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Differentiation of Type 1 and Type 2 Myocardial Infarctions Among HIV-Infected Patients Requires Adjudication Due to Overlap in Risk Factors

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Abstract

The Universal Myocardial infarction (MI) definition divides MIs into different types. Type 1 MIs (T1MI) result spontaneously from atherosclerotic plaque instability. Type 2 MIs (T2MI) are due to secondary causes of myocardial oxygen demand/supply mismatch such as occurs with sepsis. T2MI are much more common among those with HIV than in the general population. T1MI and T2MI have different mechanisms, risk factors, and potential treatments suggesting that they should be distinguished to achieve a better scientific understanding of MIs in HIV. We sought to determine whether MI type could be accurately predicted by patient characteristics without adjudication in HIV-infected individuals. We developed a statistical model to predict T2MI versus T1MI using adjudicated events from six sites utilizing demographic characteristics, traditional cardiovascular, and HIV-related risk factors. Validation was assessed in a seventh site via mean calibration, and discrimination level was assessed by the area under the curve (AUC). Of 812 MIs, 388 were T2MI. HIV-related factors including hepatitis C infection were predictive of T2MI, whereas traditional cardiovascular risk factors including total cholesterol predicted T1MI. The score predicted 69 T2MI in the validation sample resulting in poor calibration, given that 90 T2MIs were observed. The development sample AUC was 0.75 versus 0.65 in the validation sample, suggesting relatively poor discrimination. The level of discrimination to predict MI type based on patient characteristics is insufficient for individual level prediction. Adjudication is required to distinguish MI types, which is necessary to advance understanding of this important outcome among HIV populations.

Keywords: myocardial infarction, adjudication, HIV, cardiovascular disease, cohort research, Bayesian model averaging

Introduction

The Universal Definition of myocardial infarction (MI) divides MIs into five types according to mechanism of myocardial ischemia.[1] Type 1 MIs (T1MI) result spontaneously from atherosclerotic plaque instability. Type 2 MIs (T2MI) are due to secondary causes of myocardial oxygen demand/supply mismatch such as sepsis, hypotension, or cocaine-induced vasospasm, rather than atherosclerotic plaque rupture. Type 3 MIs are deaths occurring with symptoms suggestive of MI and no measures of cardiac biomarkers. Type 4 and 5 MIs occur in the setting of coronary revascularization procedures.

Questions remain unanswered about the risk of cardiovascular disease (CVD) and particularly MI among HIV-infected

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individuals. Rates of MIs are likely higher in HIV-infected individuals compared with those without HIV.[2–5] Many previous studies of MI in HIV have used unadjudicated MI outcomes and have not differentiated MI types, which may have contributed to conflicting findings regarding risks in those with HIV. We developed an MI adjudication protocol in the Centers for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS) cohort that allows us to centrally adjudicate MIs and identify MI type and characterize causes of T2MI.[6] We demonstrated that T2MI are much more common in cohorts of HIV-infected individuals than in the general population, making up approximately half of all events.[7] This contrasts with most general population studies where T2MI account for a minority of MIs,[8–15] usually <10% of all MIs.[10–15] Furthermore, HIV-infected individuals with T2MI are younger, more likely to have poorly controlled HIV, and to have less severe CVD risk scores than those with T1MI suggesting T1MI and T2MI are due to different mechanisms among different populations of HIV-infected individuals.[7] This has implications for studying MIs among HIV-infected individuals and understanding the higher MI rates and extent MI burden can be reduced by CVD risk factor modification particularly given the unclear role of atherosclerosis in T2MI. Despite the fact that T1MI and T2MI have different risk factors, treatment, and prognosis they are usually not distinguished in HIV cohort studies because clinical diagnosis codes do not discriminate between MI types.[7,16] This creates a critical gap in scientific knowledge as understanding MI types may help clarify unanswered questions regarding risk factors, risk scoring, and prognosis in HIV-infected individuals and enable development of better interventions that likely differ by type.

We distinguish T1MI from T2MI in CNICS through central adjudication, however, adjudication is complex, time-consuming, and expensive, and may not always be feasible in other cohorts. Research costs continue to climb and adjudication consumes resources. It is therefore important to know whether this costly adjudication process is necessary, or if the type of MI can be determined based on participant demographic and/or clinical characteristics, given the known heterogeneity in risk factors between T1MI and T2MI. The goal of this study was to develop an accurate equation using routinely collected demographic and clinical data to predict which type of MI (T1MI vs. T2MI) had occurred in HIV-infected individuals.

Methods

The CNICS cohort includes HIV-infected individuals receiving clinical care at eight sites across the United States.[17] CNICS sites have approval from local human subjects boards and informed consent from all participants. The CNICS data repository integrates comprehensive clinical data from all outpatient and inpatient encounters including laboratory test results such as cardiac biomarkers and lipid values; medications such as those used for diabetes, dyslipidemia, and hypertension; blood pressure values; and comorbid diagnoses.[17] Potential incident MI events at seven clinical sites were identified in the CNICS centralized data repository by the presence of an MI diagnosis or coronary intervention such as coronary artery bypass graft or elevated values of cardiac biomarkers such as troponin.[6] Sites assembled de-identified packets that included physician notes, electrocardiograms (ECGs), procedure results, and lab results. Two physician experts reviewed each packet, followed by a 3rd if discrepancies occurred. Reviewers categorized each MI as T1MI or T2MI and identified causes for each T2MI as has been described previously.[6,7] We did not include HIV-infected patients with type 3 MI because by definition, cardiac biomarkers are not measured and the event cannot be confirmed. We have previously found that Type 4 and 5 MIs are rare in HIV-infected patients and therefore are not described further.[7]

We used Chi-squared and t-tests for categorical and continuous variables to assess differences in demographic and clinical characteristics among individuals with T1MI versus T2MI. Based on the centrally adjudicated MI results, we developed a statistical model to predict T2MI versus T1MI using adjudicated events from six sites; a seventh site was used as an independent sample to validate the results (as protection from overfitting the statistical model). The variables we considered were demographic characteristics: age, race, and sex; traditional cardiovascular risk factors: lipid levels (total cholesterol, HDL cholesterol, and triglycerides), blood pressure values (systolic), pharmacologically treated hypertension, pharmacologically treated dyslipidemia, diabetes, smoking status, body mass index (BMI) categorized as <18.5, 18.5–24.9, and ≥25, and kidney status categorized as an estimated glomerular filtration rate (eGFR <30 vs. ≥30 mL/min/1.73 m^2); and HIV-related and other risk factors: total bilirubin (≤1.3 vs. >1.3 mg/dL), hepatitis C virus (HCV) co-infection, HIV viral load (VL: assessed as log10(VL + 1)), and CD4 cell count.

We used the most recent values at least 7 days before the MI. Missing data were handled using multiple imputation with three imputations combined using Rubin's rules.[18] We used a Bayesian Model averaging (BMA) approach for variable selection. BMA is a method of dealing with model uncertainty by estimating an average of the posterior distributions of a family of candidate models for the association of interest. The final estimate is weighted by the posterior model probability of each model that is within Occam's window, which gives both an averaged estimate and a posterior probability of each variable being included in the final model.[19] While it is possible to use this averaged model for inference, a common alternate approach is to use the posterior probability that a variable is in the best model with a cutoff of ≥50% posterior probability.[20] We also included age and sex in the models regardless of cutoffs based on *a priori* assumptions. We show estimates of the relative risk for the candidate risk factors using relative risk regression.[21] Validation was assessed in the 7th site via mean calibration by comparing the observed and predicted number of events and by the level of discrimination as assessed by the area under the curve (AUC). BMA models were done in R version 3.4.4 using the package BMA.[22] All other analyses were done in STATA 14.[23]

Results

There were 812 centrally adjudicated MIs at participating sites between 2000 and 2015: 424 T1MI and 388 T2MI. Among those with an adjudicated MI, 79% were men, the median age was 49 years (interquartile range IQR 43–56), and the current mean CD4 cell count was 388 cells/mm^3 (SD

Table 1. Demographic and Clinical Characteristics of HIV-Infected Individuals by MI Type at 7 Sites Across the United States in the CNICS Cohort

Variable N *(%) or mean (SD)*	*Type 1 MI*	*Type 2 MI*	*Overall*	p-*value*
N	424	388	812	
Age, years (SD)	50 (9)	49 (11)	50 (10)	.05
Female (%)	73 (17)	99 (26)	172 (21)	.004
Black race (%)	173 (41)	258 (66)	431 (53)	<.001
Risk factor (%)				<.001
MSM	206 (49)	116 (30)	322 (40)	
IDU	87 (21)	139 (36)	226 (28)	
Heterosexual	112 (26)	116 (30)	228 (28)	
Other/unknown	19 (4)	17 (4)	36 (4)	
Smoker (%)	171 (40)	147 (38)	318 (39)	.5
Pharmacologically treated dyslipidemia (%)	104 (25)	44 (11)	148 (18)	<.001
Hypertension medication use (%)	186 (44)	146 (38)	332 (41)	.07
Hepatitis C virus (%)	93 (22)	157 (40)	250 (31)	<.001
eGFR <30 (%)	38 (9)	56 (14)	94 (12)	.002
Total bilirubin >1.3 (%)	42 (10)	59 (15)	101 (12)	<.001
Diabetes (%)	86 (20)	80 (21)	166 (20)	.9
Total cholesterol mg/dL (SD)	190 (54)	164 (50)	177 (54)	<.001
HDL mg/dL (SD)	40 (14)	43 (18)	41 (16)	.01
Systolic blood pressure (SD)	132 (21)	130 (22)	131 (22)	.5
Triglycerides mg/dL (SD)	231 (217)	198 (242)	215 (230)	.08
BMI kg/m^2 (SD)	27 (6)	25 (6)	26 (6)	<.001
CD4 most recent mean (SD)	442 (304)	331 (289)	388 (301)	<.001
Log10(VL + 1) (SD)	2.4 (1.4)	3.1 (1.6)	2.8 (1.6)	<.001

Missing laboratory data before the MI included total bilirubin (11%), total cholesterol (21%), HDL (25%), VL (12%), CD4 (11%). We were also missing BMI before the event (22%) and current systolic blood pressure before the MI (25%).

Lab values were at least 7 days before MI.

BMI, body mass index; eGFR, estimated glomerular filtration rate; HDL, high density lipoprotein cholesterol; IDU, injection drug user; MI, myocardial infarction; MSM, men who have sex with men; SD, standard deviation; VL, viral load.

301). A higher proportion of those with a T2MI were female (26% vs. 17%, $p = 0.004$) and African American or Black (66% vs. 41%, $p < 0.001$) compared with those with a T1MI (Table 1). In addition, those with a T2MI had a lower mean current CD4 cell count (331 cells/mm^3 vs. 442 cells/mm^3 $p < 0.001$), and a higher proportion had a detectable VL (53% vs. 38%, $p < 0.001$) compared with those with a T1MI.

Using a BMA approach with individuals with an adjudicated MI from six sites, factors predictive of a T2MI versus T1MI included Black race and HCV infection, whereas traditional MI risk factors such as total cholesterol, pharmacologically treated dyslipidemia, and BMI $\geq 25\,kg/m^2$ were predictive of T1MI (Table 2).

We assessed the mean calibration of this risk score in the validation sample from the seventh site. The score predicted that 91 MIs (57%) in the validation sample would be T1MI and 69 would be T2MI. However, this was poor calibration given that 70 T1MI (44%) and 90 T2MI were observed. We assessed discrimination in the development sample and found that the AUC was 0.75 (0.71–0.79). In the seventh site, the AUC was 0.65 (0.57–0.74), suggesting relatively poor discrimination at the individual event level.

Table 2. Factors Predictive of Type 2 MI Versus Type 1 MI Among HIV-Infected Individuals at Six Sites in the CNICS Cohort Using a Bayesian Model Averaging Approach for Variable Selection and Relative Risk Regression ($P < .05$)

Characteristic	*BMA probability*	*Relative risk of Type 2 MI*	*95% CI*	p *value*
Black race	100	1.45	1.21–1.74	<.001
Hepatitis C virus[a]	94	1.34	1.12–1.60	.002
Pharmacologically treated dyslipidemia	94	0.57	0.41–0.81	.002
Total cholesterol (per 10 mg/dL)	94	0.97	0.95–0.99	.02
Smoker	0	0.91	0.78–1.06	.2
BMI ($\geq 25\,kg/m^2$)	100	0.79	0.67–0.94	.007
Age (per 10 years)	1	0.95	0.87–1.03	.2
Female sex	1	1.08	0.92–1.26	.4

All variables include in the model are listed in the table.

[a]As an example, there is a posterior probability of 94% that the best statistical model for separating type 2 versus type 1 MI contains Hepatitis C virus as a predictor, the presence of which is associated with a higher probability of an MI being type 2 (as opposed to type 1).

BMA, bayesian model averaging; CNICS, Centers for AIDS Research Network of Integrated Clinical Systems.

Discussion

We used a BMA variable selection method to identify patient characteristics that could be used in a statistical model to predict whether an MI was a T1MI versus T2MI among HIV-infected individuals. While we carefully adjudicate MI type in CNICS, adjudication is time consuming, costly, requires access to the primary data, and therefore is not feasible in all research contexts despite being the gold standard.[24] An algorithm that could use patient characteristics to accurately predict MI type would allow the use of data sources where privacy rules, size, or other reasons make an adjudication process infeasible. Traditional CVD risk factors such as pharmacologically treated dyslipidemia were predictors of T1MI while HIV-related factors such as HCV co-infection were more likely to predict T2MI. The risk factors were unable to account for realistic differences in event rates between sites, giving poor calibration overall. Furthermore, the discrimination was modest, even in the training sample, making it a challenge to separate the two types of events. Because too many risk factors are in common to accurately break apart the two types of MI events, a risk score is a far inferior option to an adjudication process.

While disappointing, these results point to the challenges in separating disease states with predictors in common. For example, we have previously found that diabetes is associated with both T1MI (Hazard ratio 1.9; 95% CI: 1.30–2.8) and T2MI (Hazard ratio 2.2; 95% CI: 1.6–3.2), although likely via different mechanisms.[25,26] The same predictor may act via different pathways to increase the risk of each outcome, adding to the challenge of using statistical models to distinguish outcomes. Since T1MI and T2MI are different disease processes, we hypothesized that a model based on risk factors could discriminate between them, but our results show that standard risk factors did not provide a risk score to properly discriminate MI types among HIV-infected individuals without adjudication.

This study used adjudicated events as a gold standard as has been recommended.[24] This has advantages in that many MI or CVD studies among populations with HIV rely on administrative diagnosis codes and other nonadjudicated outcomes[2,27–31] known to misclassify and overestimate true event rates.[32–34] We used multiple criteria including cardiac biomarkers to identify potential events, which has previously been shown to increase the number identified.[6,35] We used central adjudication which is preferable to local event adjudication (regardless of whether or not local adjudication includes secondary central review) as local site adjudication results in fewer true events identified.[36] Therefore, central adjudication with comprehensive clinical data leads to higher identified rates.[37–40]

Key strengths of this study include multiple sites to enhance geographic, racial/ethnic, and clinical diversity; comprehensive clinical data enabling a wide range of factors to be evaluated for their predictive ability; and proper handling of missing data. As described above, we used central adjudication as recommended with expert physician reviewers as our gold standard for event classification. While there is no guarantee they will adjudicate events correctly, we used two reviewers for all cases (with a third if discrepancies) to minimize potential errors as much as possible. A limitation of this study was that it was conducted among PLWH in care. While we included multiple clinical sites across the United States, it may not generalize to PLWH not yet diagnosed or in care or other types of nonclinical cohort settings. Further, it focused only on the comparison of adjudication or not on classification of MI by type while an additional key advantage of adjudication is eliminating the many false positive events.[6] Similarly, using cardiac biomarkers without adjudication results in false positive events with causes such as renal failure or pericarditis leading to an elevated cardiac biomarker without an MI.[6]

In conclusion, predicting MI type by clinical factors rather than adjudication would be a useful and inexpensive approach for determining the relative burden of T1MI versus T2MI in studies that lack the resources or ability to conduct formal adjudication processes. As careful centralized adjudication is rarely done in HIV cohort studies, it would greatly expand the HIV cohorts with the data available to answer key questions regarding this crucial outcome in the current HIV treatment era. However, the level of discrimination to predict MI type based on the use of covariates is insufficient for individual level prediction. Given the relatively high proportion of T2MI among HIV-infected individuals with different mechanisms, risk factors, and prognosis, HIV cohort studies would benefit from careful event adjudication that identifies MI type if they are to contribute to further understanding MI outcomes and guide prevention and treatments that likely differ greatly by MI type.

Author Contribution

All authors have contributed substantively to the study design, data acquisition, or analysis. All authors have contributed to the drafting of the article or reviewed it. In addition, H.C., S.H., and M.B. oversaw development of the adjudication protocol. H.C., J.A.C.D., and R.N. oversaw or contributed to analyses. H.C., M.K., D.D., P.H., G.B., M.M., W.C.M., R.D.M., J.J.E., P.H., E.G., and M.S. all contributed to data collection. All authors have given final approval for this article to be published.

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