International Journal of Cardiology 218 (2016) 43–46

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Heart failure in patients with human immunodeficiency virus infection: Epidemiology and management disparities

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ARTICLE INFO

Article history:
Received 6 April 2016
Accepted 12 May 2016
Available online 13 May 2016

Keywords:
HIV
Heart failure
Epidemiology

ABSTRACT

Background: Persons living with HIV are at a higher risk of cardiovascular disease despite effective antiretroviral therapy and dramatic reductions in AIDS-related conditions. We sought to identify the epidemiology of heart failure (HF) among persons living with HIV in the United States in an era of contemporary antiretroviral therapy.
Methods: Explorys is an electronic healthcare database that aggregates medical records from 23 healthcare systems nationwide. Using systemized nomenclature of medicine—clinical terms (SNOMED—CT), we identified adult patients (age > 18), who had active records over the past year (September 2014–September 2015). We described the prevalence of HF in HIV patients by demographics and treatment and compared them to HIV-uninfected controls.
Results: Overall, there were 36,400 patients with HIV and 12,208,430 controls. The overall prevalence of HF was 7.2% in HIV and 4.4% in controls (RR 1.66 [1.60–1.72], $p < 0.0001$). The relative risk of HF associated with HIV infection was higher among women and younger age groups. Patients receiving antiretroviral therapy had only marginally lower risk (6.4% vs. 7.7%, $p < 0.0001$) of HF compared to those who were untreated. Compared to uninfected patients with HF, HIV patients with HF were less likely to receive antiplatelet drugs, statins, diuretics, and ACE/ARBs ($p < 0.0001$ for all comparisons). For patients with HIV and HF, receiving care from a cardiologist was associated with higher use of antiplatelets, statins, betablockers, ACE/ARBs, and diuretics.
Conclusions: Persons with HIV are at higher risk for HF in this large contemporary sample that includes both men and women. Although the prevalence of heart failure is higher in older HIV patients, the relative risk associated with HIV is highest in young people and in women. HIV patients are less likely to have HF optimally treated, but cardiology referral was associated with higher treatment rates.

1. Introduction

With the advent of effective antiretroviral therapy (ART), HIV is now a chronic disease, with life expectancy approaching that of uninfected individuals [1]. Patients living with HIV remain at a higher risk of cardiovascular disease despite dramatic reductions in some AIDS-related conditions such as cardiomyopathy [2]. This residual risk in treated HIV infection may be mediated in part through chronic inflammation [3], similar to other inflammatory diseases such as rheumatoid arthritis. Heart failure, a common end-result of cardiac disease, appears to be more common among mostly male HIV-infected veterans compared to matched uninfected controls [4]; however, the epidemiology of heart failure in a larger, more generalizable sample of HIV infected patients is unknown. In this report, we sought to estimate the prevalence of HF in patients with HIV and to identify disparities associated with care that might provide opportunities for care improvement.

2. Methods

2.1. Data source

Explorys (Explorys, Inc.; Cleveland, Ohio) is a commercial cloud-based database that aggregates data from electronic health records of participating hospital systems. It currently encompasses 23 integrated health systems consisting of 360 hospitals, 315,000 providers, and over 50 million unique patients. It collects data through a healthcare gateway server behind the firewall of participating institutions [5]. The data are collected from billing inquiries, electronic health records, and laboratory systems.

These data aggregates are then de-identified, analyzed, normalized, and standardized into Unified Medical Language System (UMLS) ontologies to facilitate searching and indexing. Diagnoses are mapped into

Abbreviations: HIV, Human immunodeficiency virus; AIDS, Acquired Immunodeficiency Syndrome; HF, Heart Failure; CAD, Coronary Artery Disease; ART, Antiretroviral Therapy; RR, Relative Risk; CI, Confidence Interval.

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http://dx.doi.org/10.1016/j.ijcard.2016.05.027
0167-5273/

systematized nomenclature of medicine—clinical terms (SNOMED—CT) hierarchy, prescriptions mapped to RxNorm, and laboratory test observations mapped to logistical observation identifier names and codes (LOINC), established by the Regenstrief Institute.

The platform is compliant with the Health Insurance Portability and Accountability Act (HIPPAA) and Health Information Technology for Economic and Clinical Health (HITECH) Act standards; hence, this study was exempted from Institutional Review Board under a pre-specified policy. The database rounds number of patients to the nearest 10 for an added data protection. This platform has been used for research purposes and has been validated in fields of orthopedics [6], hematology [7], surgery [8], gastroenterology [5], and gynecology [9] among others.

2.2. Cohort selection and definitions

For the HIV-infected cohort, we selected all patients who were active within the last year (September 2014–September 2015) in the participating hospitals, who were at least 18 years of age and who had a diagnosis of "Human Immunodeficiency Virus Infection". For controls, we selected the same age group and excluded patients with "Human Immunodeficiency Virus Infection". We identified heart failure using the umbrella term "Heart Failure". Other used terms correspond to their SNOMED—CT. For nadir CD4, we used the lowest recorded CD4 in Explorys (categorized by groups: <200, 200–500, >500) from 1999 to 2015.

2.3. Statistical analysis

Data are presented as numbers and percentages. Pearson's chi-squared test was used to test for differences. Relative risks with 95% confidence intervals were used to report risk differences between compared groups. Statistical significance was set at $p < 0.05$.

3. Results

Of the 12,244,830 adults who had active records within the past year, we identified 36,400 patients with HIV who fulfilled the selection criteria, and those were compared with 12,208,430 HIV-free controls. Baseline characteristics including distribution by age group are displayed in Table 1. Compared to controls, patients with HIV were more likely to be male, non-caucasian race, and have Medicare or Medicaid. Patients with HIV were more likely to have co-morbidities such as diabetes, hypertension, myocardial infarction, peripheral vascular disease, coronary artery disease, and hepatitis B and C. They were also more likely to use tobacco, alcohol, cannabinoids, and cocaine.

Overall, the prevalence of HF was 7.2% in HIV patients compared with 4.4% in controls [RR (95% CI) of 1.66 (1.60, 1.72); $p < 0.001$]. The relative risk of heart failure associated with HIV infection was highest in the third decade of life (age group of 20–29 years) and decreased with age (Fig. 1). Notably, the HIV-associated risk was higher among females [RR 2.28 (2.15, 2.42) vs. RR 1.27 (1.22, 1.33), female vs. male, $p < 0.001$; Fig. 1]—a finding that was consistent across all age categories.

Among HIV-infected individuals with available CD4 counts ($n = 5700$), HF prevalence (12.9% overall in this cohort) was highest among those with CD4 nadir <200 and the prevalence decreased gradually with increasing CD4 nadirs (10.0% in CD4 between 200 and 500, and 8.8% in those with CD4 >500). A similar trend was seen among patients with high HIV viral load and decreased with decreasing viral load, Fig. 2.

Among those with HIV infection, the risk was marginally lower in those who were prescribed ART within the last year compared to those who were off therapy [6.4% (6.0, 6.8) vs. 7.7% (7.3, 8.0); ART vs. no ART, respectively; $p < 0.001$). The prevalence of HF in patients with HIV was higher in those *with* CAD [37.9% (36.3, 39.5) vs. 4.0% (3.8, 4.3), CAD vs. no CAD; $p < 0.001$) and in those *with* proteinuria [22.4% (20.3, 24.6) vs. 6.6% (6.4, 6.9), proteinuria vs. no proteinuria; $p < 0.001$); however, the relative risk of HF associated with HIV infection was higher in patients *without* CAD [1.28 (1.22, 1.33) vs. RR 2.12 (1.91, 2.01), CAD vs. no CAD; $p < 0.001$] and in those *without* proteinuria [RR 1.37 (1.13, 1.24) vs. 1.58 (1.52, 1.64), proteinuria vs. no proteinuria; $p < 0.001$]. The prevalence of HF was also highest in patients with stage V CKD compared to earlier stages of CKD [57.6% vs. 30.6%, stage 5 vs. stages 1–4; $p < 0.001$].

Table 1
Demographics and characteristics of study patients.

	HIV+ (n = 36,400)	HIV− (n = 12,208,430)	p-Value
Age group (years)			<0.0001
<65	92.7%	75.8%	
≥65	7.3%	24.2%	
Ethnicity			<0.0001
Caucasian	46.5%	72.3%	
African American	46.9%	12.2%	
Asian	4.3%	5.1%	
Male (gender)	68.8%	40.8%	<0.0001
Insurance type	0.0%	0.0%	<0.0001
Private	44.4%	55.7%	
Medicare	24.6%	21.8%	
Medicaid	24.1%	9.9%	
Self pay	9.5%	6.2%	
Comorbidities			
Diabetes mellitus	17.6%	13.0%	<0.0001
Hypertension	43.5%	34.4%	<0.0001
Myocardial infarction	5.7%	3.5%	<0.0001
Carotid artery disease	1.3%	2.1%	<0.0001
Peripheral vascular disease	14.3%	11.1%	<0.0001
Coronary artery disease	9.5%	8.5%	<0.0001
Hepatitis C	14.4%	0.9%	<0.0001
Hepatitis B	4.8%	0.2%	<0.0001
BMI			<0.0001
Normal [18.5–24.99]	32.1%	21.9%	
Overweight [25–30]	31.4%	26.7%	
Obese [>30]	29.5%	35.1%	

Among those with HF, patients with HIV were less frequently prescribed diuretics (58.6% vs. 68.8%, HIV vs. no HIV; $p < 0.001$), angiotensin converting enzyme inhibitors or angiotensin receptor blocker (ACE/ARB) use (59.7% vs. 62.0%, HIV vs. no HIV; $p = 0.015$), antiplatelet therapy (55.5% vs. 62.9%; $p < 0.001$), and beta-blockers (65.8% vs. 68.8%, HIV vs. no HIV; $p = 0.001$) but rates of cardiology visits were similar (66.2% vs. 65.5%, HIV vs. no HIV, $p = 0.5$). Among those with HIV and HF, having a cardiology visit was associated with higher rates of diuretic use [RR 1.89 (1.73, 2.07)], ACE/ARB [RR 1.85 (1.69, 2.02)], beta-blockers [RR 1.82 (1.68, 1.97)], and antiplatelets [RR 2.06 (1.87, 2.28)].

4. Discussion

Our report provides a broad epidemiologic snapshot of the risk of heart failure among patients with HIV in the United States. Overall, the risk of heart failure was nearly two-fold higher in HIV patients compared with uninfected controls. This risk associated with HIV is present across a broad spectrum of age groups and for both males and females. Patients with HIV and HF may be undertreated for HF, but specialty cardiologist care is associated with higher rates of HF treatment.

Heart failure remains a significant cause of non-AIDS morbidity and mortality among patients with HIV. Theories regarding the excess risk of heart failure in this population include a direct effect of HIV on the myocardium, autoimmunity, chronic inflammation, coronary artery disease, or side effects of ART [10]; however, data from the modern era of effective ART are relatively limited. A recent meta-analysis found a prevalence of 8.3% (95% CI 2.2–14%) left ventricular systolic dysfunction and 43% (95% CI 31–55%) diastolic dysfunction among 2242 subjects from 11 studies with >75% of subjects on combination ART [11]. The limited epidemiologic evidence for an elevated risk of clinical HF comes from