A Comparison of Comorbidities and their Contribution to Medical Resource Utilization for Matched HIV-Infected and Uninfected Individuals: A Cross-Sectional Analysis

Comorbidities and Resource Utilization among HIV infected and uninfected patients

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Abstract

HIV long-term uninfected groups. Aging with HIV involves complex interactions of factors (e.g., Individual Characteristics, Infections) that result in a 20% increase in comorbidity risk. With over half of the 1.1 million people living with HIV in the US age 50 and over, the need exists to further understand this interplay and differences in aging-related outcomes. Electronic health record data was analyzed for HIV infected (N=208) and uninfected (N=208) adult inpatients, propensity score matched by age and gender. Diagnostic codes were extracted that comprise the factors of Individual Characteristics, High Risk Behaviors, Chronic Conditions, Mental Health Conditions and Infections. Identified codes were assessed for their contributions to medical resource utilization, based on Charlson Comorbidity scores. Significant contributors to high Charslon scores for HIV infected patients were age (β=0.116; [95% CI 0.077, 0.155]) and admission frequency (β=0.159; [95% CI 0.114, 0.205]) in addition to the comorbidities of acute kidney failure (β=3.27; [95% CI 1.76, 4.78]), hypertension (β= -1.77; [95% CI -2.99, -0.551]). Significant contributors for HIV uninfected patients were age (β=0.110; [95% CI 0.087, 0.133]), length of hospital stay (β=0.006; [95% CI 0.003, 0.009]), acute kidney failure (β=1.556; [95% CI 0.611, 2.50]), heart failure (β= 1.713; [95% CI 0.717, 2.71]), and diabetes mellitus II (β= 1.385; [95% CI 0.634, 2.14]). Our findings enhance the understanding of the contributions to medical resource utilization based on HIV status and can inform intervention efficacy for improved HIV aging outcomes.

Keywords: Charlson Scores, Comorbidities, Electronic Health Records, Medical Resource Utilization

Introduction

There is a growing US population of aging persons living with HIV/AIDS (PLWH) because of diagnosis in later life or long-term survivorship [1,2]. Immune restoration with highly active antiretroviral therapy (HAART) [1,3] has contributed tremendously to these outcomes. However, long-term survivorship is characterized by the presence of and elevated risk for comorbidities [4, 5] not simply explained by the decline in AIDS-related morality and longer life [2,3,6]. Research has linked HIV infection to conditions including cardiovascular disease [7-10]. After adjusting for usual risk factors, HIV-associated rates remain the highest for PLWH who are younger, indicating accelerated aging. In fact, a recent study concluded that the HIV virus has the potential to accelerate aging by more than 14 years [11]. Therefore, aging with HIV must be further explored. The determinants of aging with HIV include complex interactions of comorbid factors including biological/clinical (e.g., diabetes) and socio-behavioral (e.g., smoking). With half of the 1.1 million PLWH, in the US estimated to be 50 or over [7,13], understanding and improving aging of PLWH is a priority.

Aging phenotype development has improved the understanding of physical and cognitive decline in populations of aging adults with multiple comorbidities [16]. Several positive aging phenotypes are characterized (e.g., physical and social functioning) to allow investigators to study avenues for healthier aging outcomes [17]. Although a frailty phenotype is proposed in middle aged HIV infected women, the application of phenotypes to HIV infection is understudied. More effective HIV interventions in aging are dependent on identifying narrower phenotypes with greater clinical validity [17]. However, barriers exist to understanding the interplay between HIV and aging. These are attributed to difficulties in comparing HIV

88 subgroups to the general population of HIV uninfected adults. With this limited understanding of
89 the link between aging in PLWH and uninfected groups [18,19], the current study seeks to fill
90 this gap. Moreover, the recent widespread adoption of electronic health records (EHR) in the US
91 has afforded us the opportunity to leverage clinical data to further HIV phenotype development.
92
93 Utilizing EHR data, we investigated the contributions to medical resource utilization
94 based on differences in Charlson comorbidity scores. We sought to understand and classify
95 between group differences in electronic clinical data of HIV infected and uninfected controls,
96 propensity score matched on gender and age. Our cross-sectional study looked at the presence of
97 comorbidities and not HIV-related contributions (e.g., disease stage and immune status) to the
98 development or proliferation of comorbidities. Higher Charlson scores are an indication of the
99 increased likelihood the predicted outcome will result in either 1-year mortality or the higher use
100 of medical resources, [20] the current study focused on the later. In this paper, we report the
101 Individual Characteristics, High Risk Behaviors, Chronic Conditions, Mental Health Conditions
102 and Infections that predict high Charlson scores by HIV status. Findings will enhance our
103 understanding of aging with HIV for effective disease management and improved outcomes in
104 HIV infected populations.
105

106 Materials and Methods

107 Patient Population

108 HIV infected (N=208) and uninfected (N=208) inpatient records were matched based
109 on age and gender for adults 18 and older between January of 2006 and December of 2014,
110 from a clinical data warehouse of electronic health records (EHR). Institutional review board

approval was obtained to analyze the de-identified data, which excluded all potentially identifiable patient information (e.g., name, address, date of birth). No patients were involved in the data analysis or interpretation. After data cleaning, we were left with a total of 16,334: HIV infected N=208) and uninfected (N=l9,216) patients for matching. Mahalanobis' propensity scoring was used to match HIV infected patients to comparable HIV uninfected patients [17]. Matching allows for meaningful comparisons between two groups and reduces confounding factors in the statistical assessment of outcomes. Diagnostic codes utilized in our analysis were extracted from encounters, past histories, and problem lists. Factors were identified as Individual Characteristics (e.g., ICD 9/10: 262 - Malnutrition), High Risk Behaviors (e.g., ICD9/10: 305.1 – use of Tobacco), Chronic Conditions (e.g., ICD9/10: 584.9 - Acute Kidney Failure), Mental Health Conditions (e.g., ICD9/10: 311- Depressive Disorders), and Infections (e.g., ICD9/10: 070.41- Hepatitis C). Group inclusion was based on the presence or absence of a diagnosis in the chart history.

Statistical Analysis

The association between Charlson scores and Individual Characteristics, High Risk Behaviors, Chronic and, Mental Health Conditions and Infections were examined. Findings are summarized using descriptive statistics. Pearson Product Moment Correlations (PPMCs) were calculated to determine the relationship between variables that comprise identified factors and Charlson scores (an indicator of medical resource utilization). T-tests were used to assess differences in continuous variables and chi square analyses were used to assess differences in categorical variables. Two independent stepwise multiple regressions (i.e., HIV+ and HIV-) were performed to identify the relevant importance of identified variables ($p<0.05$) to high Charlson

scores. The stepwise approach allows for the prevention of bias in the selection of variables in the final models [21, 22]. Betas (β) and confidence intervals (CIs) were reported for regression analyses, with the use of SPSS 23.0.

Results

A total of 416 patients were included in our analysis, ages 18 to 85, with the mean age of 50.6±13.2. The racial distribution of the HIV infected sample (N=208) includes 27.1% (N=56) Blacks; 21.4% (N=45) Whites; 0.64% (N=1) Asian; 14.3% (N=30) Mixed Race; 12.46% (N=26) Other; and24.1% (N=50) Unknown or Declined. The HIV uninfected sample (N=208) includes 10.1% (N=21) Blacks; 31.3% (N=65) Whites; 3.1% (N=6) Asian; 15.4% (N=32) Mixed race; 10.8% (N=22) Other; and 29.3% (N=61) Unknown or Declined. The frequency of patient admissions was 7.57±10.7 for HIV patients and 6.17±8.4 for HIV uninfected patients. The average length of stay for HIV patients was 86.6±159.5 and 63.4± 105 for HIV uninfected patients. The top four ICD9/10 codes for the HIV patients were Substance Abuse, Hypertension, Hyperlipidemia and Hepatitis C whereas, the top four for HIV uninfected patients were Hypertension, Diabetes Mellitus II, history of tobacco use and Substance abuse, Table 1. Charlson scores ranged from 0-21 with an average of 7.42±4.35 for HIV patients and 0-12 with an average of 3.52±2.97 for HIV uninfected patients, Table 2.

Table 1. Rank (in degrees) of Factors That Contribute to Medical Resource Utilization (Charlson Scores) Based on HIV Status

	HIV+ N=208	HIV- N=208
Individual Characteristics		
Noncompliance medical treatment/regimen	7°	15°
severe protein-calorie malnutrition	8°	11°
High Risk Behaviors		
Substance Abuse	1°	5°
Current Tobacco Use	8°	8°
History of Tobacco Use	7°	4°
Chronic Conditions		
Acute Kidney Failure	9°	5°
Diabetes Mellitus II	3°	3°
End Stage Renal Disease	14°	14°
Hypertension	2°	1°
Hyperlipidemia	4°	2°
Atherosclerosis	10°	10°
Heart Failure	9°	7°
Hyponatremia	13°	13°
Anemia	11°	6°
Uncomplicated Asthma	6°	12°
Mental Health Conditions		
Depressive Disorders	12°	9°
Suicide and self-inflicted injury	15°	16°
Intentional self-harm	16°	16°
Infections		
Hepatitis C	5°	17°
Syphilis	17°	-

Significant differences were observed from bivariate analyses between HIV infected and uninfected patients based on Charlson scores. These include the Individual Characteristics of age (t=-3.95; *df*=414), length of stay (t=-4.79; *df*=414), and admission frequency (t=-4.78; *df*=414). They also include the High Risk Behavior of substance abuse (X^2= 49.26; *df*=19); the Chronic Conditions of acute kidney disease (X^2= 88.98; *df*=19), diabetes mellitus II (X^2= 55.3; *df*=19) end stage renal disease (X^2= 28.31; *df*=19) hypertension (X^2= 46.55; *df*=19), hyperlipidemia (X^2= 41.20; *df*=19), heart failure (X^2= 32.73; *df*=19), hyponatremia (X^2= 45.14; *df*=19) and anemia (X^2= 30.54; *df*=19). Significant differences also included the Infections of Hepatitis C (X^2= 30; *df*=19) and syphilis (X^2= 40.86; *df*=19), Table 2.

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Table 2. Descriptive Statistics, Correlation, X^2/ t-test for Medical Resource Utilization (Charlson Scores)

	HIV+	HIV-	Charlson Score					
	(N=208)	(N=208)	Correlations				X^2/ T-tests	
Charlson Comorbidity Score	7.42±2.4.35	3.52±2.97	HIV+		HIV-			
Individual Characteristics								
Gender								
Male	135	135						
Female	73	73						
Age	50.6±13.2	50.6±13.2	0.354	**	0.515	**	-3.95; *df*=414	**
Length of Stay	86.6±159.5	63.4±105	0.292	**	0.283	**	-4.79; *df*=414[a]	**
Admissions Frequency	7.57±10.7	6.17±8.4	0.374	**	0.248	**	-4.78; *df*=414[a]	**
Noncompliance med treatment/regimen	27	6	0.025		-0.059		25; *df*=19	
severe protein-calorie malnutrition	25	16	0.033		0.071		16.27; *df*=19	
High Risk Behaviors								
Substance Abuse	82	26	0.092		-0.042		49.26; *df*=19	**
Current Tobacco Use	25	20	0.009		0.003		24.84; *df*=19	
History of Tobacco Use	27	38	0.088		0.005		24.8; *df*=19	
Chronic Conditions								
Acute Kidney Failure	24	26	0.384	**	0.386	**	88.98; *df*=19	**
Diabetes Mellitus II	37	44	0.167	*	0.295	**	55.3; *df*=19	**
End Stage Renal Disease	10	10	0.139	*	0.143	*	28.31; *df*=19	**
Hypertension	49	91	-0.054		0.045		46.55; *df*=19	*
Hyperlipidemia	34	61	-0.004		0.162	*	41.2; *df*=19	**
Atherosclerosis	22	18	0.104		0.073		25.92; *df*=19	
Heart Failure	24	22	0.048		0.262	**	32.73; *df*=19	*
Hyponatremia	11	12	0.071		0.082		45.14; *df*=19	**
Anemia	19	25	0.046		0.01		30.54; *df*=19	*
Uncomplicated Asthma	28	15	-0.064		-0.036		15.37; *df*=19	
Mental Health Conditions								
Depressive Disorders	18	19	0.061		-0.157	*	20.28; *df*=19	
Suicide and self-inflicted injury	5	5	0.079		0.025		19.88; *df*=19	
Intentional self-harm	3	5	-0.03		-0.006		7; *df*=19	
Infections								
Hepatitis C	32	2	0.033				30; *df*=19	*
Syphilis	2	0	0.047				40.86; *df*=19	**

[a] Equal variances not assumed ; **p < .01, *p < .05 for t-tests and chi square tests

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170 Significant differences were also observed for bivariate analyses among HIV infected and

171 uninfected patients based on age groups: under 50 years of age (<50) and 50 years of age and
172 older (≥50). For both patient populations, these include the Health Risk Behavior of Substance
173 Abuse: HIV (X^2=6.8; *df*=1) uninfected (X^2= 5.65; *df*=1) and the Chronic Conditions of
174 Hypertension: HIV (X^2=9.66; *df*=1) uninfected (X^2= 9.28; *df*=1), Hyperlipidemia: HIV
175 (X^2=11.25; *df*=1) uninfected (X^2= 15.17; *df*=1) and Atherosclerosis: HIV (X^2=6.35; *df*=1)
176 uninfected (X^2= 3.71; *df*=1). Additionally, HIV patients included the Mental Health Condition of
177 Intentional self-harm (X^2=3.91; *df*=1) and the Infection of Hepatitis C (X^2=3.75; *df*=1).
178 Significant differences in Charlson scores were observed for uninfected patients (X^2=7.28; *df*=1)
179 in addition to the Chronic Condition of Uncomplicated Asthma (X^2=5.75; *df*=1) and the Mental
180 Health Condition of Depression (X^2=7.61; *df*=1), Table 3.
181

Table 3. Age Differences of Factors that Contribute to Medical Resource Utilization (Charlson Scores)

	HIV+ <50 and ≥50			HIV- <50 and ≥50		
Mean Charlson Scores	$\bar{x}$ = 6.23	$\bar{x}$ = 8.34		$\bar{x}$ = 2.48	$\bar{x}$ = 4.32	
Individual Characteristics						
Charlson Score	-			7.28, *df* = 1		**
High Risk Behaviors						
Substance Abuse	6.8, *df*=1		**	5.65, *df* = 1		*
Chronic Conditions						
Diabetes Mellitus II	11.28, *df*=1		**	-		**
Hypertension	9.66, *df* =1		**	9.28, *df* =1		**
Hyperlipidemia	11.25, *df* =1		**	15.17, *df* =1		**
Atherosclerosis	6.35, *df* =1		*	3.71, *df* =1		
Uncomplicated Asthma	-			5.75, *df* =1		**
Mental Health Conditions						
Depressive Disorders	-			7.61, *df* =1		**
Intentional self-harm	3.91, *df* =1		*	-		
Infections						
Hepatitis C	3.75, *df* =1		*	-		

**p < .01, *p < .05

182
183 The stepwise multiple regression for the HIV uninfected patients identified the

184 individual characteristics of age (β=0.110; [95% CI 0.087, 0.133]) and length of hospital stay
185 (β=0.006; [95% CI 0.003, 0.009]) in addition to the Chronic Conditions of acute kidney failure
186 (β=1.556; [95% CI 0.611, 2.50]), heart failure (β= 1.713; [95% CI 0.717, 2.71]), and diabetes
187 mellitus II (β= 1.385; [95% CI 0.634, 2.14]), as the most important contributors ($p<0.05$)
188 associated with high Charlson scores, Table 4.
189

Table 4. Linear Regression Model of Best Fit for Medical Resource Utilization (Charlson Scores) (N=416)

	Unstandardized Coefficients Beta		95.0% Confidence Interval for B
HIV+ Model (N=208)			
Individual Characteristics			
Age	0.116	**	0.077 – 0.155
Admission Frequency	0.159	**	0.114 – 0.205
Chronic Conditions			
Acute Kidney Failure	3.27	**	1.76 – 4.78
Hypertension	-1.77	*	-2.99, -0.551
Diabetes Mellitus II	1.48	*	0.107 – 2.85
HIV- Model (N=208)			
Individual Characteristics			
Age	0.110	**	0.087 - 0.133
Length of Stay	0.006	**	0.003 - 0.009
Chronic Conditions			
Acute Kidney Failure	1.556	**	0.611 - 2.50
Heart Failure	1.713	*	0.717 - 2.71
Diabetes Mellitus II	1.385	*	0.634 - 2.14

**p < .01, *p < .05

190
191

192 The stepwise multiple regression for the HIV patients identified the individual
193 characteristics of age (β=0.116; [95% CI 0.077, 0.155]) and admission frequency (β=0.159;
194 [95% CI 0.114, 0.205]) in addition to the chronic conditions of acute kidney failure (β=3.27;

195 [95% CI 1.76, 4.78]), hypertension (β= -1.77; [95% CI -2.99, -0.551]), and diabetes mellitus II
196 (β= 1.48; [95% CI 0.107, 2.85]), as the most important contributors associated with ($p<0.05$)
197 high Charlson scores, Table 4.
198

199 # Discussion

200 The National HIV/AIDS Strategy identified the pressing need to facilitate successful
201 aging of PLWH [5]. As those with long-standing HIV infection age, comorbidities are becoming
202 increasingly common [16, 24]. To support successful aging, it is essential to improve our
203 understanding of the contribution of HIV infection to the presence of comorbidities and
204 associated clinical outcomes. To explore this further, we utilized a clinical dataset of HIV
205 infected and uninfected patients, matched on age and gender. We sought to identify significant
206 population-specific differences and their contributions to medical resource utilization, informed
207 by Charlson scores. Charlson comorbidity scores are robust predictors of mortality and medical
208 resource utilization, [21] and an important confounding factor, essential to effective
209 epidemiological investigations of aging and survival [6, 26]. Yet, studies utilizing Charlson
210 scores as indicators of medical resource utilization in populations of PLWH, are sparse. Our
211 results identified significant differences between our HIV infected and uninfected patients. Our
212 predictive models allowed us to observe the interplay of Individual Characteristics, High Risk
213 Behaviors, Chronic Conditions, Mental Health Conditions and Infections by HIV status.
214

215 Our regression models identified age as a high-level significant contributor to high
216 Charlson scores in both patient populations. In HIV uninfected patients, age was the most
217 important contributor, accounting for 50% of the model. In the HIV population, age is the second

218 highest level contributor accounting for almost 36% of the HIV model. This indicates that unlike
219 normal aging, other factors increase the utilization of medical resources for patients with HIV.
220 Although our populations were matched on age, the average Charlson score was three points
221 higher for HIV, reinforcing that the additional contributors are potential indicators of accelerated
222 aging. Additionally, our bivariate analyses of age differences identified significant within group
223 differences in Charlson scores for the uninfected patients, but not for the HIV patients. Similar
224 aging-related medical resource utilization was observed in younger and older PLWH, potential
225 evidence of accelerated aging.
226
227 Admissions frequency in HIV patients was a top predictor of high Charlson score in our
228 regression model. In populations of PLWH, admissions type, whether urgent or non-urgent, the
229 number of secondary diagnoses, and number of procedures, are significant contributors of
230 medical resource utilization and significant in our model [26]. The most severe clinical
231 conditions are often categorized by multiple diagnoses and procedures, contributing directly to
232 length of stay; seen as a top contributor to high Charlson scores in our uninfected model [26].
233 Understandably, the cost of hospitalizations is a major financial burden on the US healthcare
234 system; with HIV-related hospitalizations including the more expensive diagnostic categories
235 [26]. Although length of stay was not significant in our HIV model, our results revealed HIV
236 patients' average length of stay was 87 patient days, which are 23 days more than uninfected
237 patients. Studies have also observed that in populations of PLWH with no comorbidities, a 60%
238 increase in length of stay and 70% increase in medical resource utilization remain, compared to
239 uninfected groups [26].

Acute kidney failure in HIV infected and uninfected patient models as well as end stage renal disease in the HIV model were top predictors of high Charlson scores. HIV nephropathy has decreased with the use of anti-retroviral therapy. Yet, in populations of PLWH, compared to uninfected peer groups, risk factors for kidney disease were present in our models including diabetes for HIV uninfected patients and hypertension for HIV patients [23]. Other studies have also revealed that kidney-related comorbidities are associated with extremely high medical-related costs, as indicated in both our models as top contributors to high Charlson scores [27].

HIV patients are recognized to be at high risk for cardiovascular-related illness, with heart disease being a very common complication [23]. Interestingly, both models included cardiovascular related illnesses: hypertension (HIV+) and heart failure (HIV-) were top significant contributors in both groups [23]. Higher rates of hypertension are observed in PLWH in addition to associated illnesses [28, 29]. PLWH also have increased risk for cardiovascular-related mortality compared to uninfected groups. In fact, a study showed the risk of cardiovascular-related mortality increased steadily from 1999 to 2013 as the risk decreased among HIV uninfected people. Heart failure risk is also observed among PLWH with depression and hypertension [30]. Although not significant in our model, more heart failure existed in the HIV patients with hypertension, yet not the case for depression. Heart failure is also related to Diabetes Mellitus II and both diseases were present only in the HIV uninfected model. Understanding that some HIV medications increase the risk of type II Diabetes in PLWH in addition to the regular risk factors, it was surprising it did not contribute to high medical resource utilization as with our uninfected population [31, 32].

Limitations

Our cross-sectional study explored the top diagnoses and procedure codes. Future studies on predictive modeling should explore additional clinical factors and apply other analytic approaches to support a comprehensive evaluation of medical resource utilization for effective integrated health services delivery. We did not match our sample on other factors including socioeconomic status, due to incomplete sociodemographics in the patient records. Data that comprise EHRs is collected during clinical care and not collected for research purposes. Therefore, incomplete sociodemographics will exist for a variety of indicators including race. Our cross-sectional analysis was unable to include HIV-related contributions (e.g., immune status) to the development or severity of comorbidities, only their documented presence or absence. Future longitudinal studies should account for these additional factors, and track such factors (e.g., immune status) over time to explore their contributions to comorbidity development and medical resource utilization.

Our analysis also did not include an exploration of the contribution of HIV-related clinical indicators (CD4, viral load, antiretrovirals); the analysis of HIV-related clinical indicators one point in time (cross-sectional analysis) would not be informative to the presence and absence of the observed comorbidities. Future longitudinal studies should analyze HIV-related clinical indicators over time, as medications, including protease inhibitors, are linked to increase risk of cardiovascular related illness. This should also be explored in future predictive modeling studies [23].

Conclusions

As HIV population's age both locally and globally, preventing, identifying and managing comorbidities is increasingly important. An essential need exists to further understand the causal factors of identified aging outcomes and in the exploration of additional clinical indicators to inform optimal treatment, care and self-management. Interventions targeting aging phenotypes, specific to HIV, have been sparse. Additional contributions to the development of such phenotypes, were found in our study and critical as PLWH age. Similarities and differences were observed between our age and gender matched patients and factor-specific contributions in higher medical resource utilization observed. Our findings add to the literature on HIV and aging-related outcomes and support HIV and aging phenotype development.

List of Abbreviations

PLWH: People Living with HIV/AIDS

PPMC: Pearson Product Moment Correlations

CI: Confidence Intervals

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Authors Contributions

Authors assisted in the data interpretation (MO, SY), manuscript drafting (MO), revising intellectual content (MO, SY). This manuscript has not been published and is not under consideration for publication elsewhere.

Competing interests

We have no conflict of interest to disclose.

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Table 1. Rank (in degrees) of Factors That Contribute to Medical Resource Utilization (Charlson Scores) Based on HIV Status

Table 2. Descriptive Statistics, Correlation, X^2/ t-test for Medical Resource Utilization (Charlson Scores)

Table 3. Age Differences of Factors that Contribute to Medical Resource Utilization (Charlson Scores) Based on HIV Status

Table 4. Table 4. Linear Regression Model of Best Fit for Medical Resource Utilization (Charlson Scores) (N=416)