Title

CD4+ cell count and outcomes among HIV-infected compared with uninfected medical ICU survivors in a national cohort.

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HIV-infected medical ICU (MICU) survivors without CD4 cell recovery are at increased risk for poor outcomes regardless of viral suppression in a national cohort

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Abstract

Background: Persons living with HIV (PWH) with access to antiretroviral therapy (ART) experience excess morbidity and mortality compared with uninfected patients, particularly those with persistent viremia and without CD4 cell recovery. We compared outcomes for medical intensive care unit (MICU) survivors with unsuppressed (>500 copies/ml) and suppressed (≤500 copies/ml) HIV-1 RNA and HIV-uninfected survivors, adjusting for CD4 cell count.

Setting: We studied 4,537 PWH (unsuppressed=38%; suppressed=62%; 72% VA) and 10,531 (64% VA) uninfected Veterans who survived MICU admission after entering the Veterans Aging Cohort Study (VACS) between fiscal years 2001–2015.

Methods: Primary outcomes were all-cause 30-day and 6-month readmission and mortality, adjusted for demographics, CD4 cell category (≥350 (reference);200–349;50–199;<50), comorbidity and prior utilization using proportional hazards models. We also adjusted for severity of illness using discharge VACS Index (VI) 2.0 among VA-based survivors.

Results: In adjusted models, CD4 categories <350 cells/μL were associated with increased risk for both outcomes up to 6 months, and risk increased with lower CD4 categories (for example, 6-month mortality CD4 200–349 HR=1.35 [1.12–1.63]; CD4<50 HR=2.14 [1.72–2.66]); unsuppressed status was not associated with outcomes. After adjusting for VI in models stratified by HIV, VI quintiles were strongly associated with both outcomes at both time points.

Conclusion: PWH who survive MICU admissions are at increased risk for worse outcomes compared with uninfected, especially those without CD4 cell recovery. Severity of illness at discharge is the strongest predictor for outcomes regardless of HIV status. Strategies including intensive case management for HIV-specific and general organ dysfunction may improve outcomes for MICU survivors.

Keywords

medical intensive care unit (ICU); critical care; readmission; mortality; VACS Index 2.0; severity of illness

INTRODUCTION

Medical intensive care unit (MICU) survival has improved significantly amongst persons with HIV (PWH) over the past four decades, especially for patients with access to antiretroviral therapy (ART).[1–4] Higher CD4 count, controlled viremia, severity of illness and serum albumin have been independently associated with improved ICU survival, but assessment of survival amongst PWH with suppressed virus has been incompletely described.[3, 5, 6]

In general populations of ICU survivors, hospital readmission remains common. Compared with non-ICU hospital survivors, ICU survivors have higher hospital readmission, and mortality for readmitted ICU survivors exceeds that of patients readmitted following a non-ICU hospitalization.[7–11] ICU survivors continue to experience increased mortality risk up to 5 years following ICU survival.[9, 10, 12] In prior studies of hospitalized patients, without specification of ICU admission, PWH are at increased risk for 30-day readmission compared with similar age groups from the general population of hospital survivors.[13–15] Uncontrolled HIV infection, defined as unsuppressed HIV-1 RNA or depressed CD4 count, remained important risk factors for readmission and mortality amongst PWH who survive hospitalization, although whether virus suppression, alone, is sufficient to lessen these risks has not been determined.[13, 15–17]

Readmission and mortality risk amongst PWH with suppressed HIV-1 RNA who survive a MICU admission are not known. Comparing readmission and mortality risk for MICU survivors among unsuppressed (>500 copies/ml) and suppressed HIV-1 RNA (≤500 copies/ml) PWH versus uninfected patients is essential to understand the ongoing impact of HIV infection on important health events despite adequate virus control. Understanding these outcomes may illustrate the impact of virus suppression from antiretroviral therapy as well as the potential limitations to virus suppression after accounting for CD4 cell count as well, in terms of long-term health implications. For example, these results may inform appropriate timing of goals of care discussions and decision-making for PWH admitted to the MICU. To address these gaps, we determined the frequency of and predictors of all-cause 30-day and 6-month hospital readmission and mortality in PWH with unsuppressed vs. suppressed HIV-1 RNA, after adjusting for CD4 cell count category, compared with uninfected MICU survivors. In a subset we determined how severity of illness at hospital discharge, using VACS Index 2.0 scores, predicted outcomes in stratified models among PWH and uninfected MICU survivors to demonstrate the extent to which other, non-HIV-specific measures of organ dysfunction affect risk.

MATERIALS AND METHODS

Participants:

The Veterans Aging Cohort Study (VACS) has been described in detail elsewhere.[18] In brief, VACS is a large observational cohort of over 50,000 PWH matched 1:2 to uninfected patients on age, race, sex and site-of-care and includes demographics, comorbidities, health behaviors, pharmacy data and healthcare utilization from the electronic health record data. We included 4,537 PWH and 10,531 uninfected individuals with at least one year of VACS observation time prior to a randomly selected MICU admission between fiscal years 2001–2015 (October 1, 2000 – September 30, 2015). PWH who were included had at least one measured HIV-1 RNA between one year and up to thirty days after the index hospital admission. Because HIV-1 RNA threshold of ≤ 500 copies/ml was used in the earliest years and <400 was used into 2010, we used ≤500 copies/ml as our threshold for defining suppression status to be consistent throughout the study interval. Using the value closest to admission (62% within 90 days of hospitalization, 19% 90–365 days; 11% during hospitalization and 8% within 30 days of discharge), we defined unsuppressed HIV-1

RNA (unsuppressed) as >500 copies/ml (1,704/4,537; 37.6%) and suppressed (suppressed) as ≤ 500 copies/ml (2,833; 62.4%). CD4 cell count was treated as a mutually-exclusive categorical variable (cells/μL: <50, 50–199, 200–349, ≥350); uninfected patients were presumed to have CD4 cell count ≥350. We excluded individuals with: a MICU admission within the prior year, hospital length of stay (LOS) less than one day or greater than 30 days; who died during the hospitalization (1556/5887 (26%) PWH vs. 1967/11632 uninfected (17%)), or were discharged after March 31, 2015 as they would not have had 6 months of follow up at the time of dataset preparation and analyses.

MICU admission:

We included MICU admissions occurring in VA hospitals and other hospitals if care was paid for by Medicare. VA MICU admission was identified using bedsection codes 12 (MICU) or 13 (cardiac ICU) because until 2008 there was no separate code for cardiac ICU.[19] For the purposes of this manuscript, MICU refers to cardiac and medical ICU admissions. As we aimed to identify the risk of ICU admission from chronic medical conditions, we did not include surgical ICU admissions. Medicare MICU admissions were identified using CMS Revenue Center Codes (0200 and 0202 for general ICU and medical ICU, respectively; 0210, 0211, 0212 for general coronary care unit, myocardial infarction and pulmonary care unites, respectively) in MedPar data.

Outcomes:

The primary outcomes were 30-day and 6-month all-cause hospital readmission and all-cause mortality for the same two periods following the index, MICU-related hospital discharge. Hospital readmissions were obtained from the VA inpatient data and from CMS MedPar data. Mortality was ascertained from the VA Vital Status file which includes inpatient mortality, social security death records and VA death benefits data.[19]

VACS Risk Index 2.0:

The VACS Risk Index 2.0 (VACS Index 2.0) was calculated for participants discharged from a hospital after a VA MICU stay. The index is a composite of age, CD4 cell count, HIV-1 RNA, hemoglobin, estimated glomerular filtration rate (eGFR), hepatitis C infection and FIB-4, a measure of liver fibrosis that includes age, aspartate aminotransferase, alanine transaminase (AST/ALT) and platelet count, albumin, white blood cell count and body mass index (BMI).[20] Components of the VACS Index were used as close to hospital discharge as possible, with last value carried forward used for CD4 and HIV RNA. Assumptions made for uninfected patients are CD4 cell count >500 cells/μL and undetectable HIV. A 5-point difference in VACS Index scores is clinically meaningful for differentiating mortality risk.[20, 21] Hospital discharge VACS Index scores were available for 9,333/9,989 of VA MICU survivors (unsuppressed=93.0%; suppressed=95.2%; uninfected=93.0%), which represented 93.4% of all VA MICU survivors.

Other covariates:

We included demographics (age, race and gender) and skilled nursing facility (SNF) utilization in the year prior to MICU admission. Age was treated as a categorical variable for

modeling purposes (<50, 50–64 and ≥65 years old). Smoking status was determined from most common entry (current, former, never) in VA Health Factors.[22] Hepatitis C virus infection and diabetes were identified from laboratory tests or International Classification of Diseases, 9th Revision (ICD-9) codes.[23] Alcohol use disorder and comorbidities (hypertension, coronary artery disease, chronic obstructive pulmonary disease (COPD) and cancer) were designated if at least one inpatient or two outpatient ICD-9 codes for the condition were present prior to MICU admission. Principal diagnoses (the condition determined at discharge to be most responsible for the hospital stay) were grouped into mutually exclusive categories based on ICD-9 codes: respiratory failure, cardiovascular and infection (including pneumonia, sepsis and septic shock); conditions present for less than 1% of the sample were categorized as "Other".[21, 24] Additional clinical course variables included mechanical ventilation from ICD-procedure codes and hospital LOS. We were not able to consider MICU LOS because of data limitations.

Statistical analysis:

We compared characteristics amongst PWH with unsuppressed vs. suppressed viral load and uninfected patients. For categorical variables, we used chi-square tests to compare demographics, health behaviors, comorbidities. For continuous variables, we used parametric and non-parametric analyses as indicated. We also compared VA and Medicare-based MICU discharges for descriptive purposes. Proportional hazards regression models were used to determine adjusted hazard ratio (HR) with 95% confidence interval (95% CI) for outcomes. For VA-based survivors only, we then determined all-cause readmission and mortality risk using the discharge VACS Index 2.0 comparing PWH with uninfected MICU survivors. Statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, North Carolina, USA). Statistical significance was defined as $p<0.05$.

RESULTS

Nearly all patients (98.2%) were men and 66% had VA-based MICU admissions. Compared with suppressed and uninfected patients, unsuppressed PWH were youngest and most likely to identify themselves as black race (both $p<0.0001$). Comorbidity prevalence prior to MICU admission differed across groups. Unsuppressed PWH were most likely to have hepatitis C infection ($p < 0.0001$) (Table 1). Uninfected were most likely to have hypertension, coronary artery disease and diabetes. Amongst PWH, 91.1% were prescribed ART (unsuppressed=83%; suppressed=96%; $p<0.0001$). Median CD4 cell count/μL was significantly lower amongst unsuppressed (VA: 155 cells/μL, IQR =[33–348], Medicare: 169 cells/μL [64–356] vs. suppressed VA: 421 cells/μL [244–629], Medicare: 441 cells/μL [285–621]; $p<0.0001$).

Principal diagnosis varied by unsuppressed, suppressed and uninfected status and by VA vs. Medicare-reimbursed admissions. Infections were the most common category among unsuppressed PWH (VA: unsuppressed 32%, suppressed 16%, uninfected 7%; Medicare: unsuppressed 24%, suppressed 13%, uninfected 8%; $p<0.0001$ for all categories) (Table 2). Cardiovascular diseases were most common among uninfected (VA: unsuppressed 15%, suppressed 26%; uninfected 34%; Medicare: unsuppressed 15%, suppressed 22%;

uninfected 26%). Respiratory failure and mechanical ventilation were common in Medicare-based MICU admissions (mechanical ventilation VA 11%, regardless of HIV or suppressed status, Medicare: unsuppressed 21%, suppressed 20%, uninfected 17%). Median hospital LOS was 1–2 days longer among unsuppressed PWH in both VA and Medicare-based admissions. Evaluating non-HIV variables of the VACS Index 2.0, hemoglobin was lowest and FIB4 was highest in unsuppressed PWH compared with suppressed and uninfected MICU survivors (Table 2).

30-day and 6-month hospital readmission

Thirty-day and 6-month readmission was highest in unsuppressed PWH in both VA and Medicare MICU discharges (30-day readmissions (VA) unsuppressed 21%, suppressed 19%, uninfected 16%; (Medicare) unsuppressed 23%, suppressed 17%, uninfected 17%; all $p<0.05$). Similar readmission rates were observed at 6 months, although with a greater magnitude of difference between unsuppressed and the other two groups (VA: unsuppressed 47%; suppressed 39%; uninfected 36%; Medicare unsuppressed 50%, suppressed 37%, uninfected 38%) (Table 2).

In unadjusted models, unsuppressed and suppressed PWH MICU survivors were associated with 48% and 9% increased 6-month readmission risk, respectively (unsuppressed HR 1.48 [1.38, 1.60]; suppressed HR 1.09 [1.02, 1.17]), compared with uninfected survivors. After adjusting for demographics, CD4 cell count categories, payer source, prior hospitalizations, comorbidities, fiscal year of hospitalization, length of index hospitalization, and admission diagnosis, viral suppression was no longer associated with readmission risk at either time pointy (30-day unsuppressed HR=1.02 [0.86, 1.21], suppressed HR 1.00 [0.88, 1.13]; 6-month unsuppressed HR=1.01 [0.90, 1.14], suppressed HR=0.92 [0.85, 1.00] (Table 3). Lower CD4 cell count categories were strongly associated with readmission risk, with lower CD4 associated with increasing risk (for example, 6-month readmission [Reference=CD4 ≥ 350]: CD4 200–349 HR=1.23 [1.09, 1.39] vs. CD4 50–199 HR=1.41 [1.24, 1.60] vs. CD4 <50 1.62 [1.39, 1.90]). Prior hospitalization, longer length of stay and comorbid cancer, diabetes and hepatitis C infection were also associated with readmission. The associations between unsuppressed, suppressed and readmission risk were not substantially different in models including hospitalization-related covariates such as mechanical ventilation and diagnosis category (data not otherwise shown). In stratified models by CD4 count category amongst PWH only, unsuppressed, relative to suppressed HIV-1 RNA, was associated with additional 6-month readmission risk only among those with CD4 ≥ 350 (HR=1.32 [1.10, 1.59]; Supplemental Table 3).

30-day and 6-month mortality risk

Similar to readmission outcomes, 30-day and 6-month mortality were highest amongst unsuppressed PWH (Table 2). Thirty-day mortality was 9% among PWH compared with 6% among uninfected (10% unsuppressed vs. 8% suppressed). Six-month mortality varied with HIV and viral suppression, with unsuppressed experiencing the highest 6-month mortality (Figure 1). Survival also varied with payer source. Overall, 6-month mortality was lower in VA than Medicare (6-month VA: unsuppressed 23%, suppressed 16%, uninfected 12%, Medicare unsuppressed 33%, suppressed 19%, uninfected 16%; $p<0.05$).

After adjusting for demographics, CD4 cell count categories, comorbidity, prior hospitalization, length of stay, fiscal year of hospitalization and principal diagnosis for index hospitalization, unsuppressed status was not associated with 30-day mortality (unsuppressed HR 0.80 [0.60, 1.06]; suppressed HR 0.93 [0.76, 1.14]) or 6-month mortality (unsuppressed HR 1.04 [0.87, 1.24]; suppressed HR 0.94 [0.82, 1.07]) (Table 3). Lower CD4 cell count categories were again most strongly associated with mortality risk (6-month mortality [Reference=CD4 ≥ 350]: CD4 200–349 HR=1.35 [1.12, 1.63] vs. CD4 50–199 HR=1.73 [1.45, 2.07] vs. CD4 <50 2.14 [1.72, 2.66]). Hospitalizations in the year prior to MICU admission, principal diagnosis other than cardiovascular conditions, and longer hospital LOS were also strongly associated with 30-day and 6-month mortality risk. Comorbid cancer diagnosis and hepatitis C infection were associated with mortality risk.

VACS Index quintiles and survival in VA-based admissions, stratified by HIV status

In analyses restricted to VA-based admissions only, we found that the VACS Index score at hospital discharge, used to assess clinical severity of illness, varied by HIV status (unsuppressed median 92 (interquartile range (IQR) 77–107, suppressed 74 (60–90), uninfected 51 (39–64)). Each increase in discharge VACS index 2.0 quintile was associated with increasing risk for 6-month mortality among PWH and uninfected (Figures 2A, 2B, respectively). In models stratified by HIV status, discharge VACS Index quintile was strongly associated with 30-day and 6-month readmission and mortality in both HIV-infected and uninfected patients (Supplemental Tables 1 and 2); the association was stronger in uninfected patients.

DISCUSSION

In our large, VA-based study, MICU survivors living with HIV who had depressed CD4 cell count, even at levels of 200–349 cells/μL, were at increased risk for worse outcomes following hospital discharge compared with uninfected patients. Risk for readmission and mortality was greatest for PWH in the lowest categories of CD4 cell count, and readmission risk was not impacted by viral suppression alone. PWH with CD4 cell count < 350 continued to experience excess mortality risk 6 months following hospital discharge. These findings illustrate the high morbidity and mortality following MICU survival in PWH relative to uninfected patients. These results also suggest that, despite access to antiretroviral therapy, PWH with inadequate CD4 cell count recovery appear to have decreased physiologic reserve and worse clinical outcomes compared with PWH with higher CD4 and uninfected patients. Importantly, unsuppressed HIV-1 RNA was only associated with readmission among for those with CD4 ≥350. While virus suppression is necessary for successful aging with HIV, it does not appear to be sufficient to lead to comparable outcomes to uninfected patients following MICU survival.

Our findings of 21–50% increased 30-day readmission risk for PWH MICU survivors with CD4 cell counts 50–199 and <50, respectively, are similar to other observed readmission rates amongst PWH following general hospitalization.[13, 14, 25, 26] In the HIV Research Network in Dallas, Texas where approximately 50% of patients had CD4 counts ≤200 cells/μL, 30-day readmission was 20%.[25] Another study of 23,544 hospitalized PWH from

New York State reported 22% had a 30-day hospital readmission.[26] In a recent analysis of readmissions amongst PWH and substance use who were enrolled in a clinical trial across 11 urban sites in the U.S. (25.8% with CD4 <200 cells/μL), 18% had a 30-day readmission.[17] Another study of 1,442 PHW from Brazil (35% with HIV-1 RNA ≤400 copies/dL, 48% HIV-1 RNA >400 copies/dL) who survived a general hospitalization, reported a 30-day readmission rate of 14%.[27] Our estimated readmission rates appear to be within the range of other cohorts of hospitalized PWH, but suggest that readmission risk for PWH are only similar to those of uninfected patients among those with CD4 cell count ≥ 350 cells/μL, irrespective of HIV-1 RNA suppression status, indicating the ongoing importance of CD4 cell count on MICU survivor outcomes. However, we suggest targeting viral suppression as a key to monitoring for immune recovery, and may be beneficial to reduce readmission risk even in those with CD4 count ≥350, as this is the more clinically actionable measure in that HIV treatment.

Without focusing on HIV infection, ICU survivors have repeatedly been shown to experience substantial post-discharge healthcare utilization.[8, 11, 28, 29] Although 30-day readmission in a single academic medical center was similar between non-ICU and ICU admissions as a whole (15.8%, 16.1%, p=0.08; median age 59–66 years), readmission varied considerably by ICU type, with MICUs being highest (23%) compared with cardiothoracic (11.7%), surgical (15.5%) and neurologic ICUs (16.6%) (p<0.001 by ICU type).[11] In another cohort from New York State, readmission for ICU survivors (mean age 61–67 years) was 16.2%, although the proportion of PWH was not reported in this study.[8] In the current study of MICU survivors, 19.6% of PWH (median CD4 count prior to MICU=296 cells/μL) had a 30-day readmission and 41.8% had a 6-month readmission compared with readmission rates for uninfected of 16.6% and 36.5%, respectively. Higher readmission rates for PWH observed in VACS may reflect greater differences in social determinants of health and medical complexity. While we were unable to include direct measures for socioeconomic status, we speculate that analyzing a Veterans cohort may substantially decrease the impact of economic barriers to healthcare engagement in the United States. We also hypothesize higher observed readmission rates due to relatively high severity of illness despite younger ages in VACS MICU survivors with HIV infection, with the greatest risk experienced amongst PWH with unsuppressed HIV-1-RNA.

We and others have shown increased ICU mortality for PWH.[1–4] Importantly, we now also show that PWH experience greater mortality risk compared with uninfected patients despite successful viral suppression, with risk largely determined by CD4 count as early as CD4 count < 350 cells/μL. Given this, in addition to intensive HIV case management for those with ongoing unsuppressed HIV-1 RNA, case management for non-HIV comorbidities, especially hepatitis C and cancer, may benefit PWH. Further, these data suggest that PWH likely play a significant role in hospital readmission rates and should be considered in case-mix adjustment.

Severity of organ dysfunction, such as need for mechanical ventilation or vasopressor medications, has been most strongly associated with ICU mortality in PWH since the widespread availability of ART.[5, 6, 30] In general ICU cohorts, severity of illness at hospital discharge independently predicts poor outcomes in MICU survivors after adjusting

for hospital LOS and comorbidities.[31] Similarly, we found that the VACS Index, a marker of physiologic frailty, predicted poor outcomes in PWH and uninfected MICU survivors.[16] While CD4 and HIV-1 RNA are important predictors for outcomes among PWH, they do not reflect the full picture of ongoing organ injury or dysfunction, and associated risk for poor outcomes, in PWH. Our study suggests that the discharge VACS Index may be well suited to predict 30-day and 6-month outcomes for MICU survivors due to general organ injury, regardless of HIV status. Future studies are required to validate these findings in other populations with high representation of PWH.

Our results have significant implications for future work and further illustrate that living with HIV, even with suppressed HIV-1 RNA, remains more challenging when compared with demographically and behaviorally similar uninfected patients if CD4 cell count recovery is not achieved. High readmission and mortality rates following MICU survival may influence PWH patients' decisions to transition from pursuit of life-sustaining therapies to focusing on high-quality end-of-life care. Our findings could also be used to support interventions targeting optimal timing for goals of care discussions for MICU survivors. Patients with ongoing physiologic frailty, measured by the VACS Index, in addition to non-cardiac ICU admissions and prolonged lengths-of-stay may especially benefit from further exploration of short- and intermediate-term goals of care.

Our study has several important limitations. First, we did not include readmission diagnoses to characterize whether patients were experiencing lingering effects of the MICU-related hospitalization or if new, acute medical problems developed.[32] In addition, because many clinical sites continued to use a threshold of HIV-1 RNA < 500 copies/ml through 2010, we used this threshold in our analyses, despite evidence suggesting ongoing excess mortality risk even among those with low virus level in other studies.[33] As a result, some individuals characterized as "undetectable" may have been considered "detectable" had a more sensitive assay been employed. We also were not able to include non-VA, non-Medicare MICU admissions. Further, we were unable to determine what longer-term health outcomes associated with index MICU diagnosis are experienced by MICU survivors and how these vary with HIV status. We were unable to determine hospice referrals for MICU survivors to evaluate if there were differences across unsuppressed, suppressed and uninfected MICU survivors that could then contribute to differences in readmission and mortality rates. We also did not compare readmission rates for hospitalizations without versus with MICU to evaluate whether MICU admission, alone, conveyed differential risk for these outcomes among PWH. Finally, nearly all individuals in VACS are men, limiting our ability to generalize our findings to HIV cohorts with more women.

CONCLUSION

While HIV-1 RNA suppression is a necessary, potentially modifiable factor to decrease readmission and mortality risk among patients with CD4 ≥ 350 cells/μL. MICU survivors without improvement of CD4 cell count above 350 cells/μL continue to experience excess readmission and mortality risk among PWH compared with uninfected patients. Length of stay and severity of illness at hospital discharge are also important predictors for 30-day and 6-month outcomes. These findings represent an important step to characterizing care needs

for aging MICU survivors with and without controlled HIV disease, and begins to identify future work needed to determine additional strategies beyond virus suppression required to improve outcomes for PWH. Appropriate rehabilitation plans and exploration of patients' preferences and goals of care decision-making are essential for PWH MICU survivors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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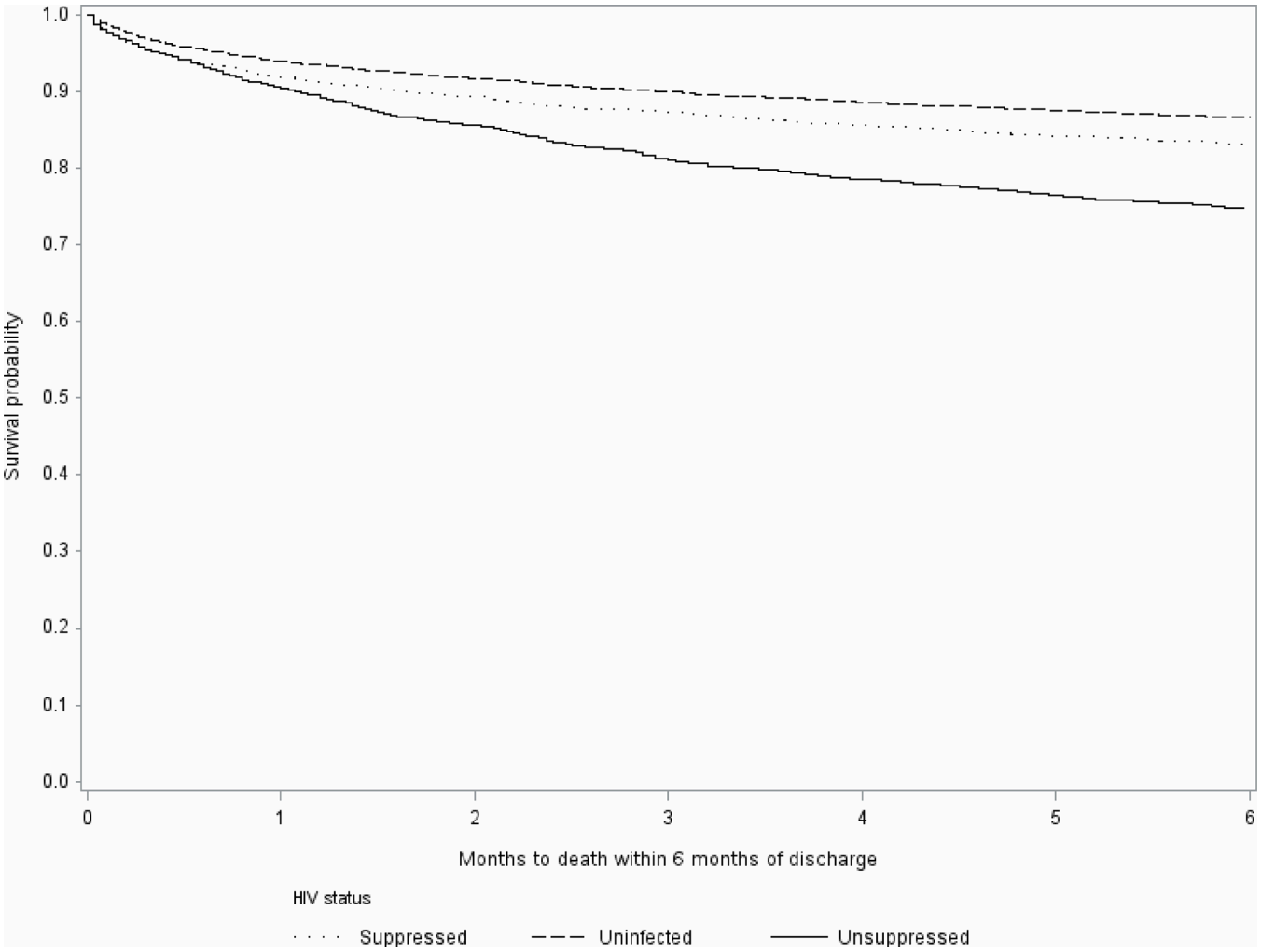
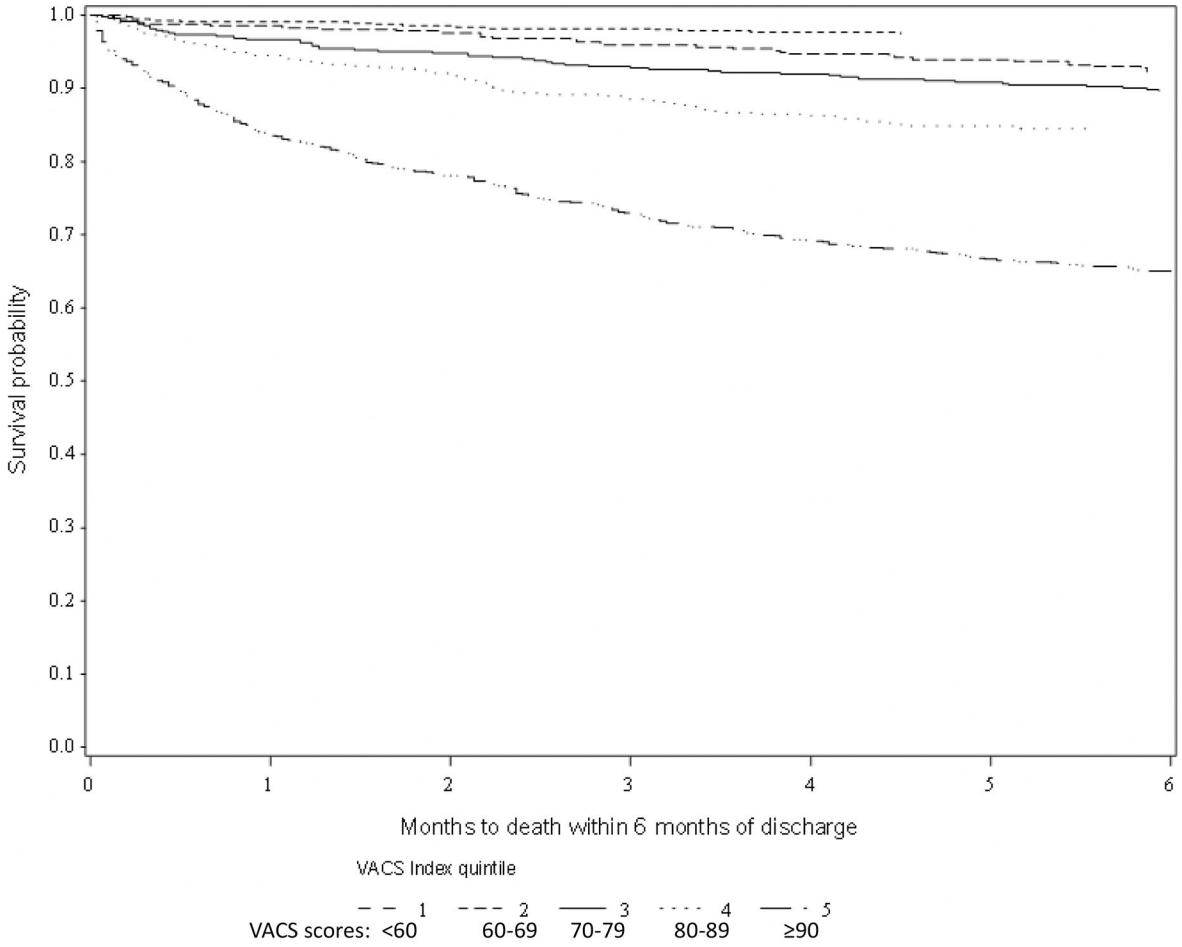
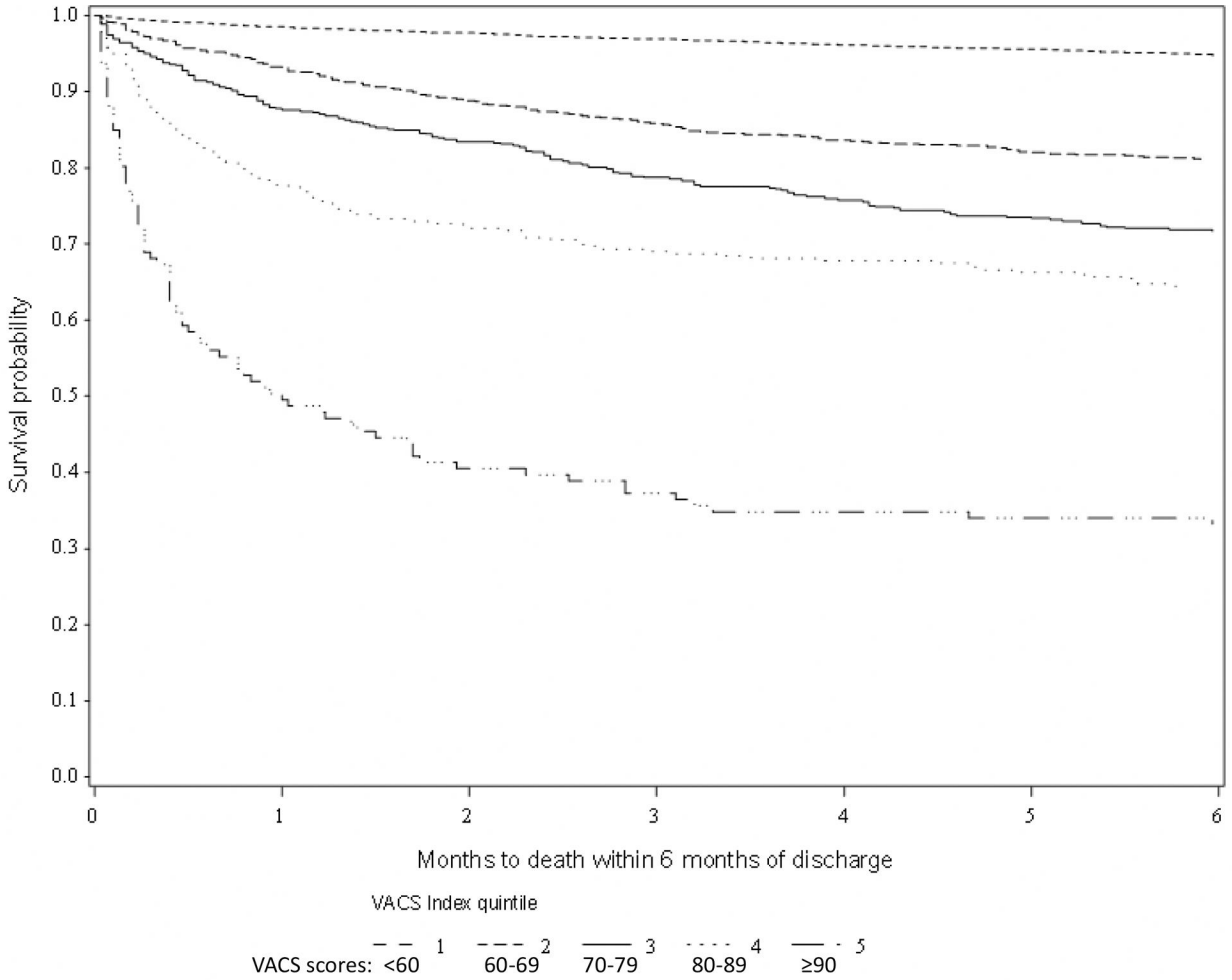


Figure 1.
Kaplan Meir plots for MICU survivors stratified by HIV status



A

Figure 2A.
Kaplan Meir plots for PWH MICU survivors stratified by VACS Index at discharge



B

Figure 2B.

Kaplan Meir plots for uninfected MICU survivors stratified by VACS Index at discharge

Table 1.

Characteristics of patients at time of admission among MICU survivors 2001–2015 *

	VA (N = 9989)			Medicare (N = 5080)		
	HIV-1 RNA >500 copies/mL	HIV-1 RNA ≤500 copies/mL	Uninfected	HIV-1 RNA >500 copies/mL	HIV-1 RNA ≤500 copies/mL	Uninfected
	(N = 1321)	(N = 1956)	(N = 6712)	(N = 383)	(N = 877)	(N = 3819)
Age, median (IQR)	51 (46–56)	58 (52–63)	57 (51–63)	52 (46–60)	60 (53–67)	63 (55–69)
<50	537 (41)	359 (19)	1249 (19)	163 (43)	124 (14)	408 (11)
50–64	710 (53)	1197 (61)	4195 (62)	157 (41)	442 (50)	1735 (45)
≥ 65	74 (6)	400 (20)	1268 (19)	63 (16)	311 (35)	1676 (44)
Race						
White	371 (28)	762 (39)	2524 (38)	154 (40)	474 (54)	1944 (51)
Black	852 (64)	992 (51)	3563 (53)	197 (51)	326 (37)	1524 (40)
Hispanic	82 (6)	165 (8)	545 (8)	27 (7)	48 (5)	251 (7)
Other	16 (1)	37 (2)	80 (1)	5 (1)	29 (3)	100 (3)
Male sex	1279 (97)	1921 (98)	6606 (98)	372 (97)	863 (98)	3768 (99)
Smoking						
Never	226 (17)	401 (21)	1319 (20)	73 (19)	210 (24)	891 (23)
Current	866 (66)	1137 (58)	3852 (57)	226 (59)	458 (52)	1792 (47)
Former	128 (10)	362 (19)	1335 (20)	33 (9)	173 (20)	972 (25)
Unknown	101 (8)	56 (3)	206 (3)	51 (13)	36 (4)	164 (4)
HIV specific						
ART use	1096 (83)	1878 (96)	N/A	322 (84)	840 (96)	N/A
CD4 cell count, median (IQR)	155 (33–348)	421 (244–629)	N/A	169 (64–356)	441 (285–621)	N/A
CD4 < 50	408 (30.9)	44 (2.3)	N/A	82 (21.4)	8 (0.9)	N/A
CD4 50–199	334 (25.3)	320 (16.4)	N/A	118 (30.8)	107 (12.2)	N/A
CD4 200–249	247 (18.7)	427 (21.8)	N/A	78 (20.4)	188 (21.4)	N/A
CD4 ≥ 350	324 (24.5)	1153 (58.9)	N/A	97 (25.3)	562 (64.1)	N/A
VACS Index 2.0, median (IQR)	78 (64–93)	61 (48–75)	41 (32–52)	78 (62–93)	59 (48–73)	42 (34–53)
Conditions						

	VA (N = 9989)			Medicare (N = 5080)		
	HIV-1 RNA >500 copies/mL	HIV-1 RNA ≤500 copies/mL	Uninfected	HIV-1 RNA >500 copies/mL	HIV-1 RNA ≤500 copies/mL	Uninfected
	(N = 1321)	(N = 1956)	(N = 6712)	(N = 383)	(N = 877)	(N = 3819)
Alcohol use disorder	616 (47)	809 (41)	2943 (44)	174 (45)	257 (29)	1058 (28)
Other drug use	670 (51)	815 (42)	2357 (35)	165 (43)	254 (29)	770 (20)
Hypertension	686 (52)	1371 (70)	5441 (81)	225 (59)	596 (68)	3101 (81)
Hepatitis C	545 (41)	716 (37)	1341 (20)	147 (38)	256 (29)	498 (13)
Diabetes mellitus	257 (19)	662 (34)	3001 (45)	90 (23)	250 (29)	1728 (45)
Coronary artery disease	220 (17)	581 (30)	2688 (40)	80 (21)	209 (24)	1496 (39)
Obstructive lung disease	340 (26)	658 (34)	2232 (33)	111 (29)	262 (30)	1228 (32)
Cancer	56 (4)	180 (9)	509 (8)	16 (4)	73 (8)	302 (8)
Congestive heart failure	130 (10)	274 (14)	1328 (20)	50 (13)	101 (12)	598 (16)
Prior year in skilled nursing facility	105 (8)	119 (6)	445 (7)	69 (18)	102 (12)	469 (12)
Prior year hospitalization						
0	609 (46)	1067 (55)	3978 (59)	152 (40)	461 (53)	2132 (56)
1	341 (26)	424 (22)	1342 (20)	74 (19)	214 (24)	765 (20)
> 1	371 (28)	465 (24)	1392 (21)	157 (41)	202 (23)	922 (24)

*All chi-square p-values <0.05 except: skilled nursing facility (VA), obstructive lung disease (Medicare).

Table 2.

Characteristics of patients during hospital admission among MICU survivors 2001–2015[*]

	VA (N = 9989)			Medicare (N = 5080)		
	HIV-1 RNA >500 copies/mL	**HIV-1 RNA ≤500 copies/mL**	**Uninfected**	**HIV-1 RNA >500 copies/mL**	**HIV-1 RNA ≤500 copies/mL**	**Uninfected**
	(N = 1321)	**(N = 1956)**	**(N = 6712)**	**(N = 383)**	**(N = 877)**	**(N = 3819)**
Hospitalization specific						
Year of MICU stay, median (IQR)	2006 (03–09)	2010 (06–12)	2009 (05–12)	2006 (03–09)	2010 (07–13)	2010 (06–13)
Length of stay, days						
<3	201 (15)	427 (22)	1809 (27)	75 (20)	175 (20)	830 (22)
3–5	307 (23)	586 (30)	2064 (31)	110 (29)	273 (31)	1209 (32)
6–9	296 (22)	420 (21)	1366 (20)	92 (24)	214 (24)	871 (23)
>9	517 (39)	523 (27)	1473 (22)	106 (28)	216 (25)	909 (24)
Median (IQR)	7 (4–13)	5 (3–10)	5 (2–9)	6 (3–11)	5 (3–9)	5 (3–9)
Principal diagnosis						
Infection[†]	425 (32)	315 (16)	457 (7)	91 (24)	118 (13)	296 (8)
Sepsis syndrome	78 (6)	86 (4)	165 (2)	28 (7)	62 (7)	178 (5)
Pneumonia	155 (12)	142 (7)	199 (3)	41 (11)	34 (4)	122 (3)
Sepsis only	50 (4)	48 (2)	108 (2)	17 (4)	48 (5)	122 (3)
Pneumonia only	127 (10)	104 (5)	142 (2)	30 (8)	20 (2)	66 (2)
Sepsis + pneumonia	28 (2)	38 (2)	57 (1)	11 (3)	14 (2)	56 (1)
Cardiovascular	194 (15)	509 (26)	2267 (34)	56 (15)	195 (22)	992 (26)
Respiratory failure[†]	172 (13)	233 (12)	670 (10)	102 (27)	263 (30)	1059 (28)
All other	530 (40)	899 (46)	3318 (49)	134 (35)	302 (34)	1472 (39)
Mechanical ventilation	151 (11)	220 (11)	755 (11)	82 (21)	174 (20)	655 (17)
Biomarkers						
VACS Index 2.0 at discharge	92 (77–107)	74 (60–90)	51 (39–64)	N/A	N/A	N/A
Hemoglobin < 10 g/dL	395 (32)	484 (26)	1171 (19)	N/A	N/A	N/A
FIB-4 > 3.25	342 (28)	444 (24)	874 (14)	N/A	N/A	N/A

	VA (N = 9989)			Medicare (N = 5080)		
	HIV-1 RNA >500 copies/mL	**HIV-1 RNA ≤500 copies/mL**	**Uninfected**	**HIV-1 RNA >500 copies/mL**	**HIV-1 RNA ≤500 copies/mL**	**Uninfected**
	(N = 1321)	**(N = 1956)**	**(N = 6712)**	**(N = 383)**	**(N = 877)**	**(N = 3819)**
eGFR < 60	275 (22)	458 (25)	1192 (19)	N/A	N/A	N/A
Outcomes: 30 days post discharge						
Hospital readmission	283 (21)	363 (19)	1095 (16)	90 (23)	153 (17)	656 (17)
Mortality	115 (9)	145 (7)	356 (5)	49 (13)	88 (10)	287 (8)
Outcomes: 6-months post discharge						
Hospital readmission	617 (47)	765 (39)	2415 (36)	193 (50)	323 (37)	1434 (38)
Mortality	304 (23)	311 (16)	817 (12)	126 (33)	170 (19)	596 (16)

*All chi-square p-values <0.05 except: mechanical ventilation (VA), length of stay (Medicare).

†Subgroups reflect diagnoses in any position, more than one may apply

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Table 3.

Multivariable models among VA and Medicare based admissions for MICU survivors.

	Readmission Hazard Ratios (HR)						Mortality Hazard Ratios (HR)					
	30-day			6-month			30-day			6-month		
	HR	95% CI		HR	95% CI		HR	95% CI		HR	95% CI	
HIV status												
Uninfected	ref			ref			ref			ref		
Suppressed	1.00	0.88	1.13	0.92	0.85	1.00	0.93	0.76	1.14	0.94	0.82	1.07
Unsuppressed	1.02	0.86	1.21	1.01	0.90	1.14	0.80	0.60	1.06	1.04	0.87	1.24
CD4 cell count category												
≥ 350	ref											
200–349	1.18	0.99	1.41	1.23	1.09	1.39	1.37	1.04	1.82	1.35	1.12	1.63
50–199	1.21	1.00	1.45	1.41	1.24	1.60	1.75	1.33	2.29	1.73	1.45	2.07
<50	1.51	1.20	1.89	1.62	1.39	1.90	2.17	1.55	3.04	2.14	1.72	2.66
Age category, in years												
<50	ref			ref			ref			ref		
50–64	1.10	0.98	1.23	1.09	1.01	1.17	1.32	1.08	1.61	1.49	1.31	1.69
≥ 65	1.19	1.04	1.36	1.21	1.11	1.33	2.15	1.73	2.69	2.11	1.82	2.44
Female sex, ref Male	0.83	0.60	1.15	0.85	0.69	1.06	0.76	0.43	1.34	0.82	0.58	1.18
Black race, ref White	1.09	1.00	1.18	1.05	1.00	1.11	0.87	0.77	0.99	0.93	0.86	1.01
SNF	0.84	0.65	1.10	1.10	0.93	1.30	1.28	0.95	1.74	1.49	1.22	1.82
Comorbidities												
Alcohol use disorder	0.97	0.88	1.07	0.99	0.93	1.06	0.93	0.79	1.08	1.00	0.90	1.11
Drug use	0.90	0.81	1.00	0.92	0.86	0.99	0.78	0.65	0.93	0.77	0.69	0.86
Cancer	1.16	1.02	1.33	1.11	1.01	1.22	1.25	1.03	1.52	1.26	1.10	1.44
Diabetes	1.17	1.08	1.27	1.15	1.09	1.21	0.98	0.86	1.11	1.00	0.92	1.09
Hepatitis C	1.17	1.06	1.29	1.22	1.14	1.31	1.52	1.31	1.77	1.42	1.28	1.57
Source of data												
Medicare, ref VA	1.01	0.93	1.10	1.02	0.96	1.08	1.07	0.94	1.23	1.11	1.01	1.21
Year of admission (fiscal)												

	Readmission Hazard Ratios (HR)				Mortality Hazard Ratios (HR)			
	30-day		6-month		30-day		6-month	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
2001–2005	ref		ref		ref		ref	
2006–2009	0.92	0.83 1.03	0.96	0.89 1.03	0.97	0.82 1.15	0.90	0.80 1.00
2010–2012	0.99	0.89 1.11	0.97	0.90 1.05	0.87	0.72 1.04	0.81	0.72 0.91
2013–2015	0.93	0.82 1.04	0.96	0.89 1.04	0.90	0.75 1.09	0.75	0.66 0.85
Principal diagnosis category								
Cardiovascular	ref		ref		ref		ref	
Infection	0.95	0.82 1.09	1.02	0.93 1.13	2.59	2.01 3.34	1.85	1.58 2.16
Respiratory	0.98	0.86 1.11	1.06	0.97 1.16	3.46	2.74 4.37	2.26	1.95 2.61
Other	0.92	0.83 1.01	0.98	0.91 1.04	2.05	1.65 2.55	1.63	1.43 1.85
Length of stay in days								
< 3	ref		ref		ref		ref	
3–5	1.23	1.09 1.38	1.15	107 1.25	1.15	0.90 1.46	1.04	0.90 1.21
6–9	1.50	1.33 1.70	1.38	1.27 1.50	1.70	1.35 2.16	1.66	1.43 1.92
≥ 10	1.66	1.47 1.88	1.51	1.39 1.63	2.53	2.02 3.17	2.26	1.97 2.60
Prior year hospitalization	Ref=zero		Ref=zero		Ref=zero		Ref=zero	
1	1.46	1.32 1.62	1.57	1.47 1.68	1.81	1.53 2.15	1.80	1.61 2.02
≥ 2	2.33	2.13 2.54	2.48	2.33 2.63	3.14	2.71 3.63	3.26	2.96 3.60