American Heart Journal Plus: Cardiology Research and Practice 20 (2022) 100193

Contents lists available at ScienceDirect

American Heart Journal Plus: Cardiology Research and Practice

journal homepage: www.sciencedirect.com/journal/american-heart-journal-plus-cardiology-research-and-practice

Research Paper

Mortality and length of stay among HIV patients hospitalized for heart failure: A multicenter retrospective study

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ARTICLE INFO

Keywords:
Acute heart failure
Human immunodeficiency virus
In-hospital mortality
Length of stay

ABSTRACT

Study objective: The purpose of our study was to determine if CD4+ T-lymphocyte count (CD4 count) was inversely associated with inpatient mortality and length of stay (LOS) among patients with HIV hospitalized for acute heart failure.
Design: Retrospective cohort study.
Setting: HCA hospitals throughout the United States.
Participants: 1704 patients with human immunodeficiency virus (HIV) hospitalized for acute heart failure with a documented, time-updated CD4 count.
Interventions: Patients were categorized by CD4 count ranges consisting of >500, 200–499, <200 cells/μL.
Main outcome measures: A multivariable negative binomial regression was performed with CD4 count as a predictor of length of stay. Multivariable logistic regression was performed with CD4 count as a predictor of mortality.
Results: A CD4 count <200 cells/μL was associated with an increased length of stay compared to a CD4 > 500 cells/μL (IRR 1.24, 95 % CI: 1.11 to 1.39, P ≤ 0.01). A CD4 of 200–499 cells/μL was associated with a shorter LOS compared to a CD4 < 200 cells/μL (IRR 0.82, 95 % CI: 0.75 to 0.89, P ≤ 0.01). A CD4 < 200 cells/μL was associated with an increased mortality compared to a CD4 > 500 cells/μL (OR 3.62, 95 % CI: 1.63 to 8.05, P ≤ 0.01). CD4 count was not independently associated with in-patient mortality after adjusting for viral load.
Conclusion: A time-updated CD4 count <200 cells/μL on hospital admission was independently associated with increased length of stay. CD4 cell count and viral load are important markers when considering the morbidity and mortality among patients with HIV hospitalized for acute heart failure.

1. Introduction

People living with human immunodeficiency virus (PLWH) are at increased risk for heart failure (HF), often developing decades earlier compared to uninfected individuals [1]. Prior studies suggest PLWH are at higher risk for cardiovascular disease (CVD) including myocardial infarction (MI), sudden cardiac death, and heart failure [2–4]. The pathogenesis of HIV-associated cardiomyopathy is multifactorial, involving myocardial inflammation and fibrosis [5], coronary microvascular dysfunction [6], and direct infiltration of cardiomyocytes [7]. PLWH hospitalized for HF are at increased risk of recurrent hospitalizations, mortality, and sudden cardiac death [8–11].

The CD4+ subtype of T-lymphocytes (CD4) is a well-known marker of immune function used for clinical staging of HIV, with decreased levels associated with increased susceptibility to opportunistic infections. A CD4 cell count <500 cells/μL is an independent risk factor for incident CVD, comparable in attributable risk to traditional cardiovascular risk factors [12], and is associated with a higher rate of CVD mortality compared to the general population [13]. Nadir CD4 counts are associated with chronic inflammation and loss of adaptive immunity

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https://doi.org/10.1016/j.ahjo.2022.100193
Received 10 May 2022; Received in revised form 6 August 2022; Accepted 6 August 2022
Available online 10 August 2022

[14]. Prior studies demonstrate an increased risk of systolic and diastolic HF with decreased CD4 counts [1,5]. Risk stratification by CD4 count could potentially serve as a prognostic marker in acute HF. The purpose of our study was to determine the association between time updated CD4 counts and inpatient mortality and length of stay (LOS) among PLWH hospitalized for acute HF.

2. Materials and methods

We performed a multi-center, retrospective, cohort analysis using the health records of adult HIV-positive patients hospitalized for HF within Hospital Corporation of America (HCA) hospitals throughout the United States from January 2016 to December 2021. 5935 medical records were initially identified for inclusion and 1704 of these were used after exclusions. HCA comprises >180 hospitals across the United States, and includes 5 % of all U.S. hospital services. All extracted data were deidentified prior to being received and included demographics (e.g., age, race, sex) and characteristics of hospital course (e.g. LOS, disposition, and ICU admission). An inpatient International Classification of Diseases (ICD)-10 code (B20.0) was required to meet criteria for HIV. Comorbidities, diagnosed from inpatient *ICD-10* codes, included coronary artery disease (CAD), hypertension, diabetes, chronic kidney disease, chronic obstructive pulmonary disease, asthma, anemia, and arrhythmia. The Elixhauser comorbidity index was used to assess the burden of comorbidities across ranges of CD4 counts [15]. Combination anti-retroviral therapy (cART) was obtained during hospital admission as a documented medication and included nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), and integrase strand transfer inhibitors (INSTIs).

Eligibility criteria included hospitalized PLWH with a discharge diagnosis of HF and a CD4 count test during the study period hospitalization. HF events including diastolic, systolic, and combined diastolic and systolic HF were identified by *ICD-10* codes (I50, I50.1, I50.20, I50.21, I50.22, I50.23, I50.30, I50.31, I50.32, I50.33, I50.40, I50.41, I50.42, I50.43, I50.9). Current guidelines were used to classify each type of HF based on ejection fraction. Time-updated CD4 counts and HIV RNA levels (copies/mL) were utilized from the current hospital admission for HF. Primary outcomes of interest were in-hospital mortality and LOS. LOS was defined as the difference between the final inpatient day rounded up and admission date. This study did not require institutional review board (IRB) oversight per the HCA Graduate Medical Education IRB. The study was approved by the local Clinical Research Committee of the affiliated hospital, HCA Houston Healthcare Kingwood.

2.1. Statistical analysis

To evaluate the influence of immunosuppression on HF outcomes, we included different ranges of CD4 counts, categorized as >500 vs. 200–499 vs. <200 cells/μL. Continuous variables were reported as medians with interquartile ranges (IQR) in descriptive analysis. Categorical variables were reported as counts with percent of the CD4 count group total. To assess length of stay, a multivariable negative binomial regression was conducted to calculate adjusted incidence rate ratios (IRR) with associated 95 % confidence intervals (CI). A multivariable logistic regression was performed for in-hospital mortality, with reported odds ratios and 95 % Wald confidence intervals. Both models were constructed with adjustments for age, sex, and selected comorbidities. Sub-analysis was conducted with HIV RNA lab values as a confounder with viral suppression defined as HIV RNA < 20 copies/mL. HIV RNA was also tested for effect modification on CD4 count categories. A p-value <0.05 was considered statistically significant. Data were cleaned and categorized using Stata 17.0, and analyzed using SAS 9.4 M3.

3. Results

We included 1704 PLWH hospitalized for HF (Fig. 1). Additionally, 762 patients had a documented CD4 count and viral load on admission. Median age was 53.0 years (IQR 44–61), predominant racial demographic was black (65.1 %) compared to others (white 28.3 %, multiracial or other 5.4 %, hispanic 0.6 %, asian 0.3 %), and 67.4 % were male (Table 1). A total of 108 patients (6 %) expired. Patients with a CD4 count <200 cells/μL had the most intensive care unit (ICU) admissions (290 [31.80 %], Table 2). The median Elixhauser comorbidity index was 8 (IQR 6–10) and consistent across all three CD4 categories. Hypertension (1315 [77.17 %]), systolic heart failure (725 [42.55 %]), and chronic kidney disease (CKD [45.36 %]) were the most common comorbidities (Table 3). Patients with a CD4 count >500 cells/μL had a higher prevalence of CAD, whereas noncardiac-comorbidities including anemia and COPD were more prevalent with a CD4 < 200 cells/μL (Table 3). The highest prevalence of diastolic HF and combined systolic and diastolic HF was seen with a CD4 count <200 cells/μL (Table 3). Median CD4 count was 182 (IQR 66–378 cells/μL), and 912 patients had a CD4 < 200 cells/μL. 504 (29.58 %) patients were documented to be on cART upon admission.

3.1. Outcomes

The median LOS in the entire cohort was 6 days (IQR 3–10). A CD4 count <200 cells/μL was associated with an increased LOS when compared to a CD4 > 500 cells/μL (IRR 1.24, 95 % CI: 1.11 to 1.39, P ≤ 0.01; Fig. 2). A CD4 of 200–499 cells/μL was associated with a shorter LOS compared to a CD4 < 200 cells/μL (IRR 0.82, 95 % CI: 0.75 to 0.89, P ≤ 0.01). A CD4 count of 200–499 cells/μL vs. CD4 > 500 cells/μL showed no significant difference in regards to LOS (IRR 1.01, 95 % CI 0.90 to 1.15). A CD4 count <200 cells/μL was associated with an increased mortality compared to a CD4 > 500 cells/μL (OR 3.62, 95 % CI: 1.63 to 8.05, P ≤ 0.01; Fig. 3), and CD4 count 200–499 cells/μL (OR 1.76, 95 % CI: 1.10 to 2.81, P ≤ 0.01). A CD4 count of 200–499 cells/μL versus >500 cells/μL showed no significant difference in regards to mortality (OR 2.06, 95 % CI: 0.88 to 4.84, P = 0.78). In our sub-analysis with the addition of HIV RNA as a covariate, the association between lower CD4 counts (<200 cells/μL vs. >500 cells/μL) and increased LOS remained statistically significant (supplementary Table 3). However, there was no significant difference in mortality among CD4 counts after adjusting for HIV RNA (supplementary Table 4). While as a confounder HIV RNA produced a difference in CD4 count significance, it did not act as an effect modifier, so no interaction terms or stratification was necessary and it could be interpreted safely as just a confounding variable.

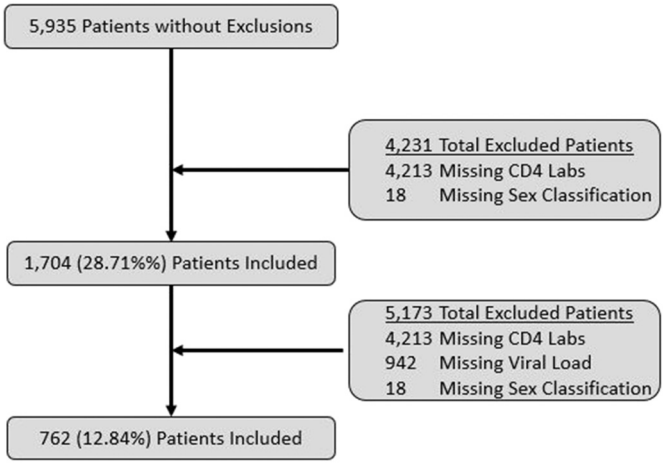

Fig. 1. Flow chart of the study population selection.

Table 1
Baseline characteristics categorized by CD4 count.

CD4 count, cells/μL	200–499 (N = 516)	<200 (N = 912)	≥500 (N = 276)	All patients (N = 1704)
Age				
Median (IQR)	54 (46–62)	52 (43–59)	56 (47–63)	53 (44–61)
Range	21–75	20–75	27–75	20–75
Race				
Asian	0 (0.00 %)	5 (0.55 %)	1 (0.36 %)	6 (0.35 %)
Black	347 (67.25 %)	588 (64.47 %)	175 (63.41 %)	1110 (65.14 %)
Hispanic	4 (0.78 %)	6 (0.66 %)	0 (0.00 %)	10 (0.59 %)
Multiracial/ other	26 (5.04 %)	54 (5.92 %)	13 (4.71 %)	93 (5.46 %)
White	138 (26.74 %)	258 (28.29 %)	87 (31.52 %)	483 (28.35 %)
Sex				
Female	160 (31.01 %)	298 (32.68 %)	97 (35.14 %)	555 (32.57 %)
Male	356 (68.99 %)	614 (67.32 %)	179 (64.86 %)	1149 (67.43 %)

IQR = interquartile range.

Table 2
Length of stay, discharge disposition and ICU admission categorized by CD4 count.

CD4 count, cells/μL	200–499 (N = 516)	<200 (N = 912)	≥500 (N = 276)	All patients (N = 1704)
Length of stay				
Median (IQR)	5 (3–9)	6 (3−11)	5 (3–8)	6 (3−10)
Range	0–54	0–114	0–82	0–114
Discharge disposition				
Expired	26 (5.04 %)	75 (8.22 %)	7 (2.54 %)	108 (6.34 %)
Carceral	36 (6.98 %)	88 (9.65 %)	27 (9.78 %)	151 (8.86 %)
Home	378 (73.26 %)	625 (68.53 %)	213 (77.17 %)	1216 (71.36 %)
Hospital transfer	15 (2.91 %)	23 (2.52 %)	6 (2.17 %)	44 (2.58 %)
Rehab transfer	61 (11.82 %)	101 (11.07 %)	23 (8.33 %)	185 (10.86 %)
ICU admission	110 (21.32 %)	290 (31.80 %)	44 (15.94 %)	444 (26.06 %)

IQR = interquartile range; ICU = intensive care unit.

4. Discussion

Due to improved life expectancy with HAART, chronic health conditions have become more prevalent among PLWH, with increased morbidity and mortality from CVD. HIV-associated cardiomyopathy, defined as reduced left ventricular systolic function or impaired diastolic function, is currently recognized as a long-term complication. Our multicenter, cohort analysis demonstrated the influence of immunosuppression in heart failure hospitalizations. The degree of immunosuppression based on CD4 count was independently associated longer LOS before and after adjusting for viral load. Differences in LOS were only notable when CD4 counts differed by a margin of at least 300 cells/μL, whereas smaller ranges (CD4 count 200–499 compared to >500 cells/μL) showed no difference in outcomes. Our findings suggest a potential CD4 threshold level required to achieve an adequate immune response and suppression of inflammation associated with decreased length of stay [16]. Although our initial analysis demonstrated an association between lower CD4 counts and increased inpatient mortality, this relationship was no longer significant after adjusting for HIV RNA. These findings suggest prognostic value of viral load in predicting inpatient mortality for HF associated hospitalizations. This is supported from a prior study which showed a greater association between LVEF <40 % and sudden cardiac death in patients with detectable vs. undetectable HIV RNA [17]. Our data suggests that the degree of immunosuppression should be correlated with viral load for predicting inpatient mortality.

Table 3
Median Elixhauser comorbidity index assessing burden of comorbidities, cardiovascular and non-cardiovascular comorbidities categorized by CD4 count.

CD4 count, cells/μL	200–499 (N = 516)	<200 (N = 912)	≥500 (N = 276)	All patients (N = 1704)
Total CD4 count				
Median (IQR)	315 (247–392)	71 (31−131)	677 (576–849)	182 (66–378)
Range	200–498	1–199	501–2072	1–2072
Combination anti-retroviral therapy				
No cART	346 (67.05 %)	677 (74.23 %)	177 (64.13 %)	1200 (70.42 %)
INSTI-based regimen	100 (19.37 %)	148 (16.23 %)	56 (20.29 %)	304 (17.84 %)
NNRTI-based regimen	17 (3.29 %)	19 (2.08 %)	22 (7.97 %)	58 (3.40 %)
PI-based regimen	53 (10.27 %)	68 (7.46 %)	21 (7.61 %)	142 (8.33 %)
Diastolic and systolic heart failure	44 (8.53 %)	82 (8.99 %)	23 (8.33 %)	149 (8.74 %)
Diastolic heart failure	87 (16.86 %)	166 (18.20 %)	39 (14.13 %)	292 (17.14 %)
Systolic heart failure	217 (42.05 %)	387 (42.43 %)	121 (43.84 %)	725 (42.55 %)
Coronary artery disease	208 (40.31 %)	313 (34.32 %)	125 (45.29 %)	646 (37.91 %)
Hypertension	415 (80.43 %)	673 (73.79 %)	227 (82.25 %)	1315 (77.17 %)
Diabetes	177 (34.30 %)	226 (24.78 %)	101 (36.59 %)	504 (29.58 %)
Chronic Kidney Disease	246 (47.67 %)	415 (45.50 %)	112 (40.58 %)	773 (45.36 %)
COPD	130 (25.19 %)	247 (27.08 %)	66 (23.91 %)	443 (26.00 %)
Asthma	41 (7.95 %)	76 (8.33 %)	24 (8.70 %)	141 (8.27 %)
Anemia	226 (43.80 %)	421 (46.16 %)	82 (29.71 %)	729 (42.78 %)
Arrhythmia	94 (18.22 %)	138 (15.13 %)	52 (18.84 %)	284 (16.67 %)

IQR, interquartile range; COPD, chronic obstructive pulmonary disease; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; INSTI, integrase strand transfer inhibitor; cART, combination anti-retroviral therapy.

Decreased CD4 counts have been associated with an increased risk of left ventricular hypertrophy, worsening left ventricular ejection fraction, and diastolic dysfunction [18,19]. In particular, we found an increased prevalence of diastolic and systolic heart failure with a CD4 count <200 cells/μL. The pathogenesis of HIV associated cardiomyopathy is multifactorial. The risk of HF extends beyond ischemic cardiomyopathy, as evident from the low prevalence of CAD with a CD4 count <200 cells/μL in our study. Epidemiology of HIV associated cardiomyopathy in the era of HAART has shifted towards an increased recognition of chronic diastolic dysfunction rather than a rapid decline in LVEF [20]. Echocardiographic abnormalities, such as increased left ventricular mass, may underlie the findings of increased diastolic dysfunction, independent of traditional cardiovascular risk factors [5]. The introduction of HAART has decreased the incidence of opportunistic infections leading to myocarditis, originally proposed to be the cause of cardiomyopathy in the pre-HAART era [21]. Elevated markers including C-reactive protein, interleukin-6 (IL-6), and D-dimer have been associated with an increased risk of CVD, suggesting an inflammatory effect of HIV on cardiac myocytes, resulting in myocardial fibrosis and cardiac dysfunction [5,20,22,23]. In the instance of suboptimal viral suppression, replication of HIV in inflammatory cells and induction of myocardial apoptosis subsequently contributes to cardiomyopathy and HF [20].

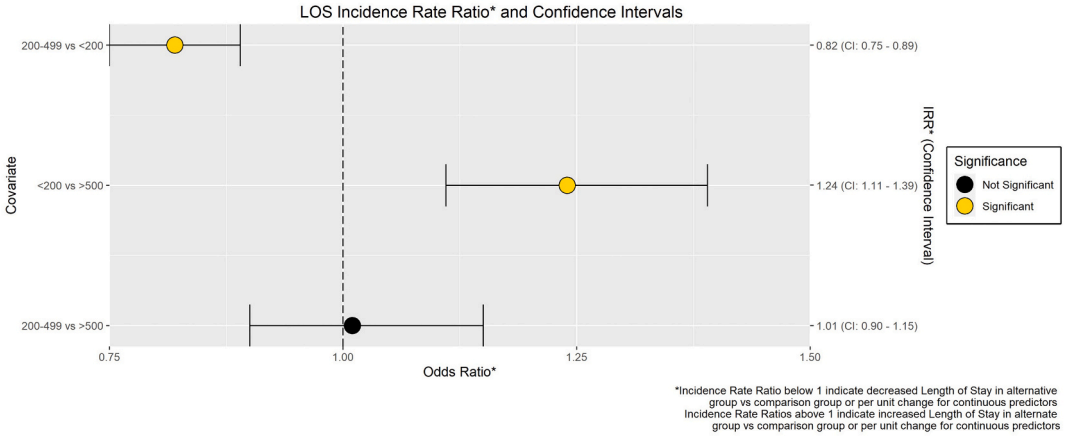

Fig. 2. Association between CD4 count as a covariate and length of stay in adults hospitalized for heart failure. LOS, length of stay. CI, confidence interval.

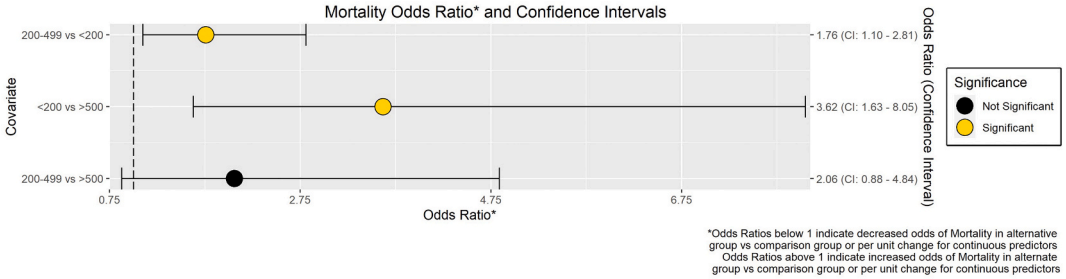

Fig. 3. Association between CD4 count as a covariate and mortality in adults hospitalized for heart failure. CI, confidence interval.

The incidence of left ventricular systolic dysfunction has decreased with the advent of HAART [11,24,25]. Despite adherence to HAART, HIV-associated cardiomyopathy remains widely prevalent, suggesting an inability of HAART to eliminate the risk of heart failure associated with latent infection. It is important to recognize that certain HAART drugs may be associated with an increased risk of HIV-associated cardiomyopathy. In particular, protease inhibitor-based regimens have been linked to dyslipidemia, CAD, lower LVEF, and increased CV mortality [26]. 8.33 % of patients in our study were on a PI-based regimen in our study. The number of patients on a PI-based regimen was relatively uniform across CD4 count categories. We were unable to determine how long patients were on cART prior to admission due to limitations in accessing home medication reconciliations. Optimal antiretroviral therapy regimens among PLWH with HF require further exploration through randomized clinical trials.

In PLWH with a CD4 count <200 cells/μL, non-cardiovascular comorbidities including anemia and chronic obstructive pulmonary disease (COPD) were most prevalent and may have affected mortality and LOS. Factors including common acquired immunodeficiency syndrome (AIDS)-related illnesses, sepsis, and life-threatening bacterial infections could explain the increase in ICU admissions with lower CD4 counts seen in our study [27]. We concluded a need to develop risk prediction models specific for PLWH in order to guide clinicians on inpatient evaluation and management for HF. Further research on the optimal heart failure medical therapy among this subset of patients is required and could potentially reduce inpatient costs for patients, decrease hospital expenditure, and decrease the risk of nosocomial transmission of opportunistic infections [28].

There are several potential limitations of our study. Since this was a retrospective observational study, causal inference could not be determined. The study was based on record review from the electronic medical records using (ICD)-10 codes which can limit the accuracy of data, although any misclassification would be randomized and unlikely to result in systematic bias, and given the importance of HIV care, would be unlikely to be overlooked on intake. Inclusion of CD4 count was a requirement, and therefore selection bias may be a factor since CD4 count is not routinely measured in the hospital. Obtaining a CD4 count may suggest that the ordering physician is concerned with uncontrolled HIV due to poor adherence to antiretroviral activity, or a potential infection during hospitalization which warrants an assessment of immunosuppression. This was evident in our study given the median CD4 count in the entire cohort was below 200 cells/μl. In addition, non-HIV causes of CD4 lymphocytopenia include infection, autoimmune diseases, and lymphoma, which were not accounted for [29].

5. Conclusion

Among a diverse cohort of PLWH with HF-associated hospitalization, a CD4 count of <200 cells/μl was independently associated with increased LOS. CD4 cell counts should be correlated with viral load for predicting inpatient mortality. Longitudinal studies are required to determine if reversal of immunosuppression reduces morbidity and mortality in CVD.

Disclosure

The authors of this manuscript have no conflicts of interest to disclose.

Funding

None of the authors received financial support for this article.

Disclaimers

“This research was supported (in whole or in part) by HCA

Healthcare and/or an HCA Healthcare affiliated entity. The views expressed in this publication represent those of the author(s) and do not necessarily represent the official views of HCA Healthcare or any of its affiliated entities."

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahjo.2022.100193.

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