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Impact of Hepatitis Co-Infection on Hospitalization Rates and Causes in a Multi-Center Cohort of Persons Living with HIV

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Abstract

Background—Chronic viral hepatitis is a potentially important determinant of healthcare utilization among persons living with HIV (PLWH). We describe hospitalization rates and reasons for hospitalization among PLWH stratified by co-infection with hepatitis B virus (HBV) and/or hepatitis C virus (HCV).

Methods—Laboratory, demographic, and hospitalization data were obtained for all patients receiving longitudinal HIV care during 2010 at 9 geographically diverse sites. Hepatitis serostatus was assessed by hepatitis B surface antigen and/or hepatitis C antibody. ICD-9 codes were used to assign hospitalizations into diagnostic categories. Negative binomial regression was used to assess factors associated with all-cause and diagnostic category-specific hospitalizations.

Results—A total of 2,793 hospitalizations were observed among 12,819 patients. Of these patients, 49.3% had HIV mono-infection, 4.1% HIV/HBV, 15.4% HIV/HCV, 2.5% HIV/HBV/HCV and 28.7% unknown hepatitis serostatus. Compared to HIV mono-infection, risk of all-cause hospitalization was increased with HIV/HBV (adjusted incidence rate ratio (aIRR) 1.55 [1.17–2.06]), HIV/HCV (1.45 [1.21–1.74]) and HIV/HBV/HCV (1.52 [1.04–2.22]). Risk of hospitalization for non-AIDS-defining infection was also higher among patients with HIV/HBV (2.07 [1.38–3.11]), HIV/HCV (1.81 [1.36–2.40]) and HIV/HBV/HCV (1.96 [1.11–3.46]). HIV/HBV was associated with hospitalization for gastrointestinal/liver disease (2.55 [1.30–5.01]). HIV/HCV was associated with hospitalization for psychiatric illness (1.89 [1.11–3.26]).

Conclusions—HBV and HCV co-infection are associated with increased risk of all-cause hospitalization and hospitalization for non-AIDS-defining infections, as compared to HIV mono-infection. Policy-makers and third-party payers should be aware of the heightened risk of

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hospitalization associated with co-infection when allocating healthcare resources and considering models of healthcare delivery.

Keywords

HIV; hepatitis B; hepatitis C; hospitalizations; healthcare utilization

BACKGROUND

Chronic viral hepatitis is common among persons living with HIV (PLWH). In the United States, Europe, and Australia, approximately 4.8–9.0% of PLWH are also chronically infected with hepatitis B virus (HBV), 20–33% are chronically infected with hepatitis C virus (HCV) and 0.5–4.0% are chronically infected with both[1–5]. Patients with HIV/HBV co-infection experience faster progression to cirrhosis, more hepatocellular carcinoma and higher risk of liver-related mortality than patients with either infection alone[5–8]. Similarly, liver disease progression and its complications are more common in HIV/HCV co-infected patients than in HIV mono-infected patients[2,8,9]. Viral hepatitis, particularly HCV, has also been associated with extrahepatic complications that can include renal disease, cardiovascular disease, diabetes, autoimmunity, metabolic bone disease and neurocognitive decline[10–16].

In the era of potent and widely available antiretroviral therapy, hospitalization rates have become an important outcome measure and an important healthcare cost among PLWH[17–19]. Comparing rates and reasons for hospitalizations among PLWH with and without hepatitis coinfection will be important to clinicians and policy-makers trying to understand the healthcare needs of these populations. Differences across these populations could suggest areas of unique clinical need and may influence the allocation of healthcare resources and the construction of healthcare delivery models.

The purpose of this study was to characterize the impact of hepatitis co-infection on inpatient healthcare utilization among HIV-infected patients in a multi-site, multi-state consortium of HIV care sites.

METHODS

Site Selection and Data Collection

The HIV Research Network (HIVRN) is a consortium of 17 sites providing longitudinal adult and pediatric HIV care in 11 U.S. cities. Sites abstract comprehensive demographic, laboratory, and treatment data from clinical records, then de-identify and submit them to a data coordinating center where they are reviewed and combined into a uniform database[20]. In 2010, nine of the participating sites submitted details of hospital admissions for adult patients (3 Northeast, 3 West, 2 South, and 1 Midwest). Seven of these sites have academic affiliations and 2 are community-based. Inclusion in this retrospective cohort study was restricted to patients who enrolled in care before July 1, 2010, and were in active care during 2010. Active care was defined as having at least one outpatient HIV provider visit and one CD4 cell count during the calendar year. Institutional review boards at each site and at the

data coordinating center at Johns Hopkins University approved the collection and use of these data for analysis and publication.

Definitions of Variables

Hepatitis serostatus was assessed by detection of hepatitis B surface antigen (HBsAg) and/or hepatitis C antibody (anti-HCV) at any time prior to or during 2010. At each site, patients are screened for chronic HBV and chronic HCV at the discretion of their providers. If a patient had multiple serologies performed over time, a single positive test was considered sufficient to categorize the patient as positive for that assay. HBV DNA and HCV RNA levels were not available. Patients were assigned to one of five hepatitis serostatus categories. Patients with negative results for both hepatitis serologies were categorized as HIV mono-infected. Patients with a positive HBsAg and negative anti-HCV were categorized as HIV/HBV co-infected. Patients with a negative HBsAg and positive anti-HCV were categorized as HIV/HCV coinfected. Patients with positive results for both hepatitis serologies were categorized as HIV/HBV/HCV tri-infected. Patients without known results from one or both tests were categorized as unknown hepatitis serostatus.

Age was assessed on July 1, 2010 and divided into 4 categories: 18–34, 35–49, 50–64 and 65 or more years. Race/ethnicity was categorized based on self-report as White, Black, Hispanic or other/unknown. HIV transmission risk factor was classified as one of four mutually exclusive categories: injection drug use (IDU), men who have sex with men (MSM), heterosexual transmission, or other/unknown. Patients who reported IDU in addition to any other risk factor were categorized as IDU. Men who reported sex with both men and women were categorized as MSM.

The CD4 T-cell count and HIV-1 RNA values used in this analysis were the first available measurements in 2010. CD4 count was categorized as ≤50, 51–200, 201–500 or >500 cells/mm^3. HIV-1 RNA was categorized as <400 or ≥400 copies/mL. Antiretroviral therapy (ART) was defined as the concurrent use of three or more antiretroviral medications from at least two classes at any time during calendar year 2010. Insurance status was categorized as Medicaid, Medicare, Private, Ryan White/Uninsured or missing. Patients with dual eligibility for Medicaid and Medicare were included in the Medicare category.

Outcomes

The primary outcome of this study was all-cause hospitalization in 2010. We also investigated cause-specific hospitalization rates using 18 diagnostic categories, including non-AIDS-defining infection, cardiovascular, gastrointestinal/liver and AIDS-defining illness (see Table, Supplemental Digital Content 1, for complete list). Using a previously published algorithm, several steps were taken to assign each hospitalization to a single diagnostic category[18,21]. First, the primary diagnostic code for the hospitalization was assigned using the first-listed ICD-9 code that did not refer to HIV (042, V08, 795.71, V01.79), chronic HBV (070.22, 070.23, 070.32, 070.33), chronic HCV (070.44, 070.54, 070.70, 070.71), or oral candidiasis (112.0). These codes represent comorbidities that are frequently recorded for billing purposes but are not, by themselves, sufficient to justify hospitalization. Second, Clinical Classifications Software (CCS) developed by the Agency

for Healthcare Research and Quality was used to assign the primary ICD-9 code into one of 18 "first-level" CCS categories [22]. Finally, we modified the CCS diagnostic categories in three ways: we reassigned infections from organ system categories to the infection category (for example pneumonia was reassigned from pulmonary to infection); we combined congenital, perinatal, and unclassified (together < 1% of admissions) into a single category; and we created an AIDS-defining illness (ADI) category according to the 1993 Centers for Disease Control and Prevention criteria [23]. After the ADI category was created, we renamed the remaining infection category "non-AIDS-defining infection" and the remaining malignancy category "non-AIDS-defining cancer."

Within each diagnostic category, ICD-9 codes were used to identify the most frequently occurring individual diagnoses. Highly similar ICD-9 codes were grouped (Appendix Table). The most common individual diagnoses were tallied and reported as percentages of admissions within the corresponding diagnostic category.

Data Analysis

Hospitalization rates were calculated as total number of admissions divided by the number of years of patient follow-up and multiplied by 100 to obtain rates per 100 person-years (PY). Patients who enrolled in care or died during the observation period contributed less than one year of follow-up, so a variable person-time denominator was used in rate calculations.

Preliminary exploration of the hospitalization count data revealed that the variance was not equal to the mean of the distribution, making negative binomial regression a more robust analytic method than Poisson regression. Unadjusted negative binomial regression was therefore used to estimate incidence rate ratios for all-cause and diagnostic category-specific hospitalization rates associated with hepatitis serostatus and other predefined clinical and demographic variables.

Adjusted negative binomial models compared incidence rates for all-cause hospitalization and diagnostic category-specific hospitalizations between each of the hepatitis serostatus groups (including the unknown group), controlling for age, race, sex, HIV risk factor, CD4, HIV RNA, ART use, and insurance. Adjusted models also included categorical indicators for each clinical care site to control for site-specific variability in healthcare utilization (results suppressed).

A sensitivity analysis was performed in which patients with one positive hepatitis serology and one missing hepatitis serology were re-categorized from the unknown hepatitis status group into either the HIV/HBV or HIV/HCV group.

A two-sided type I error of 5% was considered statistically significant. All analyses were performed using Stata 12.0 (StataCorp LP, College Station, TX, USA).

RESULTS

Demographic and clinical characteristics of the study population are presented in Table 1. Of the 12,819 patients included in this analysis, 49.4% had HIV monoinfection, 4.1%

HIV/HBV co-infection, 15.4% HIV/HCV co-infection, 2.5% HIV/HBV/HCV tri-infection and 28.7% had unknown hepatitis serostatus. IDU was reported in 17.4% of patients overall with higher percentages in the HIV/HCV (59.4%) and HIV/HBV/HCV (32.7%) groups. MSM comprised 39.4% of patients overall with higher percentages in the HIV/HBV (56.6%) and HIV-monoinfected (47.5%) groups. MSM was relatively less common as a sole HIV risk factor in the HIV/HCV (15.7%) and HIV/HBV/HCV (26.1%) groups. Median CD4 counts and percentages of patients with HIV RNA <400 copies/mL were similar across all the hepatitis serostatus groups. There were 117 deaths and 885 new enrollments in care during the study period, resulting in less than one year of observation time for these individuals. Median follow-up of these patients was 230 days among patients in the HIV/HBV group and 245 days in all other hepatitis serostatus groups.

There were 2,793 hospitalizations in total. Unadjusted all-cause hospitalization rates stratified by hepatitis serostatus are presented in Figure 1A. Rates were highest among HIV/HCV co-infected patients (41.1 hospitalizations per 100 PY [95% CI 35.7–47.2]), followed by HIV/HBV co-infected (35.4/100 PY [26.6–47.0]), then HIV/HBV/HCV tri-infected (28.2/100 PY [19.4–40.9]). All-cause hospitalization rates were similar among HIV mono-infected patients (19.5/100 PY [17.9–21.3]) and patients with unknown hepatitis serostatus (18.2/100 PY [16.2–20.5]).

Analyses of factors associated with all-cause hospitalization are presented in Table 2. Decreasing CD4 count was the strongest predictor of all-cause hospitalization with an adjusted incidence rate ratio (aIRR) of 8.14 (95% CI 6.27–10.58) for persons with CD4 <50 cells/mm^3, compared to CD4 >500 cells/mm^3. Risk of hospitalization increased in those with HIV/HBV (aIRR 1.55 [1.17–2.06]), HIV/HCV (aIRR 1.45 [1.21–1.74]) and HIV/HBV/HCV (aIRR 1.52 [1.04–2.22]) compared to HIV mono-infection. Other factors independently associated with hospitalization included age, gender, HIV transmission risk factor, HIV-1 RNA, and insurance.

In unadjusted analyses, non-AIDS-defining infections accounted for significantly more hospitalizations per 100 person-years in each of the hepatitis co-infected groups than in the HIV mono-infected group (Figure 1B). Gastrointestinal/liver-related hospitalizations were more common in the HIV/HBV (5.6 per 100 PY [2.9–10.7]) and HIV/HCV (4.0 per 100 PY [2.9–5.6]) groups than in the HIV mono-infected group (1.6 per 100 PY [1.3–2.0]). Compared to HIV mono-infected patients, patients with HIV/HCV had significantly higher unadjusted hospitalization rates in the cardiovascular, renal, psychiatric, pulmonary, and injury/poisoning categories ($p<0.001$).

Adjusted relative rates of hospitalization for the ten most common diagnostic categories are presented in Figure 2. Compared to HIV mono-infection, the relative rate of hospitalization for non-AIDS-defining infection was higher among patients with HIV/HBV (aIRR 2.07 [1.38–3.11]), HIV/HCV (aIRR 1.81 [1.36–2.40]) and HIV/HBV/HCV (aIRR 1.96 [1.11–3.46]). The relationship between hepatitis co-infection and hospitalization for gastrointestinal/liver disease was attenuated in multivariate analysis, with only HIV/HBV remaining independently associated with risk of hospitalization (aIRR 2.55 [1.30–5.01]). Patients with HIV/HCV had higher risk of hospitalization for psychiatric illness (aIRR 1.89

[1.11–3.26]) and patients with HIV/HBV had higher risk of hospitalization for non-AIDS-defining cancers (aIRR 4.75 [1.52–14.88]) than the HIV mono-infected reference group.

Table 3 lists the most common diagnostic categories and individual diagnoses within these categories. Among non-AIDS-defining infections, bacterial pneumonia was the most common diagnosis overall and among most hepatitis serostatus groups. Complications of cirrhosis (including admissions for cirrhosis, hepatic encephalopathy, portal hypertension and ascites) were the most common reason for GI/liver admissions overall, although the proportion of admissions did not differ significantly from the proportions for pancreatitis or diarrhea. Complications of cirrhosis accounted for only 4.12% of GI/liver admissions in the HIV monoinfected group. Among AIDS-defining illnesses, *Pneumocystis jiroveci* was the most common diagnosis overall and among most hepatitis serostatus groups.

In our sensitivity analysis, 67 participants from the unknown hepatitis serostatus group were recategorized as HIV/HBV co-infected and 291 as HIV/HCV co-infected on the basis of one positive serology and an unknown second hepatitis serology. Multivariable models using this definition of hepatitis serostatus yielded similar results to our original analysis. Compared to HIV mono-infection, the relative rate of all-cause hospitalization was again increased in those with HIV/HBV (IRR 1.50 [1.15–1.97]), HIV/HCV (IRR 1.38 [1.16–1.65]) and HIV/HBV/HCV (IRR 1.52 [1.04–2.22]). Inferences about the relationship between hepatitis serostatus and risk of diagnostic category-specific hospitalizations were also unchanged (data not shown).

DISCUSSION

This study is the first to demonstrate, in a contemporary cohort of PLWH, that hospitalization rates are higher among patients with HBV and/or HCV co-infection. This finding is consistent with prior studies demonstrating high rates of morbidity and mortality in co-infected populations[2,5–13,16]. Since hospitalizations are a significant driver of healthcare costs among PLWH, the higher frequency of hospitalization in hepatitis co-infected populations results in increased healthcare costs for these populations[19]. Policy-makers should be aware of the financial implications of co-infection among PLWH as they allocate scarce healthcare resources and establish capitated costs for accountable care organizations.

Non-AIDS-defining infections accounted for about a quarter of all hospital admissions, and the relative risk of hospitalization for this reason was elevated among patients in all the hepatitis-infected categories. Consistent with prior studies, the most common non-AIDS-defining infection in our study was bacterial pneumonia[24–26]. Chronic viral hepatitis is known to be associated with dysregulation of hepatitis-specific immune responses, but further investigation is needed to explore potential mechanisms underlying an increased risk of bacterial infections[27,28]. Preventable infections such as influenza and pneumococcal pneumonia should be proactively addressed in PLWH with appropriate vaccinations to potentially reduce morbidity and hospitalizations[29,30].

While complications of cirrhosis among PLWH with viral hepatitis co-infection deserve attention due to their seriousness and their associations with mortality, such hospitalizations accounted for only 2.8% (28 out of 999, Table 3) of all hospitalizations among the three viral hepatitis groups combined[5–9]. We did not perform formal diagnostic tests specifically on complications of cirrhosis because of small sample sizes. By way of comparison, however, they accounted for 0.3% (4 out of 1,160) of all hospitalizations among HIV mono-infected persons.

The increased risk for hospitalization due to psychiatric disease in the HIV/HCV co-infected group highlights the need for mental health care in this population. The most common diagnosis among psychiatric admissions was depression. Although drug use may play a role in hospitalizations related to depression, this finding is consistent with existing evidence that HIV/HCV co-infection is associated with higher prevalence and severity of neuropsychiatric disease than either infection alone[16,31]. Integrated mental health and HIV care programs have been shown to improve rates of HIV viral suppression, retention in care, substance abuse and psychiatric symptoms as well as decrease hospitalization costs[32,33]. Co-location of mental health services may offer particular benefit to the HIV/HCV co-infected population.

Interestingly, we did not observe significantly increased risk of hospitalization for renal, cardiovascular or endocrine diagnoses among HIV/HCV co-infected patients, despite evidence that morbidity and mortality related to such diagnoses are increased with HCV co-infection [10–13]. Our study may not have included enough cardiovascular events to detect a statistically significant difference. Our adjusted relative risk estimates for renal and endocrine hospitalizations, on the other hand, suggested no trend towards increased hospitalizations for these diagnoses. One possible explanation for this discrepancy is that these complications are being successfully managed in the outpatient setting and, while present, are not contributing to excess hospitalizations.

Therapy directed against hepatitis B and/or hepatitis C has been shown to decrease progression to cirrhosis among co-infected PLWH[34]. Further investigation is needed to evaluate the effects of hepatitis therapy on all-cause and cause-specific hospitalization rates. Treatment of HBV is common among PLWH, and more than 75% of HIV/HBV co-infected patients in the HIVRN are prescribed agents with activity against both HIV and HBV (Moore RD, Personal Communication on 31 May 2013). Conversely, prior studies have reported treatment rates of only 20–40% for HCV in the routine clinical care of PLWH, with less than half of these persons achieving sustained virologic response[35,36]. With the development of more effective and better tolerated anti-HCV medications, increased utilization of anti-HCV therapy among co-infected patients is expected in the near future[37,38]. If hepatitis therapy decreases hospitalization rates, this could provide an economic counterbalance to the high cost of treating hepatitis, especially with the newest anti-HCV medications[38,39].

A potential limitation of this study is the reliance on hepatitis C antibodies as evidence of hepatitis C co-infection. Unfortunately, HCV RNA data were not available to confirm chronic infection. The bias introduced by misclassifying patients who cleared HCV viremia

as being chronically infected would likely make the HIV mono-infected and HIV/HCV co-infected groups appear more similar. Inferences made based on significant differences between these groups should therefore be robust despite the misclassification. Also, HIV co-infection decreases spontaneous clearance of HCV to fewer than 10% of cases, so it is expected that most patients in this analysis with positive anti-HCV were chronically infected with HCV[40].

Use of ICD-9 codes to determine cause for hospitalization may be less accurate than physician chart review, although validation studies within individual institutions have suggested high concordance with chart review[21]. Hospitalizations occurring outside of each patient's HIV care institution may not be completely captured, though efforts are made by all HIVRN sites to capture utilization data from neighboring hospitals. The inclusion of relatively few patients with HIV/HBV/HCV tri-infection in this study limits our power to draw conclusions about this unique patient population. The population of patients at HIVRN sites is not nationally representative and our findings may not be generalizable to populations served by smaller clinics, located in more rural settings, or cared for by providers with less HIV subspecialty experience.

This study demonstrates that chronic viral hepatitis is associated with increased risk of hospitalization and therefore increased healthcare costs among PLWH. Policy-makers and third-party payers should be aware of the heightened risk of hospitalization associated with co-infection when allocating healthcare resources and considering models of healthcare delivery. Our findings also underscore the importance of targeting patients who are co-infected with HIV and viral hepatitis with preventive measures such as routine vaccinations and integrated mental health services that may help to curb their increased risk of hospitalization. Further investigation is needed to evaluate the effects of therapy against hepatitis on hospitalization rates.

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HIVRN Participating Sites

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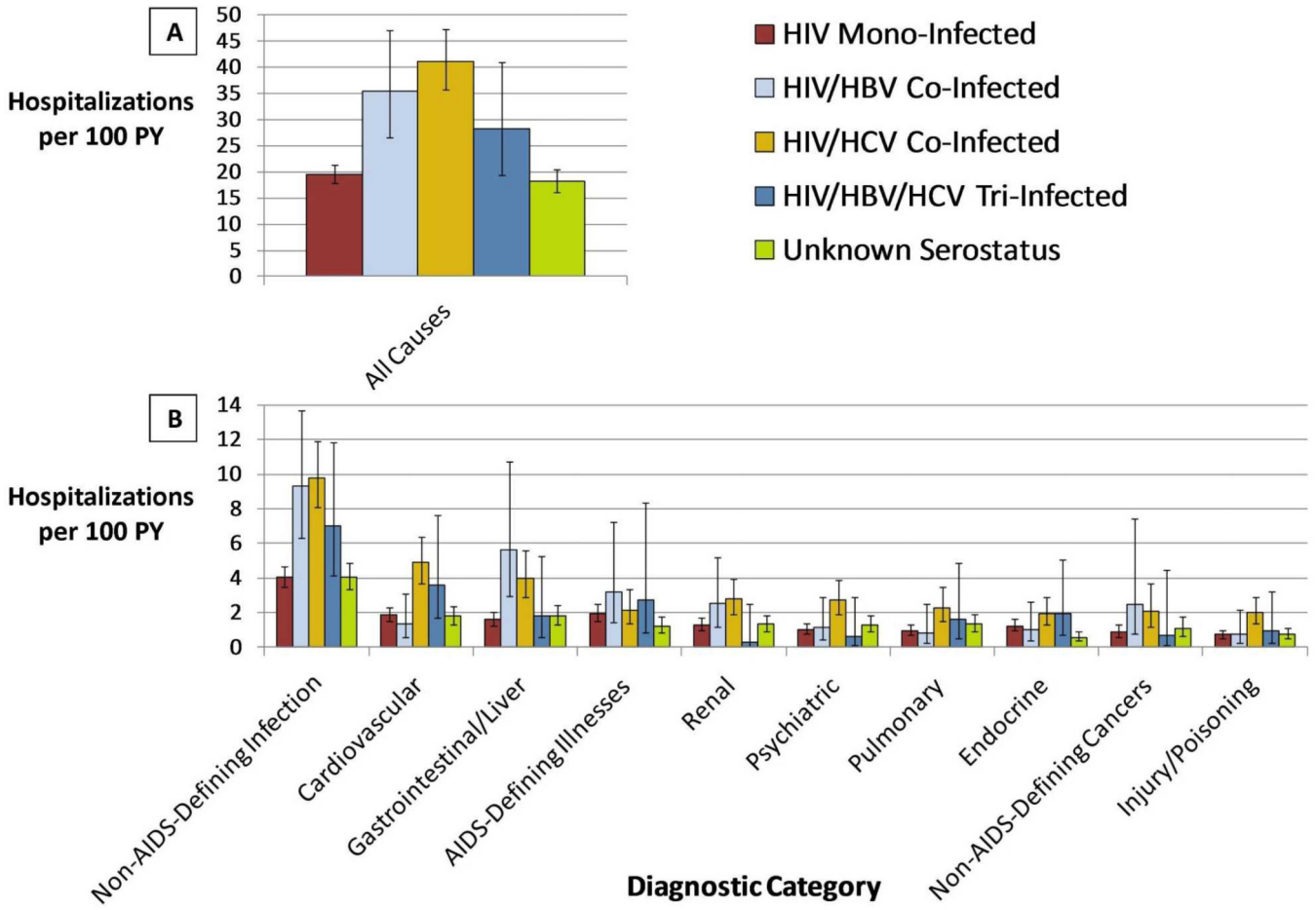

Figure 1. Unadjusted Hospitalization Rates by Diagnostic Category

Unadjusted rates of all-cause (panel A) and diagnostic category-specific (panel B) hospitalization. Rates are standardized as hospitalizations per 100 PY of AU7 follow-up. Unadjusted negative binomial regression was performed to construct 95% confidence intervals.

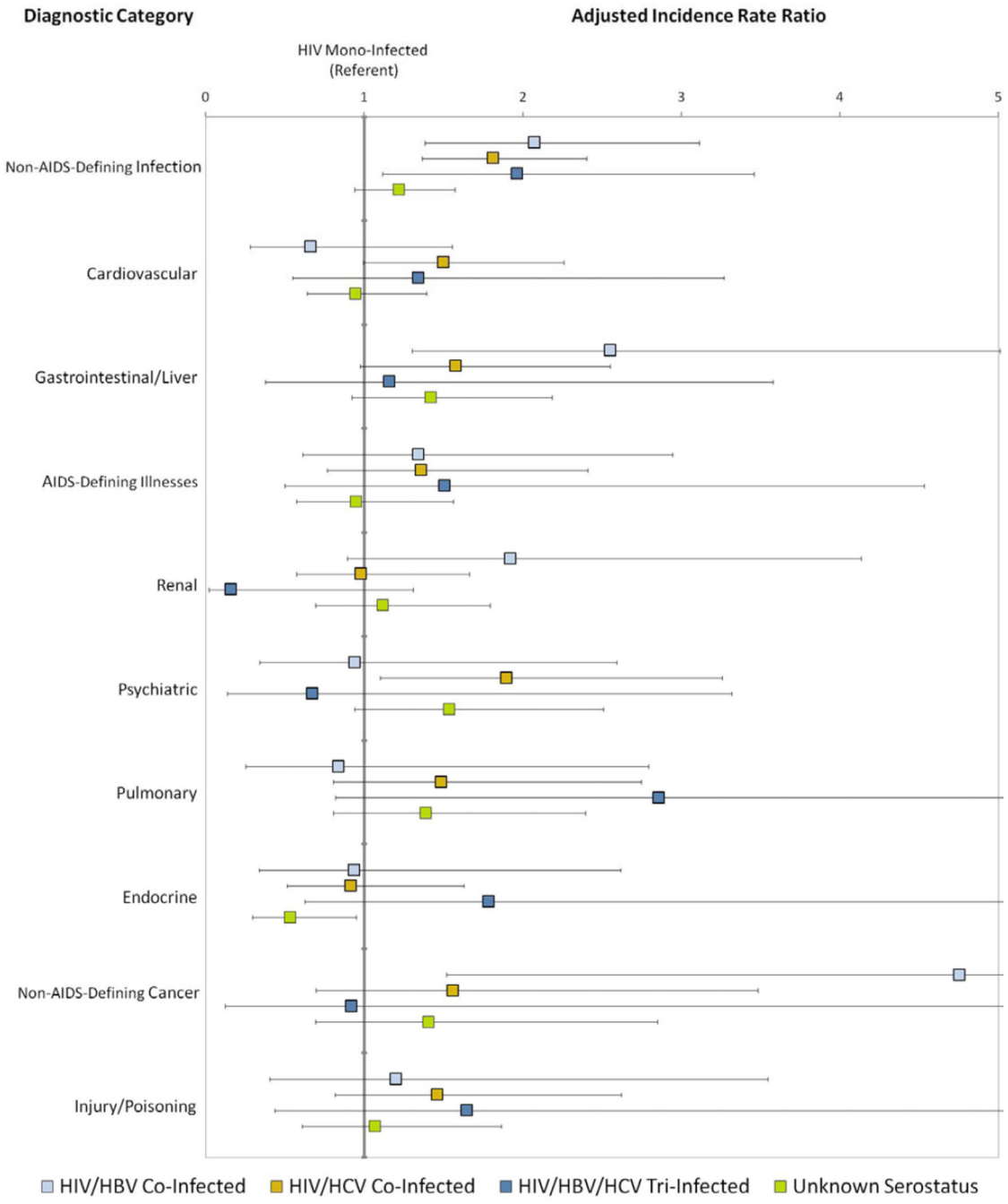

Figure 2. Adjusted Incidence Rate Ratio of Hospitalization by Diagnostic Category

Adjusted incidence rate ratios and 95% confidence intervals were calculated using negative binomial regression and are interpreted as the relative rate of admissions compared to the reference group (HIV mono-infection) after controlling for age, gender, race, HIV risk factor, CD4 count, HIV-1 RNA, ART, insurance and clinical care site.

Table 1

Study Population Characteristics Stratified by Hepatitis Serostatus

Characteristic	Overall n=12,819	HIV Mono-infected n=6,317 (49.3%)	HIV/HBV Co-infected n=532 (4.2%)	HIV/HCV Co-infected n=1,969 (15.4%)	HIV/HBV/HCV Tri-infected n=318 (2.5%)	Unknown Serostatus n=3,683 (28.7%)
Total hospitalizations in 2010 [No.]	2,793	1,160	155	762	82	634
Age on July 1, 2010 [years]						
Median (IQR)	47 (40–53)	45 (37–51)	46 (41–51)	50 (45–56)	48 (42–53)	47 (40–54)
18 – 34 [No. (%)]	1,908 (14.9)	1,244 (19.7)	56 (10.5)	93 (4.7)	25 (7.9)	490 (13.3)
35 – 49	6,112 (47.7)	3,147 (49.8)	304 (57.1)	785 (39.9)	158 (49.7)	1,718 (46.6)
50 – 64	4,348 (33.9)	1,708 (27.0)	152 (28.6)	1,032 (52.4)	127 (39.9)	1,329 (36.1)
≥ 65	451 (3.5)	218 (3.4)	20 (3.8)	59 (3.0)	8 (2.5)	146 (4.0)
Gender [No. (%)]						
Male	9,196 (71.7)	4.540 (71.9)	443 (83.3)	1,387 (70.4)	229 (72.0)	2,597 (70.5)
Female	3,623 (28.3)	1,777 (28.1)	89 (16.7)	582 (29.6)	89 (28.0)	1,086 (29.5)
Race/Ethnicity [No. (%)]						
White	3,420 (26.7)	1,860 (29.4)	201 (37.8)	429 (21.8)	86 (27.0)	844 (22.9)
Black	6,305 (49.2)	2,819 (44.6)	249 (46.8)	1,119 (56.8)	176 (55.4)	1,942 (52.7)
Hispanic	2,661 (20.8)	1,432 (22.7)	65 (12.2)	384 (19.5)	54 (17.0)	726 (19.7)
Other/unknown	433 (3.4)	206 (3.3)	17 (3.2)	37 (1.9)	2 (0.63)	171 (4.6)
HIV risk factor* [No. (%)]						
MSM	5,044 (39.4)	2,998 (47.5)	301 (56.6)	309 (15.7)	83 (26.1)	1,353 (36.7)
Heterosexual	4,824 (37.6)	2,656 (42.0)	181 (34.0)	424 (21.5)	123 (38.7)	1,440 (39.1)
IDU	2,225 (17.4)	313 (5.0)	23 (4.3)	1,169 (59.4)	104 (32.7)	616 (16.7)
Other/unknown	726 (5.7)	350 (5.5)	27 (5.1)	67 (3.4)	8 (2.5)	274 (7.4)
First CD4 count in 2010 (cells/mm^3)						
Median (IQR)	446 (268–645)	454 (278–648)	407 (231–622)	400 (233–607)	405 (220–642)	464 (289–673)
≤ 50 [No. (%)]	515 (4.0)	254 (4.0)	31 (5.8)	81 (4.1)	13 (4.1)	136 (3.7)
51–200	1,657 (12.9)	749 (11.9)	79 (14.8)	328 (16.7)	59 (18.6)	442 (12.0)
201–500	5,223 (40.7)	2,594 (41.1)	216 (40.6)	841 (42.7)	118 (37.1)	1,454 (39.5)
>500	5,424 (42.3)	2,720 (43.1)	206 (38.7)	719 (36.5)	128 (40.2)	1,651 (44.8)
First HIV-1 RNA in 2010 (copies/mL) [No. (%)]						

Characteristic	Overall n=12,819	HIV Mono-infected n=6,317 (49.3%)	HIV/HBV Co-infected n=532 (4.2%)	HIV/HCV Co-infected n=1,969 (15.4%)	HIV/HBV/HCV Tri-infected n=318 (2.5%)	Unknown Serostatus n=3,683 (28.7%)
< 400	8,637 (67.4)	4,190 (66.3)	369 (69.4)	1,299 (66.0)	219 (68.9)	2,560 (69.5)
≥ 400	3,827 (29.8)	1,949 (30.8)	153 (28.8)	616 (31.3)	94 (29.6)	1,015 (27.6)
Unknown	355 (2.8)	178 (2.8)	10 (1.9)	54 (2.7)	5 (1.6)	108 (2.9)
ART** [No. (%)]						
Yes	11,171 (87.1)	5,541 (87.7)	490 (92.1)	1,725 (87.6)	296 (93.1)	3,119 (84.7)
No	1,182 (9.2)	588 (9.3)	32 (6.0)	206 (10.5)	22 (6.9)	334 (9.1)
Unknown	466 (3.6)	188 (3.0)	10 (1.9)	38 (1.9)	0 (0)	230 (6.2)
Insurance [No. (%)]						
Medicaid	4,212 (32.9)	1,923 (30.4)	166 (31.2)	852 (43.3)	95 (29.9)	1,176 (31.9)
Medicare/dual eligible	2,655 (20.7)	1,217 (19.3)	117 (22.0)	427 (21.7)	89 (28.0)	805 (21.9)
Private	2,818 (22.0)	1,367 (21.6)	109 (20.5)	356 (18.1)	32 (10.1)	954 (25.9)
Ryan White/uninsured	2,537 (19.8)	1,497 (23.7)	122 (22.9)	287 (14.6)	79 (24.8)	552 (15.0)
Unknown	597 (4.7)	313 (5.0)	18 (3.4)	47 (2.4)	23 (7.2)	196 (5.3)

IQR interquartile range; MSM men who have sex with men; IDU injection drug use; ART antiretroviral therapy

* HIV risk factors were considered mutually exclusive; subjects who reported IDU in addition to any other risk factor were categorized as IDU, men who reported sex with men and women were categorized as MSM

** ART was defined as concurrent use of 3 or more antiretroviral medications from at least 2 classes at any time during calendar year 2010

Table 2

Univariate and Multivariate Analyses of Risk Factors for All-Cause Hospitalization

Characteristic	IRR (95% CI)	Adjusted IRR (95% CI)
Hepatitis co-infection status		
HIV mono-infection	1.0 (Ref)	1.0 (Ref)
HIV/HBV co-infection	**1.81 (1.35–2.44)**	**1.55 (1.17–2.06)**
HIV/HCV co-infection	**2.10 (1.78–2.48)**	**1.45 (1.21–1.74)**
HIV/HBV/HCV tri-infection	1.44 (0.99–2.12)	**1.52 (1.04–2.22)**
Unknown serostatus	0.93 (0.81–1.08)	1.06 (0.90–1.24)
Age (years)		
18–34	1.0 (Ref)	1.0 (Ref)
35–49	1.08 (0.89–1.30)	0.93 (0.77–1.12)
50–64	**1.40 (1.16–1.71)**	1.21 (0.99–1.48)
≥65	**1.93 (1.36–2.74)**	**1.92 (1.37–2.68)**
Gender		
Male	1.0 (Ref)	1.0 (Ref)
Female	**1.36 (1.19–1.55)**	**1.41 (1.22–1.64)**
Race		
White	1.0 (Ref)	1.0 (Ref)
Black	**1.33 (1.14–1.54)**	1.06 (0.90–1.26)
Hispanic	1.19 (0.99–1.43)	0.92 (0.76–1.12)
Other/Unknown	**0.58 (0.38–0.88)**	**0.57 (0.38–0.87)**
HIV transmission risk factor*		
MSM	1.0 (Ref)	1.0 (Ref)
Heterosexual	**1.30 (1.13–1.50)**	0.99 (0.83–1.17)
IDU	**2.29 (1.94–2.70)**	**1.37 (1.13–1.66)**
Other/Unknown	**1.70 (1.30–2.22)**	**1.41 (1.08–1.84)**
First CD4 count in 2010(cells/mm^3)		
>500	1.0 (Ref)	1.0 (Ref)
201–500	**1.72 (1.50–1.97)**	**1.67 (1.45–1.92)**
51–200	**3.85 (3.24–4.58)**	**3.57 (2.99–4.28)**
≤50	**8.39 (6.51–10.81)**	**8.14 (6.27–10.58)**
First HIV-1 RNA in 2010 (copies/ml)		
<400	1.0 (Ref)	1.0 (Ref)
≥400	**2.04 (1.80–2.31)**	**1.26 (1.10–1.44)**
ART**		
Yes	1.0 (Ref)	1.0 (Ref)
No	0.89 (0.72–1.11)	1.04 (0.84–1.30)
Unknown	**1.52 (1.12–2.07)**	1.31 (0.86–1.99)
Insurance		
Medicaid	1.0 (Ref)	1.0 (Ref)
Medicare/Dual eligible	0.87 (0.74–1.02)	0.99 (0.84–1.17)

Characteristic	IRR (95% CI)	Adjusted IRR (95% CI)
Private	**0.48 (0.40–0.56)**	**0.55 (0.46–0.66)**
Ryan White/Uninsured	**0.38 (0.32–0.46)**	**0.51 (0.42–0.62)**
Unknown/Missing	**0.41 (0.29–0.56)**	**0.62 (0.44–0.87)**

IRR incidence rate ratio; CI confidence interval; MSM men who have sex with men; IDU injection drug use; HIV human immunodeficiency virus; HBV hepatitis B virus; HCV hepatitis C virus Incidence rate ratios and 95% confidence intervals were calculated using negative binomial regression. The adjusted model included the listed characteristics as well as an indicator variable for clinical care site. IRRs in **bold** are statistically significant ($p \leq 0.05$).

* HIV risk factors were considered mutually exclusive; subjects who reported IDU in addition to any other risk factor were categorized as IDU, men who reported sex with men and women were categorized as MSM

** ART was defined as concurrent use of 3 or more antiretroviral medications from at least 2 classes at any time during calendar year 2010

Table 3

Most Common Individual Diagnoses Within Diagnostic Categories

Diagnostic Category Common Diagnoses	Overall n=2,793 (%)	HIV Mono-infected n=1,160 (%)	HIV/HBV Co-infected n=155 (%)	HIV/HCV Co-infected n=762 (%)	HIV/HBV/HCV Tri-infected n=82 (%)	Unknown Serostatus n=634 (%)
Non-AIDS-Defining Infection	**637 (22.8)**	**245 (21.1)**	**44 (28.4)**	**183 (24.0)**	**22 (26.8)**	**143 (22.6)**
Bacterial pneumonia	130 (20.4)	46 (18.8)	7 (15.9)	47 (25.7)	3 (13.6)	27 (18.9)
Sepsis/bacteremia	92 (14.4)	38 (15.5)	9 (20.4)	24 (13.1)	5 (22.7)	16 (11.2)
Cellulitis	88 (13.8)	26 (10.6)	6 (13.6)	33 (18.0)	1 (4.55)	22 (15.4)
Cardiovascular	**290 (10.4)**	**114 (9.83)**	**7 (4.52)**	**94 (12.3)**	**11 (13.4)**	**64 (10.1)**
Chest pain	57 (19.7)	17 (14.9)	1 (14.3)	28 (29.8)	1 (9.09)	10 (15.6)
Heart failure	54 (18.6)	29 (25.4)	0 (0)	9 (9.57)	8 (72.73)	8 (12.5)
CAD/MI	43 (14.8)	13 (11.4)	1 (14.3)	14 (14.9)	0 (0)	15 (23.4)
Gastrointestinal/Liver	**265 (9.49)**	**97 (8.36)**	**22 (14.2)**	**77 (10.1)**	**5 (6.10)**	**64 (10.1)**
Complication of cirrhosis*	45 (17.0)	4 (4.12)	10 (45.4)	18 (23.4)	0 (0)	13 (20.3)
Pancreatitis	41 (15.5)	10 (10.3)	0 (0)	20 (26.0)	1 (20.0)	10 (15.6)
Diarrhea	40 (15.1)	23 (23.7)	2 (9.09)	7 (9.09)	1 (20.0)	7 (10.9)
AIDS-Defining Illness	**217 (7.77)**	**113 (9.74)**	**15 (9.68)**	**41 (5.38)**	**7 (8.54)**	**41 (6.47)**
Pneumocystis jiroveci	59 (27.2)	36 (31.9)	3 (20.0)	10 (24.4)	0 (0)	10 (24.4)
Cryptococcus	33 (15.2)	22 (19.5)	1 (6.67)	9 (22.0)	0 (0)	1 (2.44)
Recurrent bacterial pneumonia	21 (9.68)	10 (8.85)	2 (13.3)	7 (17.1)	0 (0)	2 (4.88)
Renal	**191 (6.84)**	**78 (6.72)**	**12 (7.74)**	**53 (6.96)**	**1 (1.22)**	**47 (7.41)**
Acute renal failure	125 (65.4)	49 (62.8)	8 (66.7)	36 (67.9)	0 (0)	32 (68.1)
Hypertension with chronic kidney disease	8 (4.19)	5 (6.41)	0 (0)	2 (3.77)	0 (0)	1 (2.13)
Urinary calculus	8 (4.19)	3 (3.85)	0 (0)	1 (1.89)	1 (100)	3 (6.38)
Psychiatric	**169 (6.05)**	**63 (5.43)**	**6 (3.87)**	**52 (6.82)**	**2 (2.44)**	**46 (7.26)**
Depression	44 (26.0)	15 (23.8)	2 (33.3)	21 (40.4)	1 (50.0)	5 (10.9)
Drug abuse/withdrawal	40 (23.7)	13 (20.6)	0 (0)	12 (23.1)	1 (50.0)	14 (30.4)
Psychosis/schizophrenia	34 (20.1)	15 (23.8)	1 (16.7)	6 (11.5)	0 (0)	12 (26.1)
Pulmonary	**157 (5.62)**	**59 (5.09)**	**4 (2.58)**	**42 (5.51)**	**5 (6.10)**	**47 (7.41)**
Asthma/COPD	71 (45.2)	25 (42.4)	0 (0)	21 (50.0)	0 (0)	25 (53.2)
Acute respiratory failure	31 (19.8)	10 (17.0)	1 (25.0)	9 (21.4)	1 (20.0)	10 (21.3)

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Diagnostic Category Common Diagnoses	Overall n=2,793 (%)	HIV Mono-infected n=1,160 (%)	HIV/HBV Co-infected n=155 (%)	HIV/HCV Co-infected n=762 (%)	HIV/HBV/HCV Tri-infected n=82 (%)	Unknown Serostatus n=634 (%)
Pleural effusion	8 (5.10)	6 (10.2)	0 (0)	1 (2.38)	0 (0)	1 (2.13)
Endocrine	**145 (5.19)**	**76 (6.55)**	**5 (3.23)**	**37 (4.86)**	**6 (7.32)**	**21 (3.31)**
Electrolyte abnormalities	62 (42.8)	32 (42.1)	2 (40.0)	14 (37.8)	2 (33.3)	12 (57.1)
Diabetes	40 (27.6)	16 (21.0)	3 (60.0)	14 (37.8)	2 (33.3)	5 (23.8)
Cachexia	9 (6.21)	6 (7.89)	0 (0)	2 (5.41)	1 (16.7)	0 (0)
Non-AIDS-Defining Cancer	**140 (5.01)**	**53 (4.57)**	**11 (7.10)**	**38 (4.99)**	**2 (2.44)**	**36 (5.68)**
Lymphoma	41 (29.3)	25 (47.2)	1 (9.09)	9 (23.7)	0 (0)	6 (16.7)
Liver cancer	10 (7.14)	0 (0)	0 (0)	7 (18.4)	1 (50.0)	2 (5.56)
Lung cancer	6 (4.29)	2 (3.77)	0 (0)	3 (7.89)	0 (0)	1 (2.78)
Injury/Poisoning	**118 (4.22)**	**45 (3.88)**	**4 (2.58)**	**39 (5.12)**	**3 (3.66)**	**27 (4.26)**
Device/procedure complications	35 (29.7)	17 (37.8)	1 (25.0)	12 (30.8)	0 (0)	5 (18.5)
Poisoning	32 (27.1)	7 (15.6)	1 (25.0)	15 (38.5)	1 (33.3)	8 (29.6)
Fracture	24 (20.3)	9 (20.0)	1 (25.0)	6 (15.4)	2 (66.7)	6 (22.2)

Diagnostic categories and individual diagnoses are listed in order of frequency in the overall study population. The number of hospitalizations during 2010 that were associated with each diagnostic category and individual diagnosis are reported. The percentage listed for each diagnostic category represents the percentage of all hospitalizations associated with that diagnostic category. The percentage listed for each individual diagnosis represents the percentage of hospitalizations within that diagnostic category. See Appendix Table for ICD-9 codes used to identify each diagnosis.

CAD coronary artery disease; MI myocardial infarction; COPD chronic obstructive pulmonary disease

*Complication of cirrhosis includes admissions for cirrhosis, hepatic encephalopathy, portal hypertension, and ascites