trend was observed in patients who had HCV and HIV during the cohort (Tables 25 and 26).

4.3.2 Unadjusted Survival Analysis

Among persons who eventually died during the 2000-2010 time period, the median survival time was 92 weeks (Q1, Q3: 25, 207 weeks). The unadjusted survival shows that HCV discharges had longer survival than the group of persons with no HCV discharge (Figure 5, Table 22). However, persons with HCV were younger (mean 37 years compared to 41 years), and were more frequently male, from large central metro counties, ever had alcohol, tobacco discharges, and had a mental disorder at index visit. The unadjusted HIV survival curves showed that persons with HIV had shorter survival times compared to persons without HIV (Figure 6, Table 23). Persons with HIV had a higher proportion of patients reporting Black race. However, HIV and non-HIV patients did not have much difference in mean age at index visit (41 and 40 years old). Persons in urban counties compared to rural counties of residence did not have much difference in survival over time (Figure 7).

4.3.3 Accelerated Failure Time Analysis

For models comparing HCV, the interaction between index age and HCV discharge was statistically significant when adjusting for all other covariates. Therefore, the AFs at 5-year age intervals were reported (Figure 3). In patients who had their first opioid-related visit at 15 years old, there was a 1.23 times (95% CI: 1.08, 1.41) longer survival time for HCV compared to without HCV. However, starting at age 20 the survival length of the same comparison showed that the association was not statistically significant. By 30 years old, those with HCV was 0.91 times (95% CI: 0.84, 0.99) the survival time compared to without HCV (approximately 9% shorter survival time). In older groups the survival length became shorter when comparing HCV to non-HCV discharges.

The HIV models showed that persons with HIV had 0.31 times (95% CI: 0.28, 0.35) the survival compared to those without HIV, when adjusting for all covariates. It was also found that inpatients residing in urban counties had the same survival length AF = 1.00 (95% CI: 0.93, 1.07) compared to those in rural counties (Table 11). Both HIV and urbanicity comparisons did not have significant interactions with index age.

4.4 DISCUSSION

This analysis found that the opioid cohort, with 13% who died. However, there is the potential for more deaths because almost 20% of the cohort had an index opioid visit in 2009 or 2010. The opioid cohort consisted of mainly white, with median age of 37 years at the first opioid visit, and males. These persons had characteristics with discharges over 20% of the time for alcohol,

tobacco, mental disorder, and illegal drugs. The most common causes of death were categorized as circulatory and drug-related. Survival of persons with HCV differed by age at first opioid visit. In fact, 15-year-old patients had, on average, better survival if they were discharged with HCV. However, in patients ≥30 years old at index opioid visit, HCV was associated with shorter time to death. HIV discharge was associated with shorter time to death and residence county urbanicity was determined not to have a difference in survival length.

The percent of patients in the opioid cohort who had a drug-related underlying cause of death is very similar to Hser et al., who found that 19.8% of their analytic sample had a drug-related cause of death[136]. However, our analysis had a much larger sample size. Classifying 20% of the deaths as "Drug-related" does not necessarily mean that 80% died from issues unrelated to drugs. It is possible that an opioid user could have had a respiratory depression and subsequently listed as having a death caused by an issue with the respiratory system, or opioid-related cardiac arrest.

The result showing that HCV was associated with shorter time to death in this cohort is intuitive, due to the typical clinical presentation of HCV infection. Udompop et al. showed that among adults with HCV infection, the proportion of those with liver cirrhosis are increasing (an estimated 17% [170,000 adults] in 2007-2012)[140]. Hepatitis C infection increases one's risk of hepatocellular carcinoma and death, and is more likely to occur in persons at more advanced ages and usually 25-30 years after being chronically infected with the virus[124].

Persons who acquire HCV are often chronically infected and some are not aware of their infection status[126], until the onset of liver disease and cirrhosis. Therefore, it is important to treat the infection before long-term health problems can occur. There are cost-effective treatments to clear HCV, and could be especially important in persons with opioid-related hospitalizations.

HIV is also associated with shorter time to death in our analysis and in the existing literature. Age is a major determinant of the incubation period for HIV; persons acquiring HIV at old ages have shorter incubation periods[125]. Our analysis found associations of HIV infection and increasing age with shorter time to death, but did not find the interaction of HIV infection and age to be significantly significant.

Urbanicity was found not to have any differences in time to death, both univariable and multivariable survival analyses. This is despite the PHC4 reports showing rural counties have a larger rate of increase in opioid hospitalizations in than urban counties and overall higher hospital rates in urban counties[32].

Using methadone or buprenorphine treatment may have broad, societal benefits among a population with OUD. White et al.[141] studied illicit opioid users in England 2008 to 2011, using ICD-10 codes to determine death. There were 3,731 deaths despite 741 (20%) receiving treatment for OUD near the time of death. They found that there would be about 6,372 deaths in the absence of methadone or buprenorphine (equivalent to 880 excess deaths per year). This is consistent with a British study by Cornish et al. that show mortality rates, adjusting for age, sex, and comorbidity, is approximately one-half in patients with OUD on treatment compared to patients who left treatment[142].

A related study was performed by Evans et al.[137], which examined persons under treatment for opioid dependence in California during 2006-2010. The analysis linked datasets, including prescription and mortality information, to analyze time to death and crude mortality rates. There were 1,031 deaths among 32,322 individuals over a 5-year follow-up (median 2.6 years). HCV and HIV accounted for 4.2% and 1.4% of deaths.

A major strength of this study is the development of a database of statewide inpatient records, linked with death records. This encompasses all hospitalizations and their associated deaths in the state of Pennsylvania, but do not include hospitalizations from the Veterans Affairs. AFT models were used after finding violations with the proportional hazards assumptions.

There are several limitations to this analysis. The ICD-9-CM and ICD-10 discharge codes are for billing purposes. It is possible that there could be inherent bias in the diseases reported. In addition, HCV and HIV discharges may be underrepresented due to possible asymptomatic cases of the infections. Mental disorders are also underdiagnosed, and other substance use could also be undetected through hospital visits. Another limitation is the censoring of time in our analysis. It is possible that the first lifetime opioid visit was not captured within the 2000-2010 time frame. As mentioned, there could be higher death rates if patients entering the cohort in 2009 and 2010 are followed as long as the other patients. However, with a large sample size, the associations should not have a substantial change.

These results suggest that HCV and HIV should be carefully monitored among persons hospitalized for opioid-related reasons. They have shorter survival times, especially in patients age 30 years and older. Cost-effective treatments for these diseases[133,134] could limit mortality in this population. It would be helpful for these patients entering healthcare systems should be screened to better understand this relationship between opioids and HCV and/or HIV. Persons with opioid hospitalizations are at higher risk for transitioning to heroin[22,39–42], who have a higher chance of sharing HCV and/or HIV-infected needles. Persons who inject drugs need to use with caution, as acquiring these viruses could increase morbidity and decrease time to death.

4.5 TABLES AND FIGURES

Table 9. Descriptive Characteristics of Opioid Cohort

Characteristics	*N=136,463*
Age Group	
9-14 yrs	428 (0.3%)
15-24 yrs	28,657 (21%)
25-34 yrs	31,335 (23%)
35-44 yrs	28,933 (21.2%)
45-54 yrs	22,987 (16.8%)
55-64 yrs	9,366 (6.9%)
65-74 yrs	5,994 (4.4%)
75-84 yrs	5,837 (4.3%)
85+ yrs	2,926 (2.1%)
Mean Age	37
Sex	
Male	75,426 (55.3%)
Female	61,027 (44.7%)
Race	
White	101,861 (74.7%)
Black	18,128 (13.3%)
Asian/Pac Is/HIian	313 (0.2%)
American Ind/AK Nat	1,783 (1.3%)
Other/Multiple	6,402 (4.7%)
Unknown	7,919 (5.8%)

Table 9. Descriptive Characteristics of Opioid Cohort, continued

Characteristics	*N=136,463*
County of Residence Urbanicity	
Large central metro	50,445 (37.2%)
Large fringe metro	32,827 (24.2%)
Medium metro	32,361 (23.8%)
Small metro	5,234 (3.9%)
Micropolitan	12,589 (9.3%)
Noncore	2,338 (1.7%)
Alcohol	27,564 (20.2%)
Tobacco	56,159 (41.2%)
Any Mental disorder	33,117 (24.3%)
Marijuana, Cocaine, Barbiturates	31,865 (23.4%)
Opioid Discharges	
OUD only	94,994 (69.6%)
Opioid Poison	8,453 (6.2%)
Heroin Poison	893 (0.7%)
OUD and any overdose	9,917 (7.3%)
Adverse Events only	22,206 (16.3%)
HIV	3,662 (2.7%)
HCV	27,122 (19.9%)

Table 10. Underlying Causes of Death, Opioid Cohort 2000-2010

	Number of Deaths (% among the deaths)			
UNDERLYING CAUSE OF DEATH	**Overall**	**HCV**	**HIV**	**Urban**
Drug Poisoning[143]	4162 (23.5%)	1089 (27.0%)	134 (13.7%)	3780 (24.2%)
Heart Disease	3972 (22.4%)	583 (14.4%)	98 (10.0%)	3427 (21.9%)
Other*	2393 (13.5%)	428 (10.6%)	53 (5.4%)	2068 (13.2%)
Respiratory	1658 (9.4%)	210 (5.2%)	35 (3.6%)	1400 (9.0%)
Injuries/trauma	1145 (6.5%)	214 (5.3%)	30 (3.1%)	1015 (6.5%)
Other liver-related	727 (4.1%)	447 (11.1%)	28 (2.9%)	676 (4.3%)
Other Circulatory	701 (4.0%)	111 (2.8%)	21 (2.1%)	623 (4.0%)
Genitourinary	585 (3.3%)	97 (2.4%)	19 (1.9%)	506 (3.2%)
Infection	536 (3.0%)	151 (3.7%)	50 (5.1%)	480 (3.1%)
HIV	487 (2.8%)	345 (8.5%)	474 (48.4%)	474 (3.0%)
Mental and behavioral disorders	423 (2.4%)	62 (1.5%)	4 (0.4%)	364 (2.3%)
Digestive, non-liver	367 (2.1%)	33 (0.8%)	8 (0.8%)	315 (2.0%)
Cancer	295 (1.7%)	30 (0.7%)	8 (0.8%)	262 (1.7%)
HCV	221 (1.3%)	208 (5.2%)	13 (1.3%)	203 (1.3%)
Other Hepatitis	34 (0.2%)	26 (0.6%)	3 (0.3%)	32 (0.2%)
OUD	15 (0.1%)	6 (0.2%)	2 (0.2%)	13 (0.1%)

*Other: Congent. malformation, diabetes, external cause, fungal, musculoskeletal, nervous system, pregnancy, skin/tissue

Table 11. Estimates of Acceleration Failure - HCV, HIV, and Urbanicity

Factor	AF Estimate (95% CI)*	p-value
HIV	0.31 (0.28, 0.35)	<0.001
Urbanicity (Urban/Rural)	1.00 (0.93, 1.07)	0.99
HCV	†	†

*Adjusted for age, race, sex, alcohol, tobacco, illegal drugs, mental disorder, and opioid history
† Not reported because of significant age interaction with HCV; linear combination plotted in Figure 3

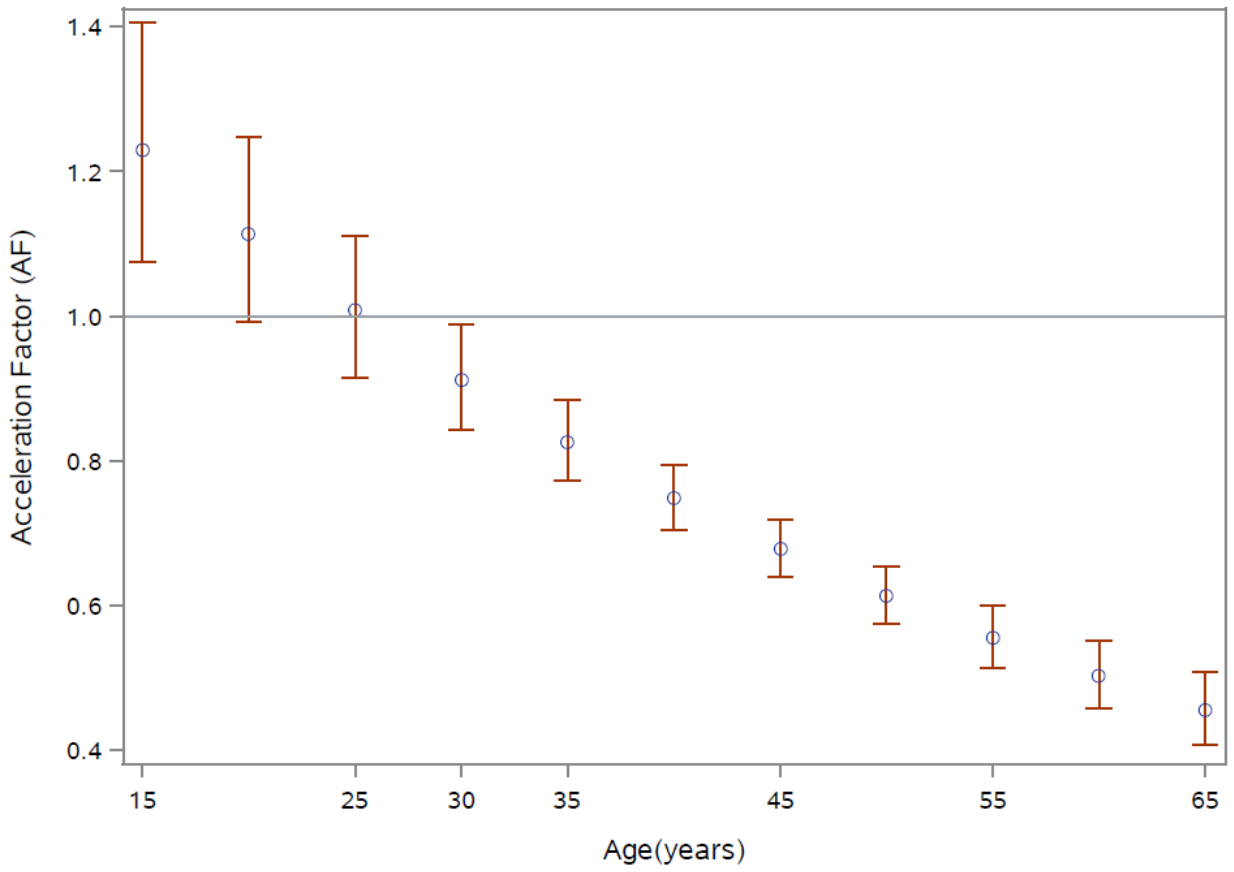

Figure 3. Estimates of Acceleration Failure*, Hepatitis C by Age

*Adjusted for age, race, sex, alcohol, tobacco, illegal drugs, mental disorder, index year, and opioid history

Age (years)	AF (95% CI)	p-value
15	1.23 (1.08, 1.41)	0.003
20	1.11 (0.99, 1.25)	0.07
25	1.01 (0.91, 1.11)	0.88
30	0.91 (0.84, 0.99)	0.03
35	0.83 (0.77, 0.88)	<.0001
40	0.75 (0.70, 0.79)	<.0001
45	0.68 (0.64, 0.72)	<.0001
50	0.61 (0.57, 0.65)	<.0001
55	0.55 (0.51, 0.60)	<.0001
60	0.50 (0.46, 0.55)	<.0001
65	0.45 (0.41, 0.51)	<.0001

5.0 OVERALL CONCLUSIONS

5.1 SUMMARY OF RESULTS

Using primary and/or secondary opioid discharges, we demonstrated the following results using a database of administrative hospital discharge data. Latent class analyses of 430,569 visits from 2000-2014 yielded 5 subgroups of patients hospitalized for opioid-related reasons. The class consisting of mainly pregnant women with OUD had the highest percentage of visits with HCV discharges: 5,273 visits (26.3% within the class); the class of Black, OUD, cocaine discharges had the most visits with HIV: 6,490 (6.9%). A latent class of persons with mental disorders and multiple drug discharges was the most common (58.3% of the sample). The number of visits that were classified in this group increased over time from years 2000 to 2014, while the number of visits in other groups remained stable.

In a cohort of individuals hospitalized from 2000-2010 with at least one opioid diagnosis code, individuals with at least one hospitalization with an HCV discharge code had a 1.11 times higher re-hospitalization rate compared to those without any HCV discharge codes, adjusting for demographics, mental disorders, and other substance use discharges. Those who had an HCV diagnosis code at any time from 2000-2010 had shorter survival lengths for those age 30 years or older at their index opioid visit. A 30-year-old patient with HCV had about 9% shorter survival when compared to a 30-year-old patient without HCV. Persons with HIV had a 1.38 times

higher re-hospitalization rate, and those with HIV infection at any time during cohort had 0.31 times the length of survival. Residents of urban counties had a 1.14 times higher re-hospitalization rate compared to rural residence counties; there was no difference in survival length when comparing urban to rural residents.

5.2 OVERALL STRENGTHS

5.2.1 Sampling and Representativeness

Our study used opioid-related hospitalizations from the PHC4, which collects data from all 239 licensed hospitals and 284 freestanding ambulatory surgery centers in Pennsylvania. There are an average of 4.5 million discharges per year in these hospitals/surgery centers. The 9 Veterans Affairs Medical Centers in Pennsylvania are not included, however visits to VA hospitals only constitute about 27,000 patient visits per year[144]. These results are valid for all non-veteran Pennsylvanians seeking care in hospitals.

5.2.2 Analytic Techniques

The first analysis uses a latent class analysis, which shows that opioid-related hospitalizations have certain clustering of people with shared characteristics, specifically among this hospital cohort in Pennsylvania. This is particularly useful for large datasets where associations of certain characteristics are not well-established.

The second and third analyses use a cohort of patients hospitalized for opioid-related reasons. This cohort with linked patient visits and mortality records provided the opportunity to show the impact of HCV and HIV infection statuses on hospitalization rate and survival time. The specific methods were best for these longitudinal, survival analyses: semi-parametric mixed Poisson models for recurrent events, and accelerated failure time models. We applied the most appropriate methods after finding violations in the proportional hazards assumptions for Cox Proportional Hazards survival models.

5.3 OVERALL WEAKNESSES

There are several limitations in the analyses presented. As mentioned in previous sections, there could be some misclassification of persons with HCV and/or HIV, due to lack of uniform testing for infection(s). Without laboratory tests and test dates, it is possible that the HCV and HIV groups are a combination of persons with longstanding infection or acute infection. For example, acute HCV infection would not be differentiated from chronic infection.

In addition, patients may be discharged for OUD at one point during the cohort and may not have an OUD discharge in a follow-up hospitalization. For example, it was shown that the second visit (n=83,018) during opioid cohort had 36.1% OUD discharges (Table 21), as opposed to 75.2% OUD at the index opioid visit (Table 5). This difference in percentage of OUD between first and second visits is unlikely to be a true representation of difference in opioid behaviors among these patients. Since some providers may not always include an OUD code in future hospitalizations, the difference in percentage of OUD between first and second visit might be an overestimate of the percentage of patients who have been treated and/or cured of OUD.

The analytic sample is from an administrative database and may not necessarily reflect true health conditions, that would only be captured from medical record abstraction and the reporting physician's input. However, due to high specificity of these ICD-9-CM codes[14], we can consider the reported diseases as underestimates of the true prevalence of opioids, and other diagnoses.

Another important issue is the possibility of Berkson's bias in our study. Berkson's bias is a type of selection bias, which describes the tendency to observe and/or report more diseases based on being admitted in a hospital. It is more likely that, for example pregnant women, in our analyzed cohort may have higher risk of identifying a disease compared to those not in hospitalized. It is possible that pregnancy is the first opportunity for a woman to receive medical testing, therefore disease reporting would be higher in pregnant women than other patients who enter hospital care.

5.4 OVERALL IMPLICATIONS

The latent class analyses showed that the pregnant women latent class has the highest prevalence of concurrent discharge for HCV. This implies that pregnant women should be targeted for more education to prevent HCV acquisition, screening, as well as treatment in those infected. It is important to inform healthcare policy-makers to recommend HCV and HIV screening for those with opioid-related hospitalizations. It would help benefit the patient in the long-term, and it may be more cost-effective to treat infections earlier[133].

Persons who inject opioids and other drugs should be mindful of sharing equipment, as HCV and HIV may increase morbidity and shorten survival length. There may be an opportunity

to publicize use of syringe and needle exchange programs in Pennsylvania[70,72,145,146]. Unfortunately, Pennsylvania does not have as many programs as, for example, New York State. Lawmakers will need to be educated on the public health implications of these programs.

5.5 FUTURE DIRECTIONS

To have a complete picture of the association of long-term survival of persons with OUD, opioid poisoning, and heroin poisoning it would be important to perform similar analyses on more datasets. These include electronic health records from emergency room and outpatient information, clinical data, and information from the patient's medical history. It is also important to study recent trends from opioid users; fentanyl and synthetic opioid-related deaths have sharply increased since 2013 and are an important aspect of the next, ongoing chapter of the opioid epidemic.

During this ongoing opioid epidemic, the increase in opioid hospitalizations could increase risks for more HCV and HIV infections. To better illustrate the differences in HCV and HIV over time, it is important to better understand the transmission of HCV and HIV infections in this population. Collecting more information about substance use history, methods, social networks, on a sample of these persons hospitalized for opioids could provide better insight on how to prevent HCV and HIV rates from sharply increasing in the United States.

APPENDIX A: PAPER 1 ADDITIONAL TABLES/FIGURES

Table 12. ICD-9-CM Codes for Opioid, Co-morbidities, Pregnancy, and Diseases of Interest

Discharge description	*Code*
Opioid	
Opioid dependence	304.00-304.03
Opioid other dependence	304.70-304.73
Opioid abuse	305.50-305.53
Opium poisoning	965.00
Heroin poisoning	965.01, E850.0
Poisoning by other opiates and related narcotics	965.09
Accidental poisoning by other opiates/related narcotics	E850.2
Other opiates and related narcotics causing adverse effects in therapeutic use	E935.2
Co-morbidity	
Major depressive disorder	296.2X, 296.3X
Schizophrenia	295.0, 295.1-.3, 295.50-55, .6, .9, 295.80-.85, 295.90-.95
Psychosis	289.0-.1, .8-.9, 290.8
Anxiety	293.84, 300, 300.00, .02, .09
Bipolar disorder	296.0, 296.01, .02, 296.4X-.7X, 296.80, .89
Anti-social behaviors	301.7, V71.01-.02
Alcohol	303, 305, 94.53,.6, 980, E860, E947.3
Tobacco	305.1, 649.0, V15.82, 989.84, E869.4
Marijuana	304.30-.33, 305.20-.23
Cocaine	304.2-.23, 305.6-.63
Barbiturates	304.1-.13, 305.4-.43
Pregnancy	630-679, V22, V23, V24, V28
Disease	
Hepatitis C	V02.62, 070.7, 070.41, 070.51, 070.70, 070.71, 070.44, 070.54
HIV	V08, 042, 079.53, 795.71

Table 13. Descriptive Characteristics: PHC4 Opioid Hospitalizations, First Visit by Patient, 2000-2014

Characteristics	*N=202,126*
Age Group	
9-14 yrs	454 (0.2%)
15-24 yrs	39178 (19.4%)
25-34 yrs	47287 (23.4%)
35-44 yrs	38932 (19.3%)
45-54 yrs	33917 (16.8%)
55-64 yrs	17036 (8.4%)
65-74 yrs	10793 (5.3%)
75-84 yrs	9688 (4.8%)
85+ yrs	4841 (2.4%)
Sex	
Male	107990 (53.4%)
Female	94117 (46.6%)
Pregnancy	9069 (4.5%)
Race	
White	155730 (77.1%)
Black	25827 (12.8%)
Asian/Pac Is/HIian	487 (0.2%)
American Ind/AK Nat	1827 (0.9%)
Other/Multiple	9279 (4.6%)
Unknown	8915 (4.4%)
County of Residence Urban	
Large central metro	67816 (33.6%)
Large fringe metro	51005 (25.2%)
Medium metro	50912 (25.2%)
Small metro	13595 (6.7%)
Micropolitan	14126 (7.0%)
Noncore	4672 (2.3%)

Table 13. Descriptive Characteristics: PHC4 Opioid Hospitalizations, First Visit by Patient, 2000-2014, continued

Characteristics	*N=202,126*
Heroin Poisoning	4175 (2.1%)
Any OUD (abuse or dependence)	150109 (74.3%)
Opioid Poisoning	17256 (8.5%)
Alcohol history/related	17684 (8.7%)
Tobacco	43697 (21.6%)
Any Mental disorder	54531 (27.0%)
Marijuana	17188 (8.5%)
Cocaine	26071 (12.9%)
Barbiturates	11423 (5.7%)
HIV	3106 (1.5%)
HCV	16668 (8.2%)

Table 14. Posterior Probabilities (%) for 5-class membership. Sample of PHC4 Opioid Hospitalizations, first visit by patient, 2000-2014

		Latent classes (percentage of analytic sample, n=202,126)				
Variable	Outcome	LC1 (4.5%)	LC2 (17.7%)	LC3 (51.0%)	LC4 (8.7%)	LC5 (18.3%)
Age Group	9-14 yrs	0.0	0.7	0.1	0.3	0.1
	15-24 yrs	**41.1**	1.0	**29.8**	17.6	7.4
	25-34 yrs	**50.2**	2.1	29.6	19.1	23.7
	35-44 yrs	8.7	5.2	19.8	22.7	**30.9**
	45-54 yrs	0.0	9.8	14.9	25.7	**26.9**
	55-64 yrs	0.0	**17.6**	4.8	11.7	9.2
	65-74 yrs	0.0	**24.1**	0.9	2.7	1.6
	75-84 yrs	0.0	**26.2**	0.1	0.2	0.2
	85+ yrs	0.0	**13.3**	0.0	0.0	0.0
Sex	Male	0.0	32.2	59.5	48.2	**71.5**
	Female	**100.0**	**67.8**	40.4	51.7	28.5
Pregnancy		**100.0**	0.0	0.0	0.4	0.0
Race	White	81.4	**89.6**	**90.9**	82.3	30.8
	Black	10.8	6.5	1.8	11.2	**44.8**
	Asian/Pac Is/HIian	0.3	0.3	0.2	0.3	0.3
	American Ind/AK Nat	0.1	0.0	1.8	0.0	0.3
	Other/Multiple	2.1	1.0	2.2	2.9	**14.6**
	Unknown	5.2	2.5	3.1	3.3	9.4

Table 14. Posterior Probabilities (%) for 5-class membership. Sample of PHC4 Opioid Hospitalizations, first visit by patient, 2000-2014, continued

		Latent classes (percentage of analytic sample, n=202,126)				
Variable	Outcome	LC1 (4.5%)	LC2 (17.7%)	LC3 (51.0%)	LC4 (8.7%)	LC5 (18.3%)
Residence County	Large central metro	30.1	17.6	22.7	20.1	**79.4**
	Large fringe metro	27.0	27.9	32.2	28.6	5.0
	Medium metro	22.8	32.9	26.2	29.5	14.7
	Small metro	7.6	8.4	8.0	9.6	0.9
	Micropolitan	9.7	10.1	8.1	9.5	0.0
	Noncore	2.8	3.2	2.8	2.8	0.0
Heroin		0.1	0.0	1.8	**9.7**	1.5
OUD		**90.8**	10.5	**100.0**	3.7	**98.1**
Opioid poison		0.1	10.6	1.5	**62.1**	0.9
Alcohol		2.0	0.3	11.3	10.5	10.9
Tobacco		12.7	6.3	**29.7**	23.1	17.5
Any Mental Disorders		10.4	7.7	**38.4**	29.8	19.5
Marijuana		8.8	0.0	**12.9**	3.0	8.0
Cocaine		10.2	0.0	13.6	3.6	**27.2**
Barbiturates		3.0	0.1	8.7	0.8	6.2

Table 15. Descriptive Characteristics, PHC4 Opioid Hospitalizations, Primary Opioid Visits, 2000-2014

Characteristics	*N=82,880*
Age Group	
9-14 yrs	69 (0.1%)
15-24 yrs	18,620 (22.5%)
25-34 yrs	24,615 (29.7%)
35-44 yrs	18,446 (22.3%)
45-54 yrs	13,562 (16.4%)
55-64 yrs	4,940 (6.0%)
65-74 yrs	1,638 (2.0%)
75-84 yrs	690 (0.8%)
85+ yrs	299 (0.4%)
Sex	
Male	52,740 (63.6%)
Female	30,135 (36.4%)
Pregnancy	178 (0.2%)
Race	
White	61,553 (74.3%)
Black	8,633 (10.4%)
Asian/Pac Is/HIian	147 (0.2%)
American Ind/AK Nat	2,642 (3.2%)
Other/Multiple	3,384 (4.1%)
Unknown	6,487 (7.8%)
County of Residence Urban	
Large central metro	30,851 (37.2%)
Large fringe metro	23,644 (28.5%)
Medium metro	19,664 (23.7%)
Small metro	3,476 (4.2%)
Micropolitan	3,983 (4.8%)
Noncore	1,262 (1.5%)

Table 15. Descriptive Characteristics, PHC4 Opioid Hospitalizations, Primary Opioid Visits, 2000-2014, continued

Characteristics	*N=82,880*
Heroin Poisoning	7,156 (8.6%)
Any OUD (abuse or dependence)	68,671 (82.9%)
Opioid Poisoning	14,689 (17.7%)
Alcohol history/related	5,172 (6.2%)
Tobacco	15,877 (19.2%)
Any Mental disorder	15,619 (18.8%)
Marijuana	4,348 (5.2%)
Cocaine	9,458 (11.4%)
Barbiturates	5,045 (6.1%)
HIV	1,057 (1.3%)
HCV	8,404 (10.1%)

Table 16. Posterior Probabilities (%) for 5-class membership, PHC4 Hospitalizations, Primary Opioid Visits, 2000-2014

Variable	Outcome	LC1 (15.7%)	LC2 (26.9%)	LC3 (24.8%)	LC4 (5.4%)	LC5 (27.2%)
Age Group	9-14 yrs	0.5	0.0	0.0	0.0	0.0
	15-24 yrs	10.2	**33.2**	**30.0**	**33.2**	10.5
	25-34 yrs	12.9	30.6	**37.3**	33.6	29.9
	35-44 yrs	17.6	19.4	18.6	16.0	**32.3**
	45-54 yrs	**26.2**	12.8	10.7	11.8	20.4
	55-64 yrs	**17.0**	3.0	2.9	4.8	5.5
	65-74 yrs	**8.6**	0.7	0.3	0.4	1.3
	75-84 yrs	**4.8**	0.1	0.1	0.1	0.1
	85+ yrs	2.2	0.0	0.0	0.1	0.0
Sex	Male	46.5	62.0	59.5	**73.5**	**77.2**
	Female	**53.5**	38.0	40.5	26.4	22.8
Pregnancy		0.1	0.3	0.4	0.1	0.1
Race	White	86.1	84.8	**94.3**	87.1	35.6
	Black	9.5	0.4	1.8	5.9	**29.2**
	Asian/Pac Is/HIian	0.2	0.2	0.2	0.1	0.2
	American Ind/AK Nat	0.0	**13.5**	0.0	0.0	0.0
	Other/Multiple	1.9	1.0	1.2	3.4	11.1
	Unknown	2.3	0.1	2.4	3.4	23.9
Residence County	Large central metro	21.5	21.3	32.1	28.7	**66.7**
	Large fringe metro	30.1	**54.1**	28.7	35.2	4.3
	Medium metro	26.6	15.7	24.9	22.3	28.0
	Small metro	9.1	2.0	6.1	6.4	0.9
	Micropolitan	9.9	5.0	6.3	5.5	0.1
	Noncore	2.8	1.9	1.9	1.9	0.0

Table 16. Posterior Probabilities (%) for 5-class membership, PHC4 Hospitalizations, Primary Opioid Visits, 2000-2014, continued

Variable	Outcome	LC1 **(15.7%)**	LC2 **(26.9%)**	LC3 **(24.8%)**	LC4 **(5.4%)**	LC5 **(27.2%)**
Heroin		0.0	0.1	7.8	**100.0**	4.3
OUD		11.7	**100.0**	**100.0**	36.4	**100.0**
Opioid poison		**100.0**	0.0	5.3	4.6	1.3
Alcohol		8.9	0.0	10.6	**12.1**	4.5
Tobacco		16.7	0.1	**37.6**	25.1	16.9
Any Mental Disorders		**28.4**	6.9	**30.7**	20.3	11.3
Marijuana		2.3	0.1	**13.1**	3.0	3.8
Cocaine		3.2	3.2	**18.4**	8.0	16.7
Barbiturates		1.0	1.2	**14.9**	1.1	5.1

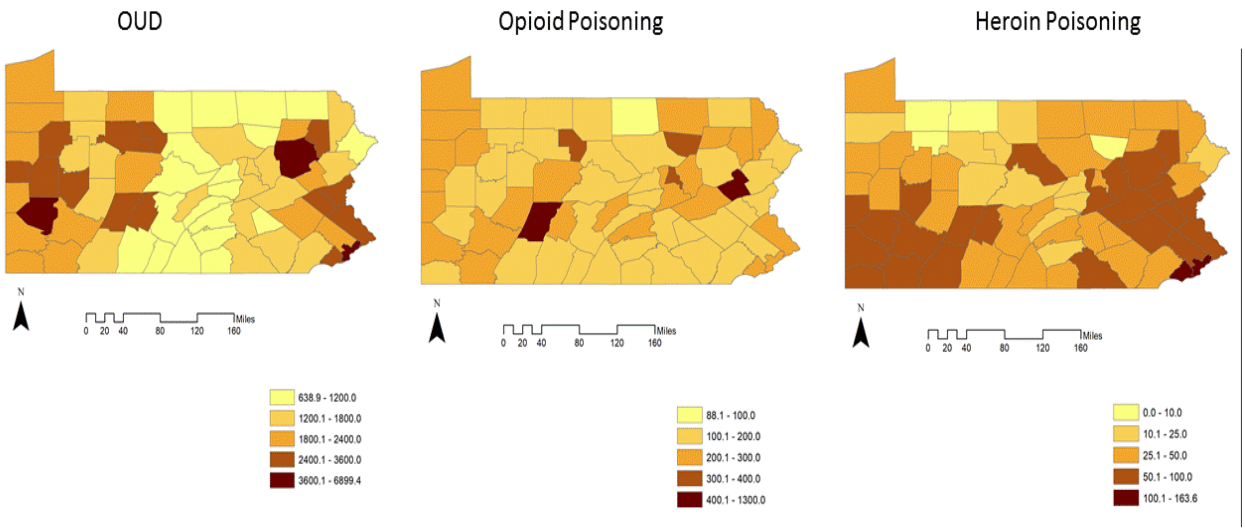

Figure 4. Hospital Visit Crude Rates (per 100,000 population) for Opioid Types, 2000-2014

APPENDIX B: PAPER 2 ADDITIONAL TABLES/FIGURES

Table 17. Descriptive Characteristics of Visits, Opioid Cohort, 2000-2010

Characteristics	*N=560,480*
Age Group	
9-14 yrs	1,000 (0.2%)
15-24 yrs	70,102 (12.5%)
25-34 yrs	120,889 (21.6%)
35-44 yrs	131,126 (23.4%)
45-54 yrs	122,279 (21.8%)
55-64 yrs	51,843 (9.2%)
65-74 yrs	26,563 (4.7%)
75-84 yrs	24,188 (4.3%)
85+ yrs	12,490 (2.2%)
Median Age (Q1, Q3)	41.0 (30.0 : 52.0)
Mean Age (SD)	43.1 (16.7)
Sex	
Male	303,253 (54.1%)
Female	257,118 (45.9%)
Race	
White	404,394 (75.9%)
Black	103,504 (19.4%)
Asian/Pac Is/HIian	985 (0.2%)
Other/Multiple	23,669 (4.4%)

Table 17. Descriptive Characteristics of Visits, Opioid Cohort, 2000-2010, continued

Characteristics	*N=560,480*
County of Residence Urbanicity	
Large central metro	232,560 (41.7%)
Large fringe metro	128,306 (23.0%)
Medium metro	124,149 (22.3%)
Small metro	20,234 (3.6%)
Micropolitan (rural)	44,804 (8.0%)
Noncore (rural)	7,704 (1.4%)
Alcohol	45,407 (8.1%)
Tobacco	105,846 (18.9%)
Any Mental disorder	158,497 (28.3%)
Marijuana, Cocaine, Barbiturates	107,817 (19.2%)
OUD	223,391 (39.9%)
Opioid Poison	14,394 (2.6%)
Heroin Poison	5,265 (0.9%)
HIV	16,683 (3.0%)
HCV	75,606 (13.5%)

Table 18. Description of Re-Hospitalizations by HCV, HIV, and Urbanicity

Number of Hospitalizations per Individual	*Opioid Cohort N=132,674 individuals*	*HCV at any discharge*	*Never HCV*	*HIV at any discharge*	*Never HIV*	*Urban*	*Rural*
1	29,707 (22.4%)	3,725 (2.8%)	25,982 (19.6%)	482 (0.4%)	29,225 (22%)	26,671 (20.2%)	2,788 (2.1%)
2	19,894 (15%)	3,468 (2.6%)	16,426 (12.4%)	355 (0.3%)	19,539 (14.7%)	17,542 (13.3%)	2,252 (1.7%)
3	15,422 (11.6%)	3,160 (2.4%)	12,262 (9.2%)	348 (0.3%)	15,074 (11.4%)	13,493 (10.2%)	1,871 (1.4%)
4	11,793 (8.9%)	2,850 (2.1%)	8,943 (6.7%)	315 (0.2%)	11,478 (8.7%)	10,364 (7.9%)	1,382 (1.0%)
5	9,165 (6.9%)	2,410 (1.8%)	6,755 (5.1%)	266 (0.2%)	8,899 (6.7%)	8,071 (6.1%)	1,056 (0.8%)
6-10	24,824 (18.7%)	7,260 (5.5%)	17,564 (13.2%)	840 (0.6%)	23,984 (18.1%)	21,793 (16.5%)	2,918 (2.2%)
11-20	14,767 (11.1%)	4,664 (3.5%)	10,103 (7.6%)	677 (0.5%)	14,090 (10.6%)	13,037 (9.9%)	1,665 (1.3%)
21-50	6,277 (4.7%)	2,112 (1.6%)	4,165 (3.1%)	397 (0.3%)	5,880 (4.4%)	5,637 (4.3%)	615 (0.5%)
51-100	733 (0.6%)	235 (0.2%)	498 (0.4%)	50 (0.0%)	683 (0.5%)	674 (0.5%)	54 (0.0%)
>100	92 (0.1%)	34 (0.0%)	58 (0.0%)	11 (0.0%)	81 (0.1%)	91 (0.1%)	1 (0.0%)

Table 19. Primary Diagnosis at Last Visit during Opioid Cohort, by Age Group, 2000-2010

	HCV		HIV		Neither Disease	
Primary Discharge	*Age <35 yrs (n=8,818)*	*Age ≥35 yrs (n=16,841)*	*Age <35 yrs (n=518)*	*Age ≥35 yrs (n=3,059)*	*Age <35 yrs (n=45322)*	*Age ≥35 yrs (n=63213)*
Opioid Dependence	764 (8.7%)	928 (5.5%)	36 (7%)	106 (3.5%)	7102 (15.7%)	3880 (6.1%)
Opioid Abuse	14 (0.2%)	10 (0.1%)	1 (0.2%)	2 (0.1%)	76 (0.2%)	48 (0.1%)
Heroin Poisoning	134 (1.5%)	134 (0.8%)	5 (1%)	25 (0.8%)	986 (2.2%)	413 (0.7%)
Opioid Poisoning	32 (0.4%)	110 (0.7%)	3 (0.6%)	13 (0.4%)	971 (2.1%)	1373 (2.2%)
HIV	20 (0.2%)	312 (1.9%)	50 (9.7%)	495 (16.2%)	-	-
HCV	105 (1.2%)	183 (1.1%)	3 (0.6%)	17 (0.6%)	-	-
Infectious/Parasitic Diseases	135 (1.5%)	547 (3.3%)	15 (2.9%)	121 (4%)	461 (1%)	1865 (3%)
Endocrine	81 (0.9%)	381 (2.3%)	3 (0.6%)	62 (2%)	388 (0.9%)	1576 (2.5%)
Blood Diseases	26 (0.3%)	97 (0.6%)	6 (1.2%)	26 (0.9%)	219 (0.5%)	255 (0.4%)
Mental Disorders	3463 (39.3%)	5283 (31.4%)	168 (32.4%)	681 (22.3%)	19126 (42.2%)	16119 (25.5%)
Nervous System	82 (0.9%)	254 (1.5%)	9 (1.7%)	49 (1.6%)	486 (1.1%)	1387 (2.2%)
Circulatory	78 (0.9%)	1026 (6.1%)	9 (1.7%)	177 (5.8%)	378 (0.8%)	5587 (8.8%)
Endocarditis/Cardiomyopathy*	66 (0.8%)	126 (0.8%)	2 (0.4%)	25 (0.8%)	89 (0.2%)	213 (0.3%)
Respiratory	198 (2.3%)	1360 (8.1%)	24 (4.6%)	366 (12%)	980 (2.2%)	5043 (8%)

*ICD-9-CM discharges: 421-425

Table 19. Primary Diagnosis at Last Visit during Opioid Cohort, by Age Group, 2000-2010, continued

	HCV		HIV		Neither Disease	
Primary Discharge	*Age <35 yrs (n=8,818)*	*Age ≥35 yrs (n=16,841)*	*Age <35 yrs (n=518)*	*Age ≥35 yrs (n=3,059)*	*Age <35 yrs (n=45322)*	*Age ≥35 yrs (n=63213)*
Digestive	245 (2.8%)	912 (5.4%)	15 (2.9%)	128 (4.2%)	1347 (3%)	4818 (7.6%)
Liver-related**	36 (0.4%)	544 (3.2%)	1 (0.2%)	64 (2.1%)	78 (0.2%)	274 (0.4%)
Genitourinary	117 (1.3%)	395 (2.4%)	13 (2.5%)	72 (2.4%)	733 (1.6%)	2381 (3.8%)
Pregnancy	1821 (20.7%)	202 (1.2%)	40 (7.7%)	11 (0.4%)	4884 (10.8%)	628 (1%)
Skin	510 (5.8%)	922 (5.5%)	45 (8.7%)	138 (4.5%)	1365 (3%)	1792 (2.8%)
Musculoskeletal	126 (1.4%)	681 (4%)	10 (1.9%)	92 (3%)	637 (1.4%)	5261 (8.3%)
Congenital Anomalies	1 (0%)	11 (0.1%)	0 (0%)	3 (0.1%)	45 (0.1%)	87 (0.1%)
Symptoms/Signs/Ill-defined	202 (2.3%)	892 (5.3%)	22 (4.3%)	162 (5.3%)	1008 (2.2%)	3941 (6.2%)
Injury/Poisoning	562 (6.4%)	1531 (9.1%)	38 (7.3%)	224 (7.3%)	3963 (8.7%)	6272 (9.9%)

**ICD-9-CM discharges: 570-573

Table 20. Hospitalization Rate Multipliers for HCV, HIV, and Urbanicity with Covariates

Rate Multiplier (95% CI)	*Covariate of Interest*		
	Hepatitis C discharge at any visit, at mean age	*HIV discharge at any visit*	*County of Residence*
Covariate of Interest	1.11 (1.10, 1.13)	1.38 (1.34, 1.42)	1.14 (1.12, 1.16)
Index Age (year)	1.0082 (1.0078, 1.0086)	1.0093 (1.0089, 1.0097)	1.0095 (1.0091, 1.0099)
Index Age - interaction Covariate of Interest	1.013 (1.012, 1.014)	N/A	N/A
Female Sex	1.015 (1.009, 1.020)	0.91 (0.90, 0.92)	0.91 (0.90, 0.92)
Alcohol	1.07 (1.05, 1.08)	1.08 (1.06, 1.09)	1.08 (1.07, 1.09)
Tobacco	1.08 (1.07, 1.09)	1.09 (1.08, 1.10)	1.09 (1.08, 1.10)
Mental Disorder	1.22 (1.20, 1.23)	1.22 (1.20, 1.23)	1.22 (1.20, 1.23)
Illegal Drug	1.05 (1.03, 1.06)	1.04 (1.03, 1.06)	1.05 (1.04, 1.06)
OUD	0.80 (0.79, 0.81)	0.80 (0.80, 0.81)	0.80 (0.79, 0.81)
Opioid Poisoning	1.27 (1.24, 1.30)	1.27 (1.24, 1.30)	1.27 (1.24, 1.30)
Heroin Poisoning	1.16 (1.11, 1.22)	1.17 (1.12, 1.22)	1.16 (1.11, 1.22)

Table 21. Descriptive Characteristics of Second Visit, Opioid Cohort, 2000-2010

Characteristics	*N=83,018*
Age Group	
9-14 yrs	122 (0.1%)
15-24 yrs	13,847 (16.7%)
25-34 yrs	19,041 (22.9%)
35-44 yrs	17,933 (21.6%)
45-54 yrs	15,323 (18.5%)
55-64 yrs	6,390 (7.7%)
65-74 yrs	3,989 (4.8%)
75-84 yrs	4,146 (5.0%)
85+ yrs	2,227 (2.7%)
Median Age (Q1, Q3)	42.1 (17.7)
Mean Age (SD)	39.0 (28.0 : 51.0)
Sex	
Male	43,954 (53.0%)
Female	39,034 (47.0%)
Race	
White	62,317 (80.1%)
Black	11,559 (14.9%)
Asian/Pac Is/HIian	161 (0.2%)
Other/Multiple	3,728 (4.8%)

Table 21. Descriptive Characteristics of Second Visit, Opioid Cohort, 2000-2010, continued

Characteristics	*N=83,018*
County of Residence Urbanicity	
Large central metro	31,058 (37.6%)
Large fringe metro	19,677 (23.8%)
Medium metro	19,726 (23.9%)
Small metro	3,269 (4.0%)
Micropolitan (rural)	7,562 (9.1%)
Noncore (rural)	1,354 (1.6%)
Heroin Poison	625 (0.8%)
OUD	29,977 (36.1%)
Opioid Poison	896 (1.1%)
Alcohol	6,289 (7.6%)
Tobacco	15,807 (19.0%)
Any Mental Disorder	22,194 (26.7%)
Marijuana, Cocaine, Barbiturates	14,112 (17.0%)
HIV	1,793 (2.2%)
HCV	8,848 (10.7%)

APPENDIX C: PAPER 3 ADDITIONAL TABLES/FIGURES

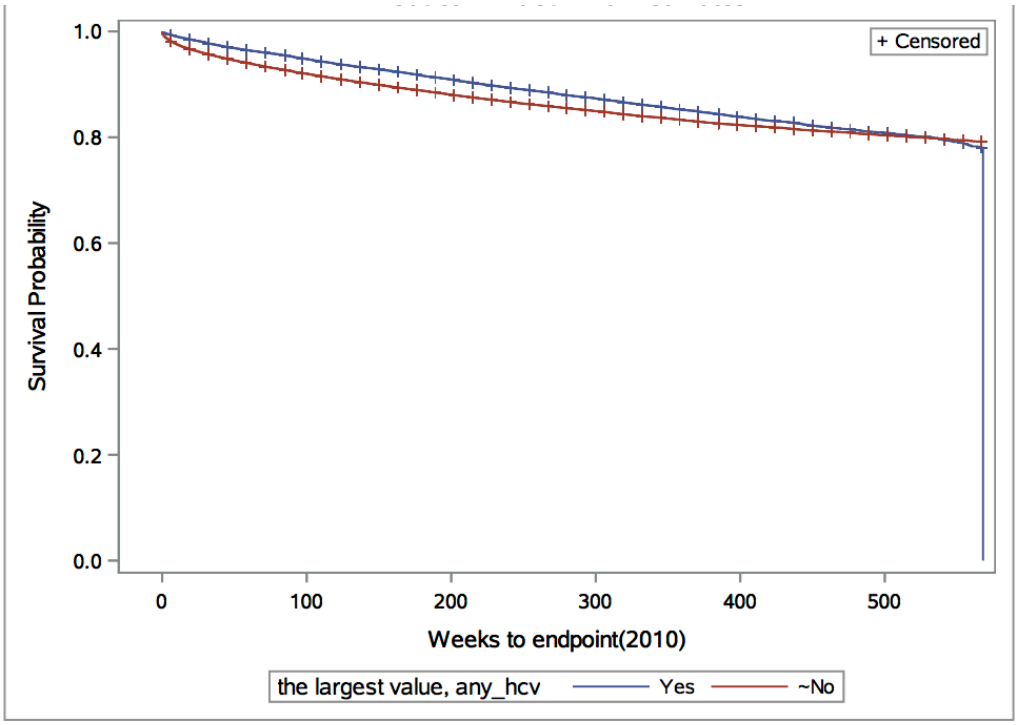

Figure 5. Deaths in Opioid Cohort by HCV, unadjusted, 2000-2010

Table 22. Descriptive Characteristics of Opioid Cohort by HCV, 2000-2010

Characteristics	*No HCV n= 109,341*	*HCV n= 27,122*
Mean Age (SD)	41 (18.5)	37 (12.0)
Median Age (Q1, Q3)	37 (26, 51)	37 (26, 47)
Sex		
Male	58,716 (53.7%)	16,710 (61.6%)
Female	50,617 (46.3%)	10,410 (38.4%)
Race		
White	83594 (76.5%)	18267 (67.4%)
Black	13573 (12.4%)	4555 (16.8%)
Asian/Pac Is/HIian	277 (0.3%)	36 (0.1%)
American Ind/AK Nat	1553 (1.4%)	230 (0.9%)
Other/Multiple	4604 (4.2%)	1798 (6.6%)
Unknown	5692 (5.2%)	2227 (8.2%)
Alcohol	18481 (16.9%)	9083 (33.5%)
Tobacco	39938 (36.5%)	16221 (59.8%)
Any Mental disorder	26468 (24.2%)	6649 (24.5%)
Marijuana, Cocaine, Barbiturates	24108 (22.0%)	7757 (28.6%)
Opioid Discharges		
OUD only	71861 (65.7%)	23133 (85.3%)
Opioid Poison	8040 (7.4%)	413 (1.5%)
Heroin Poison	789 (0.7%)	104 (0.4%)
OUD and any overdose	6762 (6.2%)	3155 (11.6%)
AE only	21889 (20%)	317 (1.2%)

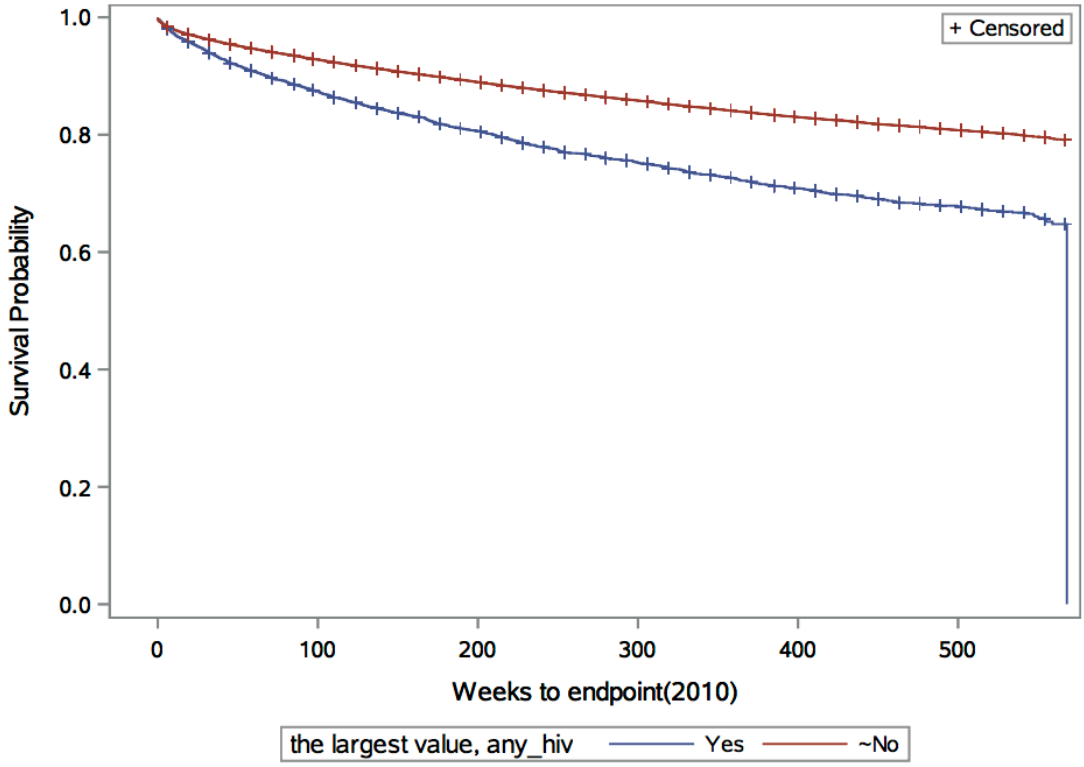

Figure 6. Deaths in Opioid Cohort by HIV, unadjusted, 2000-2010

Table 23. Descriptive Characteristics of Opioid Cohort by HIV, 2000-2010

Characteristics	*No HIV n= 132,792*	*HIV n= 3,671*
Mean Age (SD)	40 (17.7)	41 (9.6)
Median Age (Q1, Q3)	37 (26, 49)	42 (35, 48)
Sex		
Male	72967 (55%)	2459 (67%)
Female	59815 (45%)	1212 (33%)
Race		
White	100631 (75.8%)	1230 (33.6%)
Black	16581 (12.5%)	1547 (42.2%)
Asian/Pac Is/HIian	307 (0.2%)	6 (0.2%)
American Ind/AK Nat	1768 (1.3%)	15 (0.4%)
Other/Multiple	5962 (4.5%)	440 (12%)
Unknown	7495 (5.7%)	424 (11.6%)
Alcohol	26389 (19.9%)	1175 (32%)
Tobacco	54281 (40.9%)	1878 (51.2%)
Any Mental disorder	32356 (24.4%)	761 (20.7%)
Marijuana, Cocaine, Barbiturates	30620 (23.1%)	1245 (33.9%)
Opioid Discharges		
OUD only	91802 (69.1%)	3192 (87%)
Opioid Poison	8378 (6.3%)	75 (2%)
Heroin Poison	880 (0.7%)	13 (0.4%)
OUD and any overdose	9619 (7.2%)	298 (8.1%)
AE only	22113 (16.7%)	93 (2.5%)

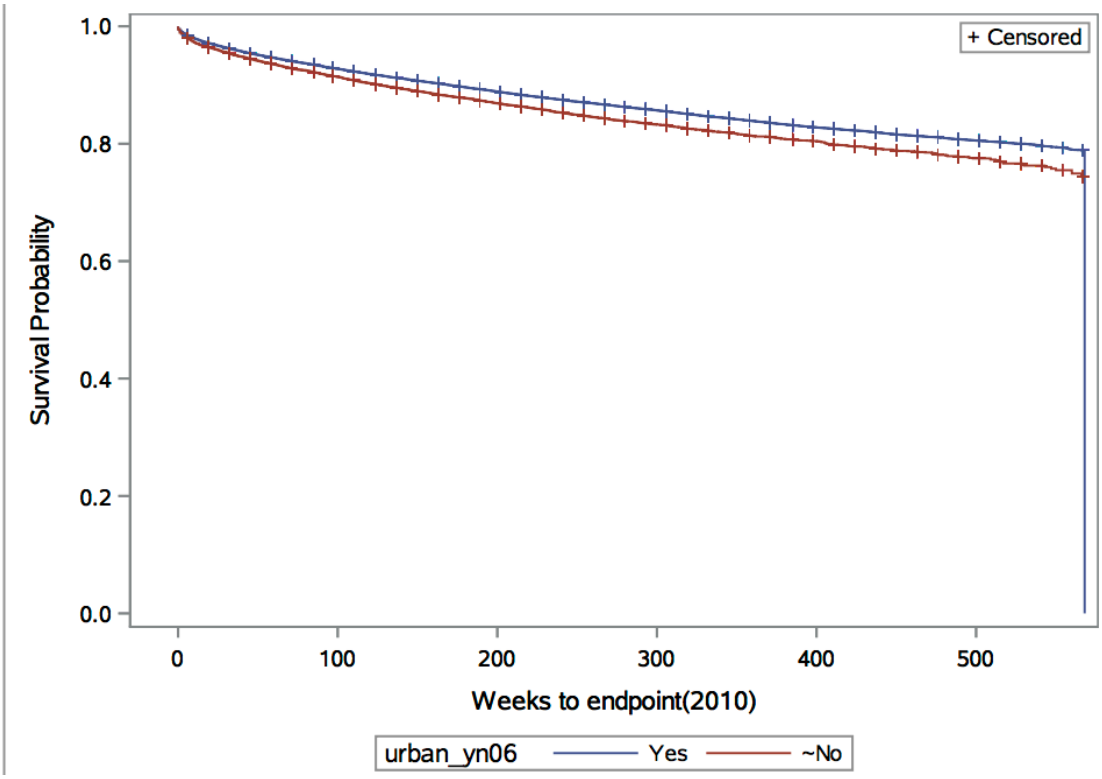

Figure 7. Deaths in Opioid Cohort by Urbanicity, unadjusted, 2000-2010

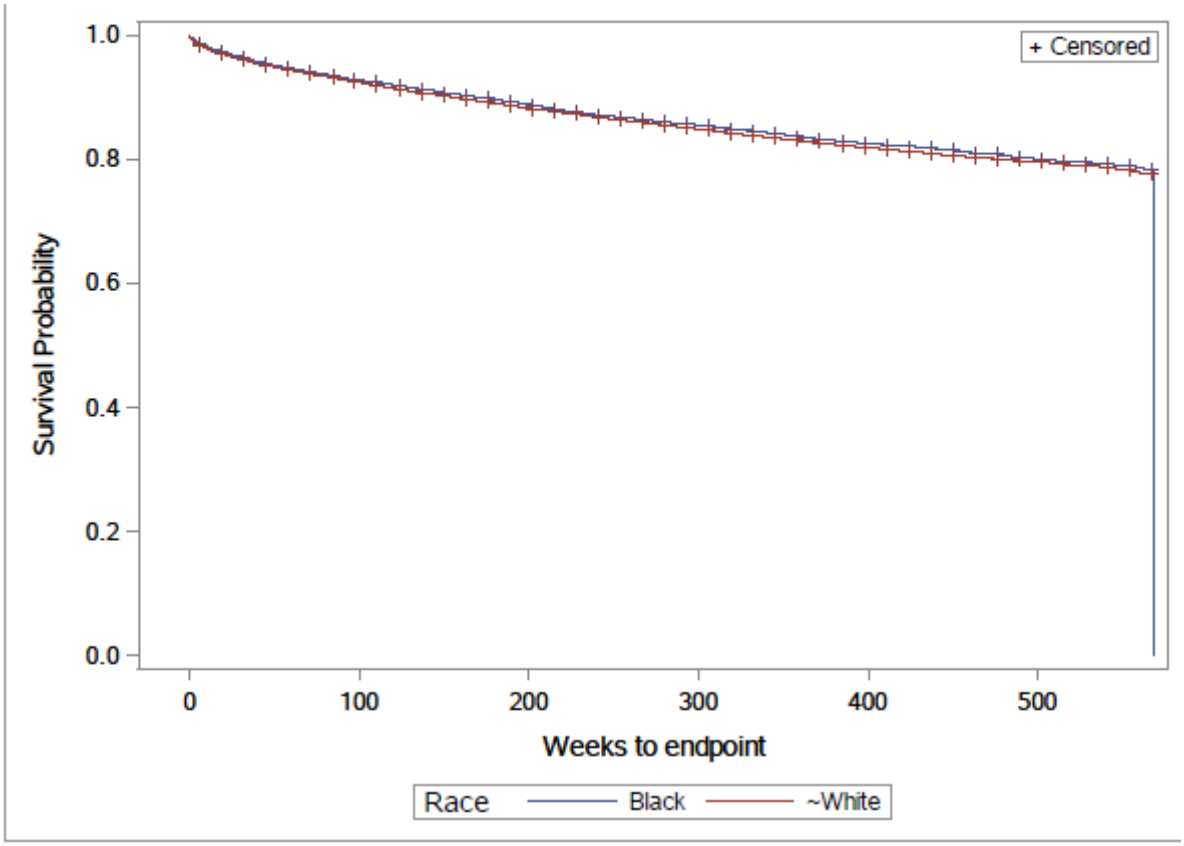

Figure 8. Deaths in Opioid Cohort by Race, unadjusted, 2000-2010

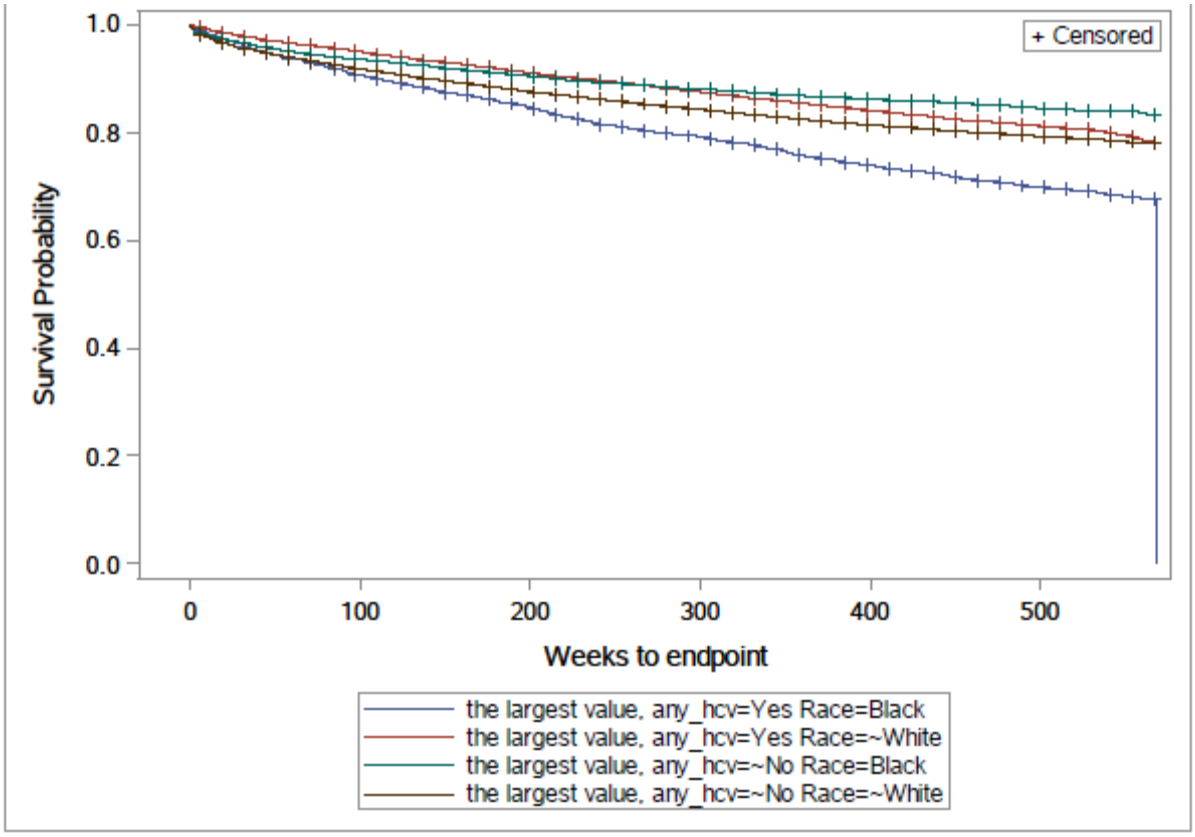

Figure 9. Deaths in Opioid Cohort by HCV and Race, unadjusted, 2000-2010

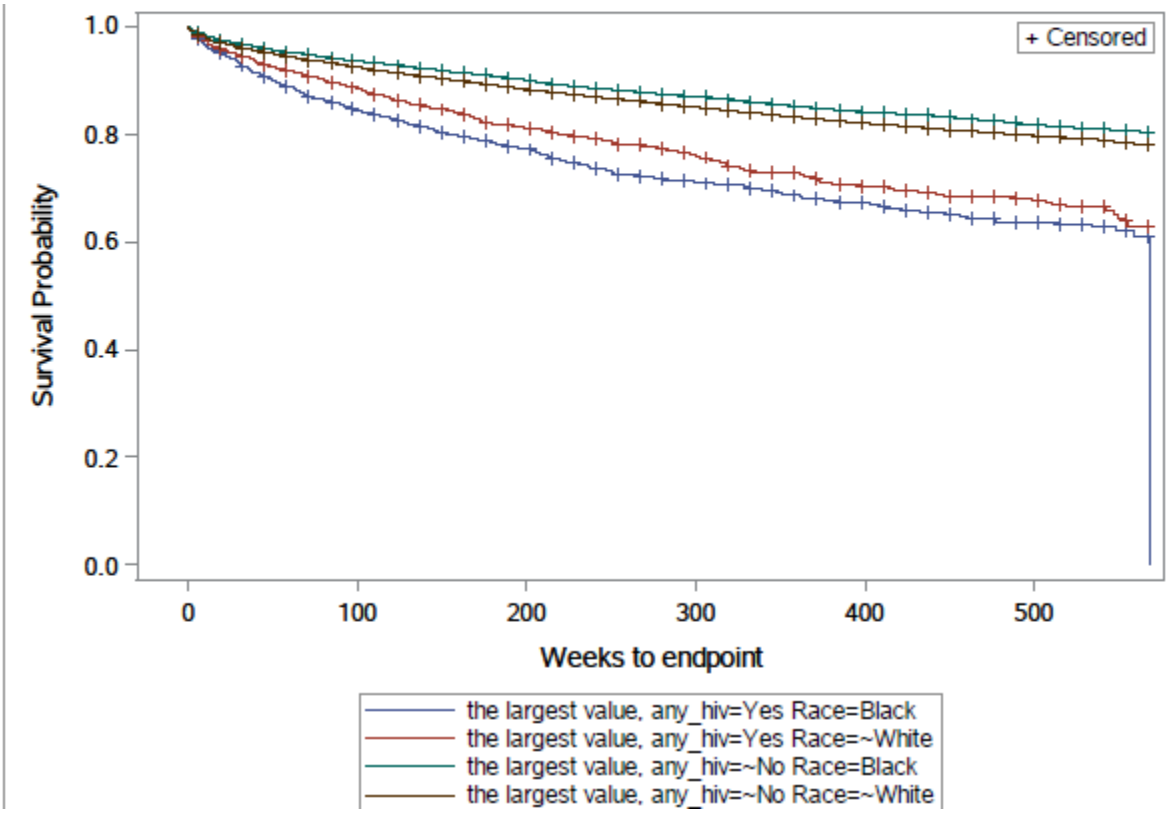

Figure 10. Deaths in Opioid Cohort by HIV and Race, unadjusted, 2000-2010

Table 24. Underlying Cause of Death, by Age Group (<35 years and 35 years and over)

Underlying Causes of Death	*<35 years old*	*%*	*≥35 years old*	*%*	*Total*
Drug Poisoning	1847	59.0	2315	15.9	4162
Heart Disease*	148	4.7	3824	26.3	3972
Respiratory	49	1.6	1609	11.1	1658
Injuries/Trauma	423	13.5	722	5.0	1145
Liver-related†	28	0.9	699	4.8	727
Other Circulatory ‡	42	1.3	659	4.5	701
Infection	25	0.8	511	3.5	536
Genitourinary	23	0.7	502	3.5	525
HIV	58	1.9	429	3.0	487
Mental and Behavioral Disorders	46	1.5	377	2.6	423
Digestive, non-Liver§	13	0.4	354	2.4	367
Cancer	6	0.2	289	2.0	295
HCV	7	0.2	214	1.5	221
Other Hepatitis	0	0.0	34	0.2	34
OUD	9	0.3	6	0.0	15
Other¶	407	13	1986	13.7	2393
Total	3131	100	14530	100	17661

*Heart Disease: Hypertensive, ischemic heart, pulmonary heart diseases, pericardia, endocardia, myocardia, cardiomyopathy

†Liver-related: Liver diseases (K70-K77) and liver cancer (C22, D376)

‡Other Circulatory: Cerebrovascular Disease and Blood Disorders

§Digestive, non-Liver: all diseases of the digestive system codes but excludes diseases of the liver codes (K70-77)

¶Other: Congenital malformation, diabetes, external cause, fungal, musculoskeletal, nervous system, pregnancy, skin/tissue

Table 25. Underlying Causes of Death, HCV discharges by Age Group (<35 years and 35 years and over)

Underlying Causes of Death	*<35 years old*	*%*	*≥35 years old*	*%*	*Total*
Drug Poisoning	388	56.2	701	20.9	1089
Heart Disease*	49	7.1	534	15.9	583
Respiratory	8	1.2	202	6.0	210
Injuries/Trauma	69	10.0	145	4.3	214
Liver-related†	11	1.6	436	13.0	447
Other Circulatory ‡	8	1.2	103	3.1	111
Infection	12	1.7	139	4.2	151
Genitourinary	6	0.9	89	2.7	95
HIV	33	4.8	312	9.3	345
Mental and Behavioral Disorders	12	1.7	50	1.5	62
Digestive, non-Liver§	2	0.3	31	0.9	33
Cancer	2	0.3	28	0.8	30
HCV	7	1.0	201	6.0	208
Other Hepatitis	0	0.0	26	0.8	26
OUD	2	0.3	4	0.1	6
Other¶	81	11.7	347	10.4	428
Total	690	100	3348	100	4038

*Heart Disease: Hypertensive, ischemic heart, pulmonary heart diseases, pericardia, endocardia, myocardia, cardiomyopathy

†Liver-related: Liver diseases (K70-K77) and liver cancer (C22, D376)

‡Other Circulatory: Cerebrovascular Disease and Blood Disorders

§Digestive, non-Liver: all diseases of the digestive system codes but excludes diseases of the liver codes (K70-77)

¶Other: Congenital malformation, diabetes, external cause, fungal, musculoskeletal, nervous system, pregnancy, skin/tissue

Table 26. Underlying Causes of Death, HIV discharges by Age Group (<35 years and 35 years and over)

Underlying Causes of Death	*<35 years old*	*%*	*≥35 years old*	*%*	*Total*
Drug Poisoning	33	26.6	101	11.8	134
Heart Disease*	7	5.6	91	10.6	98
Respiratory	1	0.8	27	3.2	28
Injuries/Trauma	8	6.5	22	2.6	30
Liver-related†	0	0.0	3	0.4	3
Other Circulatory ‡	7	5.6	46	5.4	53
Infection	5	4.0	45	5.3	50
Genitourinary	2	1.6	17	2.0	19
HIV	56	45.2	418	48.8	474
Mental and Behavioral Disorders	0	0.0	4	0.5	4
Digestive, non-Liver§	0	0.0	8	0.9	8
Cancer	0	0.0	8	0.9	8
HCV	0	0.0	13	1.5	13
Other Hepatitis	3	2.4	18	2.1	21
OUD	0	0.0	2	0.2	2
Other¶	2	1.6	33	3.9	35
Total	124	100	856	100	980

*Heart Disease: Hypertensive, ischemic heart, pulmonary heart diseases, pericardia, endocardia, myocardia, cardiomyopathy

†Liver-related: Liver diseases (K70-K77) and liver cancer (C22, D376)

‡Other Circulatory: Cerebrovascular Disease and Blood Disorders

§Digestive, non-Liver: all diseases of the digestive system codes but excludes diseases of the liver codes (K70-77)

¶Other: Congenital malformation, diabetes, external cause, fungal, musculoskeletal, nervous system, pregnancy, skin/tissue

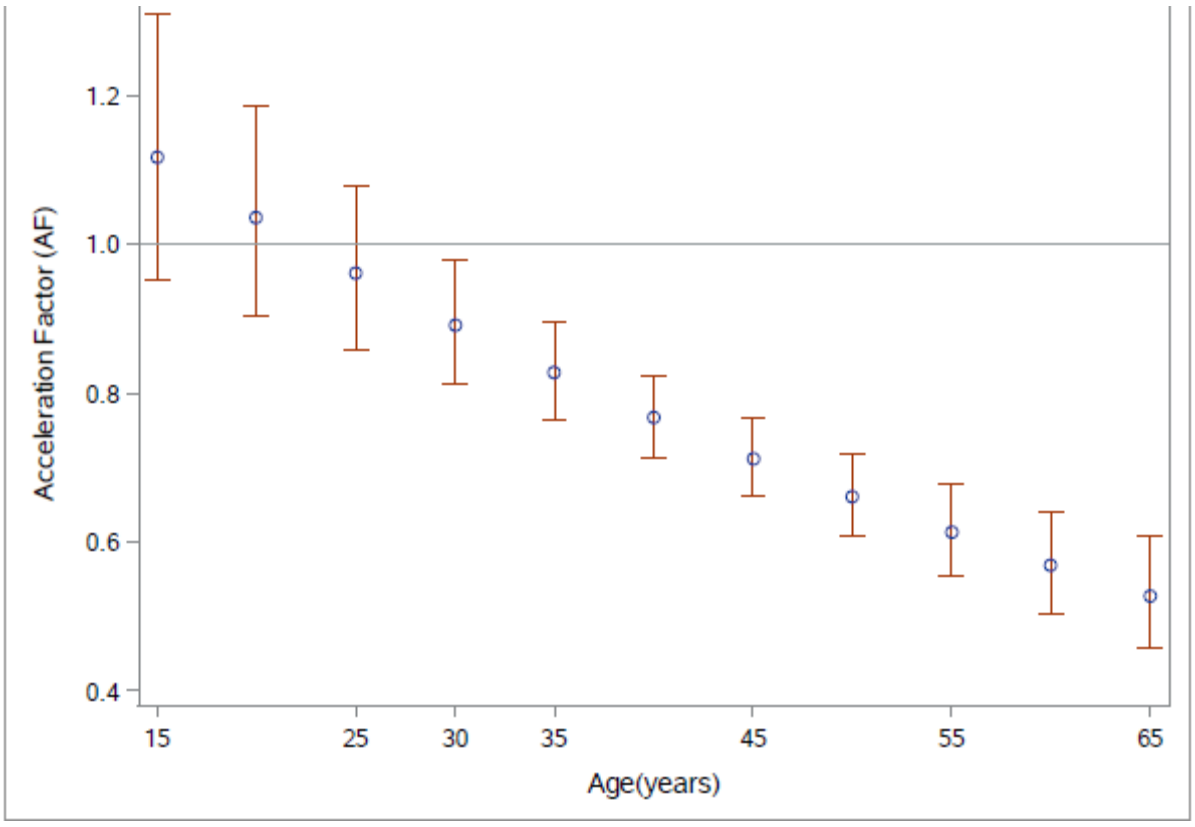

Figure 11. Accelerated Failure Time Model for HCV by Age in White Race only, 2000-2010

Table 27. Accelerated Failure for HIV, White Race Only

Age (years)	AF (95% CI)	p-value
15	1.12 (0.95, 1.31)	0.17
20	1.04 (0.91, 1.19)	0.60
25	0.96 (0.86, 1.08)	0.50
30	0.89 (0.81, 0.98)	0.02
35	0.83 (0.76, 0.90)	<.0001
40	0.77 (0.71, 0.82)	<.0001
45	0.71 (0.66, 0.77)	<.0001
50	0.66 (0.61, 0.72)	<.0001
55	0.61 (0.55, 0.68)	<.0001
60	0.57 (0.50, 0.64)	<.0001
65	0.53 (0.46, 0.61)	<.0001

Table 28. Accelerated Failure for HIV, by Race, 2000-2010

Race	AF (95% CI)	p-value
White	0.35 (0.29, 0.42)	<.0001
Black	0.23 (0.20, 0.28)	<.0001

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