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Effect of substance use on premature mortality among severely hypertensive African Americans

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Abstract

Low-income African Americans residing in impoverished neighborhoods confront myriad barriers to adhering to antihypertensive regimens. Substance use may thwart medication adherence and lifestyle modification efforts, which has implications for excess cardiovascular disease mortality. The Inner-City Hypertension and Body Organ Damage (ICHABOD) Study was a longitudinal cohort study that evaluated causes of mortality among African Americans who lived in urban areas, had severe, poorly controlled hypertension, and were admitted to a local hospital between 1999–2001 and 2002–2004. The authors employed Cox proportional hazards models to assess mortality associated with illicit substance use, including use of heroin and cocaine, as well as by use of tobacco and alcohol. Among192 participants with poorly controlled hypertension, 30% were active illicit substance users (specifically, 22.7% heroin users, 19.8% were cocaine users, and 30.7% were both cocaine and heroin users). The mean age among substance non-users was 52.3 years versus 48.7 years among those reporting current use. Mortality over 7.6 years of follow-up was 52.5% among substance users and 33.8% among nonusers *(p-value, 0.01)*. After adjusting for potential confounders, the hazard ratio (HR) for cocaine use was 2.52 (95% confidence interval (CI) 1.38–4.59), while the HR for heroin use was 2.47 (95% CI 1.42–4.28) and the HR for both was 2.75 (95% CI 1.60–4.73). Substance use was associated with increased mortality among urban black Americans with poorly controlled hypertension. These data suggest the need for targeted interventions to support African Americans who have poorly controlled hypertension and use illicit substances, as a means of reducing excess mortality.

KEYWORDS
alcohol and hypertension, epidemiology, hypertension in African Americans

1 | INTRODUCTION

The life expectancy of urban-dwelling African Americans is significantly lower than that of other racial/ethnic groups, due to the convergence of a multitude of structural determinants of health.[1–3] This disparity is largely attributed to deaths from cardiovascular disease arising from poorly controlled blood pressure.[2–4] Indeed, hypertension is a major driver of cardiovascular and all-cause mortality among all African Americans, irrespective of socioeconomic status,[5–7] but the higher prevalence of hypertension, greater hypertension severity, and higher rate of insufficient treatment observed among low income African Americans is particularly concerning in its relationship to a higher risk of comparatively earlier death.[6,8,9] Improved BP control has been shown to greatly reduce the disparity in CVD-related life expectancy.[10,11]

One factor that influences poor blood pressure control and insufficient treatment among hypertensive patients is low adherence to medication. Poor adherence is an independent predictor of long-term mortality among African Americans with hypertension.[9,12] We and others have identified several factors that are associated with low adherence to hypertension treatment.[9,13,14] In our prior work, we found that poor access to care, as reflected by lower levels of insurance coverage and difficulty paying for medications, was associated with nonadherence to medications among severely hypertensive African Americans residing in an urban area, supporting prior work demonstrating a strong and consistent association of poor access to care with nonadherence. In addition, we found that measures of treatment ambivalence, such as lower hypertension knowledge or forgetfulness, were also associated with nonadherence.[9]

The use of non-prescribed, illicit drugs may contribute to nonadherence of prescribed medications. Approximately 22.6 million Americans report substance use such as marijuana, heroin, cocaine, hallucinogens, inhalants, or non-prescribed medications.[15,16] As with many parts of the United States, the prevalence of substance use is high in Baltimore City, where a 2010 survey suggests that 14.3% of the population engages in illicit drug use.[17] Mortality due to illicit drug use increased by 75% from 2015 to 2016.[18] It is possible that substance abuse may negatively impact adherence to prescribed medications, thereby contributing to poorly controlled hypertension and other cardiovascular disease-related outcomes. To examine this hypothesis, we investigated the long-term mortality of a cohort of urban-dwelling African Americans admitted to an academic hospital located in the Baltimore with severe, poorly uncontrolled hypertension, stratified by substance use status.

2 | METHODS

The Inner City Hypertension and Body Organ Damage (ICHABOD) Study is a longitudinal cohort study of mortality among 192 urban-dwelling African American patients admitted to a hospital with severe, uncontrolled hypertension. The study was reviewed and approved by the Johns Hopkins Medicine Institutional Review Board. We screened patients who self-reported as African American, resided in Baltimore, and admitted to medicine units at an urban academic medical center in Baltimore, MD, during the periods of August 1999 to June 2001 and February 2002 to December 2004. Severe uncontrolled hypertension was defined as systolic blood pressure greater than or equal to 180 mm Hg and diastolic blood pressure greater than or equal to 110 mm Hg measured on two separate occasions using an automatic oscillatory device (Dinamap) in the emergency department. To exclude isolated systolic hypertension, only patients with both an elevated systolic and diastolic blood pressure were enrolled. Patients with hypertension due to secondary causes and/or age less than 18 years were excluded.

Over the course of the study, 485 individuals were admitted with blood pressures above 180/110. Of these individuals, 192 (40%) were excluded from the study because they either had an identifiable cause of elevated blood pressure or were unable to give consent. Among those eligible to participate, 7% died in the hospital before enrollment. Of the 272 living and eligible individuals, 192 completed the study (71% response rate).

2.1 | Measurements

Upon patients' admission into the hospital, trained interviewers administered a structured questionnaire and reviewed their admission history, physical examination, and the discharge summary. The questionnaire included items adapted from previous survey instruments used in trials conducted with similar populations that aimed to improve the control of hypertension and diabetes, and was further refined through a pilot study.[20,29–31] The questionnaire was designed to assess the patient's medical history, lifestyle behaviors (including diet and exercise), sociodemographic background, adherence behaviors, reasons for non-adherence, history of substance use, hypertension knowledge, access to care, insurance coverage, and ability to pay for health care.

2.2 | Outcome

The main outcome was mortality, defined as death in hospital or following discharge till 2006 using data from the National Death Index (NDI) and the Social Security Index (SSI). Cause-Specific mortality was described using International Classification of Disease, Ninth Revision (ICD-9) codes and classified into 6 broad categories: cardiovascular disease, end stage renal disease, infectious causes, overdose, diabetes, and other.

2.3 | Independent variables

Substance use status was identified at the time of admission to the hospital through self-report and urine toxicology in all participants. A study participant was considered to be a current substance user if they reported illicit drug use such as, cocaine and/or heroin use during the 2 weeks prior to admission or if the urine toxicology was positive for

non-prescribed opiates or cocaine on admission. A study participant was considered to be a former substance user if their self-reported last substance use was more than 2 weeks prior to the admission, and the urine toxicology was negative for non-prescribed opiates and/or cocaine. Alcohol use was based on self-report and defined as heavy if the participant was a man and drank more than two drinks per day or a woman and drank more than one drink per day. Current and former tobacco use was based on self-report.

The number and severity of participants' comorbidities was evaluated through self-report, chart review, and discharge diagnoses. Discharge diagnoses were coded using the International Classification of Disease, Ninth Revision, Clinical Modification [ICD-9-CM]. Disease Severity was captured through the risk of mortality and disease complexity score from the 3 M All Patient Refined Diagnostic Related Groups (APR-DRGs) scoring system, V20).[38]

2.4 | Analysis

The study examined participants' baseline characteristics overall and by substance use status using t-test (comparison of means for continuous variables) or χ^2 test (categorical variables) including only participants with complete data. Similar analyses were used to determine association of substance use with comorbidities, adherence to medications, lifestyle modifications, access to care, concurrent alcohol use and smoking. Sixteen participants were missing at least some of the sociodemographic variables or variables describing medication adherence. To minimize bias, we used multiple imputation to account for missing values in our data set, with analyses based on 192 patients, we generated Kaplan-Meier plots by substance use status and performed log rank tests to evaluate statistical significance. Mortality risk by substance use status was assessed first through univariate hazard ratio stratified by heroin use, cocaine use, tobacco use, and heavy alcohol consumption. Subsequently, we employed multiple logistic regressions, utilizing Cox proportional hazards models, that adjusted for age, sex, comorbidity, disease severity, socioeconomic status, adherence to medications, adherence to healthy lifestyle and access to care. All statistical analyses were performed using Stata 14 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX, USA: StataCorp LP.)

3 | RESULTS

3.1 | Baseline characteristics and measures of adherence

Table 1 shows the baseline characteristics by substance use status among 192 persons with severe, poorly uncontrolled hypertension. Substance use status was defined as current use illicit drug such as, heroin and/or cocaine. Current substance users were younger (mean 48 years old compared to 52.3 years old), more likely to have been unemployed, incarcerated, and have less income compared to the substance non-users. There were no significant differences in sex and education level between current substance users and non-users. The mean systolic/diastolic blood pressure measured among substance non-users was 201.3/122.6 mm Hg and 203/124.2 mm Hg among users. There was no difference in the prevalence of end stage renal disease and HIV by substance use status. Smoking tobacco and heavy alcohol use were more common among the substance users. Duration of hypertension, severity of the disease, and costs associated with medications and health services were similar by substance use status.

Current substance users differed from non-users in several ways. Alcohol consumption was more common among current substance users than non-users (Table 1). Substance users tended to be discharged on fewer medications than non-users and were more likely to have difficulty finding pharmacy near them compared to non-users. There were significant differences in the lifestyle habits. Current substance users were more likely to add salt to their food (p value < 0.01) and consume more canned foods (p value = 0.01). Mortality was significantly higher among substance users (52.5%) compared to non-users (33.8%) (p value = 0.01).

Figure 1 shows survival among current and non-substance users. The median survival time for substance users was 5.6 years and the median survival of non-users was 7.1 years. Survival was significantly lower among substance users than among non-users (Log rank test, p = 0.01). Figure 2 shows survival time among current substance users, former substance users, and never users. The former substance users were more likely to die initially but then their risk of dying leveled off after the first year.

3.2 | Stratified analysis by substance use adjusting for potential confounders

Table 2 shows the risk of premature death among substance users when compared to the non-users, stratified by the current use of cocaine, heroin, or both. The risk of dying was approximately 2.5–2.75 times higher among current users of cocaine, heroin, and both than the risk observed among never-users after adjusting for age, sex, comorbidities and severity of disease (HR (95% CI) for cocaine user = 2.52 (1.38–4.59), HR (95% CI) for heroin use = 2.47(1.42–4.28), HR (95% CI) for both = 2.75 (1.60–4.73)). A similar pattern was seen for tobacco users: the mortality rate was higher among current tobacco users compared to never users, adjusting for age, sex, comorbidities and disease severity.

3.3 | Influence of adjusted effect modifiers on substance use

Table 3 shows the multivariable logistic regression using Cox proportional hazards model. After adjusting for age, sex, and comorbidities, we observed that the mortality rate was twice as high among current substance users as compared with non-users (p value = 0.001). After controlling for potential confounders, we found that the effect of

TABLE 1 Baseline characteristics among 192 Blacks admitted with severe hypertension to an urban hospital

Characteristics	Overall	No Substance Use	Current Substance Use	p value
N	192	133	59	
Died, N (%)*	76 (39.6)	45 (33.8)	31 (52.5)	0.01
Demographics				
Age, mean (SD)*	50.9(0.9)	52.3 (1.2)	47.7 (1.1)	<0.01
Female (%)	45.3	48.1	39.0	0.2
Finished HS/GED(%)	52.4	52.1	58.6	0.76
Currently employed (%)*	27.6	33.6	20.3	0.04
History of incarceration (%)*	47.9	38.1	60.8	<0.01
Monthly Income ($) (SD)*	672.3 (59.8)	756.4 (80.1)	486.5 (56.8)	0.04
Disease characteristics				
Mean SBP, mm Hg (SD)	201.8 (1.4)	201.3 (1.7)	203.0 (2.4)	0.58
Mean DBP, mm Hg (SD)	123.1 (1.0)	122.6 (1.0)	124.2 (2.3)	0.44
Comorbidities				
ESRD (%)	15.1	17.3	10.2	0.21
HIV (%)	6.3	5.3	8.5	0.40
No. of Medications on Discharge, mean (SD)	2.5 (0.1)	2.5 (0.1)	2.3 (0.1)	0.09
Admissions in last 5 years, mean (SD)	3.9 (0.30	3.9 (0.3)	3.9 (0.7)	0.93
Medication cost, $ (SD)	54.7 (1.9)	56.1 (2.4)	51.6 (2.8)	0.27
Substance use				
Current tobacco smoking (%)	51.3	42.1	72.4	<0.01
Current cocaine use (%)	19.8	0	65.5	–
Current heroin use (%)	22.7	0	79.3	–
Current heroin or cocaine use (%)[c]	30.7	0	100	–
Current heavy alcohol use (%)[b]	11.5	7.4	18.8	0.09
Adherence to medications				
Hypertension knowledge, (%)[a]	62.6	64.0	64.3	0.96
Misses > 1 apt per 10 (%)	52.0	59.6	65.5	0.47
Runs out of meds > 3 times / year (%)	22.7	23.2	32.4	0.21
Misses at least one dose / week (%)	69.8	68.3	77.6	0.19
Adherence to diet (%)				
Adds salt to food (%)*	46.34	39.7	68.0	<0.01
Fast food (%)	57.5	54.9	67.2	0.12
Fried food (%)	77.8	77.6	84.5	0.28
Canned food (%)*	61.3	54.7	74.1	0.01
Cold cuts (%)	75.0	72.7	79.3	0.25
Changed diet (%)	74.0	74.6	67.2	0.28
Tried to lose weight (%)	39.5	42.9	34.7	0.26
Exercise > 3 times/ week (%)	33.6	35.7	38.3	0.53
Access to care				
Difficulty paying for meds (%)	50.1	53.3	50.0	0.81
Medical insurance[d]				0.78
None (%)	34.7	31.0	39.7	
No medication coverage (%)	7.4	7.1	8.6	
Medication copays (%)	25.5	37.3	1.4	
Full medication coverage (%)	32.6	24.6	37.9	

[a]Hypertension knowledge defined via a set of eight true/false questions.
[b]Current heavy alcohol use defined as greater than one drink per day for women and two drinks per day for men by self-report.
[c]Current heroin and/or cocaine use defined as use of either substance within 2 weeks of hospital admission by self-report or positive urine toxicology.
[d]Insurance status defined through a combination of self-report, chart review, and hospital billing data.
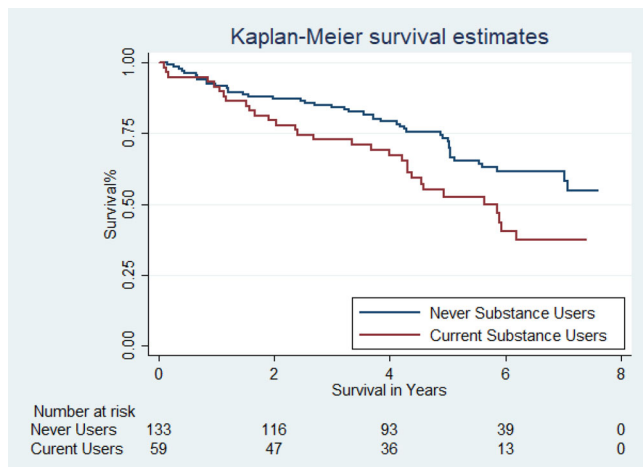
FIGURE 1 Kaplan-Meier plot of survival among 192 severely hypertensive Black patients admitted in an urban hospital by current versus never substance use status. X-axis: indicates event-free survival time; y-axis represents the percentage of patient's event-free survival. The red line represents patient who are current substance users and the blue line represents patients who are not current substance users
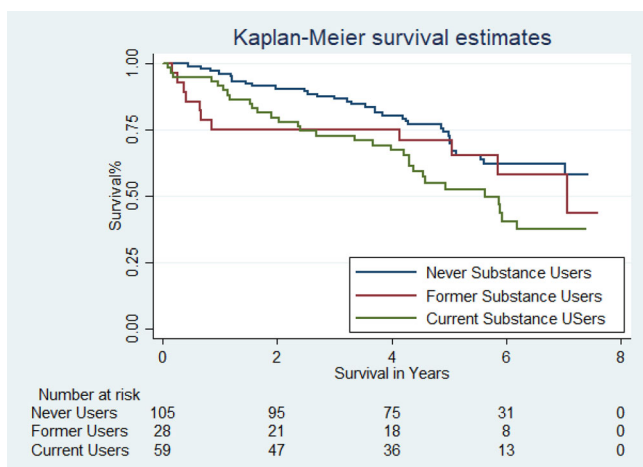

FIGURE 2 Kaplan-Meier plot of survival among 192 severely hypertensive Black patients admitted in an urban hospital, by comparing current substance users versus former versus never users. X-axis: indicates event-free survival time; Y-axis: indicates the percentage of patients' event free survival. The blue line represents patients who are never users, the red line represents patients who were former users and now stopped using and the green line represents patients who are current substance users

substance use on mortality was moderately attenuated by adherence to medications and socioeconomic status. Concurrent use of tobacco and alcohol mildly attenuated the effect of substance use on mortality. Adjustment for disease severity increased the strength of the association of substance use with mortality.

TABLE 2 Risk of dying by substance use status among 192 persons admitted with severe, uncontrolled hypertension[a]

Variable	HR (95% CI)	p value
Tobacco use		
Never	1.00	
Former	1.38 (0.66–2.91)	0.10
Current	2.68 (1.36–5.27)	0.03
Cocaine use		
Never	1.00	
Former	1.39 (0.75–2.56)	0.15
Current	2.52 (1.38–4.59)	0.04
Heroin use		
Never	1.00	
Former	2.01 (0.93–4.38)	0.06
Current	2.47 (1.42–4.28)	0.002
Heroin and/or cocaine use		
Never	1.00	
Former	1.34 (0.66–2.72)	0.37
Current	2.75 (1.60–4.73)	0.04
Heavy alcohol use	1.67 (0.84–3.33)	0.10

[a]Adjusted for age, sex, and comorbidities. Those who never used the substance are the reference.

TABLE 3 Risk of dying by substance use status among 192 persons admitted with severe, uncontrolled hypertension adjusted for age, sex, and comorbidities, other substance use, disease severity, SES, Adherence to medications and lifestyle, access to care

Model	HR (95% CI)	p value
Model 1	2.35 (1.44–3.84)	0.001
Model 2	2.05 (1.23–3.42)	0.005
Model 3	2.63 (1.56–4.42)	<0.001
Model 4	1.94 (1.15–3.28)	0.013
Model 5	2.16 (1.31–3.58)	0.003
Model 6	2.31 (1.39–3.84)	0.001
Model 7	2.19 (1.33–3.59)	0.002
Model 8	2.11 (1.21–3.69)	0.008

Model 1: General baseline – age, sex, comorbidities like HIV, ESRD; Model 2: Other substance use – age, sex, co-morbidities, current tobacco use, heavy alcohol use; Model 3: Disease Severity- age, sex, disease severity, co-morbidities, number of medications on discharge, number of admissions past 5 years; Model 4: Socioeconomic Status – age, sex, co-morbidities, education, employed, history of incarceration, income; Model 5: Adherence to medications- age, sex, co-morbidities, missed medications prior to admission, runs out of prescription 3 or more times per year, misses a dose of medication every week; Model 6: Adherence to lifestyle- age, sex, comorbidities, adds salt, tried losing weight, changed diet, exercises at least 3 times/week; Model 7: Access to care- age, sex, co-morbidities, missed medications prior to admission, runs out of prescriptions 3 or more times per year, missed a dose of medication every week; Model 8: Combined model- age, sex, co-morbidities, employed, cost of medications on discharge, current tobacco use, misses a dose of medication every week, adds salt, unable to afford medications.

TABLE 4 Cause specific mortality of deaths among both substance user and non-users

Cause of death	Number of deaths among non-substance user	Number of deaths among current substance user	Total
CVD	18(40%)	14(45.1%)	32(42.1%)
ESRD	10(22.2%)	5(16.1%)	15(19.7%)
Infection	9(20%)	4(12.9%)	13(17.1%)
Other	6(13.3%)	3(9.6%)	9(11.8%)
Over Dose	1(2.2%)	3(9.6%)	4(5.3%)
Diabetes	1(2.2%)	2(6.5%)	3(3.9%)
Total	45	31	76

3.4 | Cause-specific mortality

Table 4 shows the cause specific mortality among the substance users and non-users. Roughly 68% of the deaths among the 31 substance users who died were due to cardiovascular diseases including hypertensive urgency, aneurysm, hemorrhagic or ischemic stroke, myocardial infarction, congestive heart failure, diabetes, and end stage renal disease. Only 6.5% died due to overdose. Cardiovascular diseases were the leading cause of death among non-users as well. Further, a sensitivity analysis stratified by cardiovascular versus non-cardiovascular mortality showed that the hazard ratio was 1.26 (0.48, 3.32, p value = 0.64) vs. 0.53 (0.23, 1.24, p value = 0.14), respectively, indicating the importance of adherence for management of chronic conditions.

4 | DISCUSSION

Among urban-dwelling African Americans patients admitted with severe, poorly controlled hypertension, 31% were current illicit substance users. The long-term mortality among substance users was high, reaching 53% over 7 years of follow-up. The risk of premature death among substance users was twice that of non-users. The leading cause of death was cardiovascular diseases among both users and non-users, which accounted for the majority of the deaths.

We and others have shown that nonadherence to medications is a major risk factor for mortality among urban black Americans with hypertension.[9,21,22] Furthermore, we have examined factors related to nonadherence and found that poor access to medications was common and associated with higher odds of missed medication and with running out of pills. We further identified ambivalence about taking hypertension medicines as key driver of nonadherence. Factors related to ambivalence included lower hypertension knowledge, forgetfulness, the experience of side effects, and attitudes about medications.[9] Here, we have identified substance use as another important factor impacting mortality among hypertensive patients.

Our analysis suggests that those with poorly controlled blood pressure and using substances are at elevated risk for premature mortality. Long-term use of substances like cocaine can hasten left ventricular hypertrophy and renal arteriosclerosis through repeated vasoconstriction and spikes in blood pressure.[23–25] In addition to the patho-

physiologic changes, our findings suggest that substance use may interfere with adherence to medications and an anti-hypertensive lifestyle, including the adoption of a healthy diet, resulting in a higher burden of illness.[26,27] Other investigators suggest that the competing demands associated with drug seeking and drug use on the one hand, and medication regimens on the other, may converge with ambivalence about treatment and the compromised judgement emerging from substance use, all of which may lead to medication nonadherence.[12,21,28,29] However, it is not only the individual risk factors that are associated with poor health outcomes but also social factors such as low socioeconomic status, homelessness, incarceration, discrimination, lack of social support, and residential segregation that are determinants of both individual substance-use behavior and poor health outcomes.[30–32] In our study, nonadherence modestly attenuated the association of substance use with mortality. This suggests that the influence of substance use on premature mortality among severely hypertensive African Americans who are substance users may be operating through other mechanisms. A critical implication of this finding is that supporting adherence among hypertensive patients who are actively using substances requires a multi-pronged approach that must be combined with ongoing efforts to engage patients in treatment for substance use. One possible strategy entails an adaptation of the collaborative care model that incorporates behavioral health specialists with expertise in substance use among those with poorly controlled hypertension and other chronic conditions in inpatient and outpatient settings.[33,34]

Mortality during the first year of follow-up was highest among former substance users compared to current users and never users (Figure 2). This trend may reflect a similar pattern that has been observed among tobacco users: namely, sicker patients tend to quit smoking and using substances, but have a higher mortality than healthier patients due to their underlying health conditions.[35,36] Therefore, quitting substance use may be an indicator of increased disease severity. Consistent with this hypothesis, adjustment for disease severity attenuated the association of substance use with mortality, suggesting that patients who are more seriously ill are less likely to be active substance users. Importantly, the risk of dying among former users decreases after the first year, further suggesting that the initial high mortality rate is due to confounding by disease severity. The decrease in mortality after the first year likely demonstrates the benefit of quitting substance use on survival among hypertensive patients.

In accordance with prior work, concurrent use of alcohol and smoking was found to increase the risk of premature death among substance users.[37–41] Notably, substance users were also more likely to add salt to their food, illustrating the clustering of several other unhealthy behaviors alongside substance use.[42] The preponderance of those with substance use who also reported eating canned food is consistent with the presence of a number of social determinants of health, including food insecurity and the paucity of healthier options and presence of food deserts in poor, urban, predominantly African American communities.[43] In our study, we found that poverty reduced the association between substance use and premature mortality. Since poverty is associated with a complex web of factors that impact chronic disease management—including, for example, low income, unemployment, low educational attainment, serial incarceration, poor housing conditions, homelessness, a lack of resources for physician appointments and dearth of funds for purchasing and refilling prescriptions—our findings support the notion that structural factors contribute to the association between substance use and premature mortality among African Americans with hypertension.

5 | LIMITATIONS

There are several important limitations to this study. First, the study population was restricted to severely hypertensive African Americans who live in a major metropolitan area. Therefore, these results might not generalize to other racial/ethnic groups residing in non-urban areas or to those grappling with other chronic conditions. Hence to validate this results, further research involving a control group of non-hypertensive participants with substance use is required. Second, internalized stigma may have led to under-reporting of substance use. The addition of urine toxicology as an objective evaluation of substance use mitigated this limitation. Third, we measured substance use at only one point in time. It is notable, however, that a single measure of substance use was strongly associated with mortality years out from the assessment. Fourth, we could not adjust for dyslipidemia in our analyses as we did not measure lipids in our participants. Fifth, missing data could have biased our results. This was addressed through the use of multiple imputation methods, which provide conservative, non-biased estimates of missing values. Sixth, our sample size was small, which decreased the precision of our estimates and decreased power to detect associations.

6 | CONCLUSIONS

Among a sample of African Americans with severe hypertension who resided in an urban area, we found that substance use was a strong predictor of premature mortality. Current users had twice the risk of mortality than former and never-users. Importantly, former users had decreased mortality after an initial period of increased mortality, likely due to confounding by disease severity. While our findings indicate that substance use increases cardiovascular disease mortality, it is also imperative to mention that the root causes of negative social determinants of health such as living in the neighborhoods that have faced systemic racism and disinvestment, led to health disparities and thereby poorer health outcomes in this population. Therefore, the increased mortality is not related to race or to the fact that African Americans are more prone to hypertension, but rather that the sum of social and structural determinants of health affect impact life expectancy regardless of race. Hence, our data suggest the need to develop, implement, and evaluate interventions that dually attend to substance use and social determinants of health. Doing so may reduce the seemingly intractable burden of early mortality among substance users residing in historically disinvested communities.

AUTHOR CONTRIBUTIONS

V.V.- Conception, design, analysis, and interpretation of data, writing and revising manuscript. J.Y.- Conception, design, reviewing and editing the manuscript. C.I.- Writing, editing, and revising the manuscript. All authors contributed to the manuscript and approved the submitted version.

CONFLICT OF INTEREST

No Conflict of interest

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