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The Impact of Cocaine Use and the Obesity Paradox in Patients with Heart Failure With Reduced Ejection Fraction due to Non-Ischemic Cardiomyopathy.

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Abstract

The Impact of Cocaine Use and the Obesity Paradox in Patients with Heart Failure With Reduced Ejection Fraction due to Non-Ischemic Cardiomyopathy.

By Adedoyin A. Akinlonu

Background: Obesity and illicit drugs are independent risk factors for developing heart failure. However, recent studies have suggested that patients who already have heart failure and are obese have better clinical outcomes; this has been called the obesity paradox. There currently exists a paucity of data on cocaine use and heart failure outcomes. Also, the effect of cocaine use on the obesity paradox has not been studied. **Objectives:** To assess the impact of cocaine use on the obesity paradox in patients with heart failure with a reduced ejection fraction (HFrEF) due to non-ischemic cardiomyopathy. **Methods:** In a single-centric, retrospective chart analysis, we reviewed all patients with ICD-10 codes for the diagnosis of HFrEF who were admitted at Metropolitan Hospital in New York City between 1/2013 and 12/2016. We studied the association between Body Mass Index (BMI) categories: non obese (<30 kg/m^2) and obese (>30 kg/m^2), cocaine use, and the primary outcome (30-days readmission). The interaction between cocaine use and obesity status, and its association with the primary outcome was also assessed. **Results:** 261 patients were identified; low BMI and cocaine use were associated with an increased hazard of readmission in 30-days for all subjects (HR: 2.28, 95% CI: 1.03 – 5.20; p=0.049 and HR: 3.12, 95% CI: 1.42 - 6.86; p=0.004, respectively). In addition, cocaine users who were non-obese were over 6 times more likely to be re-admitted in 30-days compared to non-cocaine users who were obese (HR: 6.45, 95% CI: 2.39 – 17.41; p=0.0002). **Conclusions:** Low BMI and continued use of cocaine have a negative additive effect in impacting heart failure outcomes.

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Introduction

The economic burden of heart failure (HF) in the United States (US) was estimated at $20 billion in 2012; this amount is projected to reach about $53 billion by 2030 (1). Much of this cost is a result of emergency department visits and hospital readmissions, with about 25% of HF patients being readmitted within one month of hospital discharge (1). Measures to reduce the economic burden of HF, which can potentially help with curbing rising healthcare costs in America, have become a priority for the healthcare community nationwide. The Center for Medicare and Medicaid services (CMS) for example has employed the hospital re-admissions reduction program (HRRP), a provision of the Affordable Care Act (ACA), to prevent rehospitalizations by penalizing healthcare entities for readmissions within 30 days of hospital discharge (2). Nonetheless, hospital readmissions decreased by only 2% two years after HRRP inception in January of 2012 (2). Another initiative that could be beneficial is modifying some of the social and behavioral risk factors that predispose to HF readmissions. Obesity is considered an independent risk factor for cardiovascular disease; its age-adjusted prevalence in the US reached an estimated 40.6% in 2018 (3). However, in persons who already have cardiovascular disease, obese or overweight status seems to be associated with better prognosis compared to normoweight, a phenomenon labeled as the obesity paradox (4). Use of illicit drugs like cocaine has also been associated with poor overall cardiovascular outcomes (5), however, there is paucity of data on the association of cocaine use with HF outcomes after index hospitalization. Given the rising rate of obesity and substance abuse in the US (5), an understanding of the roles these factors play in hospital readmissions among patients with HF can potentially inform a targeted public health action towards reducing rehospitalization. This article will focus mainly on the association of cocaine and obesity with outcomes in patients with HF with reduced ejection fraction (HFrEF) secondary to Non-Ischemic Cardiomyopathy (CM).

Literature Review

Definition and classification of HF

HF is a clinical syndrome that results from a dysfunction in the heart's ability to pump or to be filled with blood with associated clinical, laboratory and/or imaging evidence including but not limited to breathlessness, elevated natriuretic peptide level and vascular congestion on chest imaging (6,7). This distorted structural and physiological function of the heart may result from co-morbid conditions such as hypertension, diabetes, arrhythmias and coronary artery disease (6,7). The etiology of HF has traditionally been classified into two broad categories: Ischemic CM and Non-Ischemic CM (8,9). Ischemic CM results from a partial or total occlusion of one or more coronary arteries that supply blood and oxygen to a part of the heart muscle, leading to myocardial (heart muscle) dysfunction. Non-Ischemic CM causes include valvular dysfunction, hypertension, viral injury, stress, obesity, direct toxic effect (as from illicit drug use), and others (8,9). Regardless of the cause of HF, the degree of ventricular dysfunction in patients varies, and thus they are further classified as either having a preserved ejection fraction (HFpEF, if EF >40%) a reduced ejection fraction (HFrEF, if EF <=40%) or a mildly reduced ejection fraction (HFmrEF, if EF is 41% to 49%). Other symptoms experienced by patients with HF include fatigue, weakness, swelling of the abdomen, legs, and ankles, as well as an increased need to urinate at night (7–9).

Epidemiology and Economic Burden of HF

The global prevalence of HF was estimated to be 37 million people in 2016 and about 6 million of these individuals reside in the US (1,10). The prevalence of HF in the US is projected to increase by 25% in the year 2030; this means that more than 8 million people in the US will be suffering from HF in the next 10 years (1,10). Despite advancements in medical diagnostics and

therapeutics, rehospitalization for HF remains a challenge across health systems in America. An estimated 25% of Medicare patients will have a HF readmission within 30 days of discharge from HF hospitalization (2,11). The public health implications of this are many, including reduction in workforce and manpower, an increase in annual direct and indirect medical costs of HF, increase in overall healthcare costs in the US and diversion of funds from important sectors of the economy. Thus, new strategies are needed to curb the growing readmission rates and resulting cost burden.

Current Readmission Reduction Initiatives.

The HRRP was instituted by policy makers due to the perception that rehospitalizations were largely driven by poor in-hospital quality of care and could be avoided by quality improvement programs (11). The HRRP usually risk adjusts the 30-day readmission rates by patients' characteristics such as age, sex, and medical comorbidities (2,11). Studies that evaluated the impact of HRRP found that the program achieved a very limited success as all-cause readmission rates fell only 2% since inception, and HF readmissions saw only a 9% reduction compared to the 25% goal (2,12,13). While poor inpatient care, especially in low resource hospitals, is a major contributing factor to rehospitalization, a myriad of other external factors like socio-behavioral influences needs to be considered. Exacerbations of HF that lead to readmission can result when people engage in high-risk behaviors like eating unhealthy diet, physical inactivity, and abusing illicit drugs.

Assessing Behavioral Risk Factors for HF.

In the US, more than 30% of adults do not engage in physical activity, and about two-thirds are either overweight or obese (3,14). Obesity affects the body's hemodynamics including a leftward shift of the Frank-Starling curve secondary to increased blood volume, ultimately leading to left ventricular dilation and hypertrophy (15,16). The resultant heart muscle remodeling causes a distortion to its pumping or relaxing ability, leading to HF. The obesity paradox, which refers to the lower risk of adverse outcomes for people with HF in the overweight and obese categories, was first postulated by researchers at the turn of the millennium (17,18). Horwich et al studied about 1200 patients with advanced HF due to multiple etiologies and found higher body mass index (BMI) to be associated with a trend towards better survival (17). This finding has been corroborated by other studies like the CHARM trial (19) and the ADHERE registry (20).

The exact mechanism for the beneficial effect of obesity on the survival of patients with HF is still not well understood, however, researchers have proposed that the metabolic reserve conferred by high BMI protects patients from the high catabolic state of HF (21–23). Furthermore, it was postulated that some neuroendocrine profiles of the adipose tissue in obese patients help neutralize inflammatory cytokines like tumor necrosis factor alpha, which is known to negatively impact the outcomes of patients with HF (21,24). In addition, obese patients tend to have higher arterial blood pressure, making them more tolerable to higher doses of GDMT for HF, which could potentially lead to favorable outcomes (25).

A rising trend was observed for cocaine use among adolescents in the U.S between 2012 – 2018, and it accounted for thousands of disability-adjusted life years (26,27). Left ventricular systolic dysfunction is one of the many cardiovascular complications associated with cocaine use and the severity of myocardial dysfunction is directly related to the number of years a person has

actively used cocaine (28). Cocaine prevents presynaptic reuptake of catecholamines, thus enhancing their sympathomimetic activity. Moreover, the metabolism of accumulated catecholamines releases toxic substances that affect cardiac myocytes by causing oxidative stress and mitochondria dysfunction (29,30). In addition, heavy cocaine use alters the body's intracellular calcium levels, which results in a negative inotropic effect, worsening HF symptoms (5,31). Indeed, continuous use of cocaine in patients with HF increases the risk of rehospitalization after a HF-related admission (32).

Hypothesis

Improving the quality of life of patients with HF and curbing the associated costs to the economy is highly dependent on reduction in symptoms and number of hospitalizations through optimal inpatient clinical care, adherence to guideline directed medical therapy and modification of the risk factors that predispose to HF exacerbation. Since obesity has been shown to provide a protective effect for patients with existing HF diagnosis, whereas cocaine has shown deleterious effects on HF outcomes, we aimed to study the impact of cocaine use on the obesity paradox phenomenon. We hypothesized that the obesity paradox (worse outcomes in normoweight vs overweight/obese) will be stronger in cocaine users than in non-users due to a combined negative effect of cocaine use and low body mass index.

Methodology

This was a single-centric, retrospective chart review and analysis of adult patients (age ≥ 18 years) with HFrEF treated at Metropolitan Hospital Center in New York City between January 2013 and December 2016. Patients were included in the study if they were age 18 and above, had history of HF with ejection fraction less than or equal to 40% and were admitted with an HF exacerbation diagnosis. Patients with coronary artery disease, volume overload for any reason other than HF, patients with end-stage renal disease, pregnant patients and patients with life expectancy less than 30 days were excluded. Manual review of the patient's chart was used to retrieve demographic information, echocardiographic measurements as well as clinical and laboratory parameters. Active cocaine use was derived from the medical chart information and defined as either self-reported continued cocaine use, or the finding of cocaine consistently in urine drug screen of the patient. Obesity was defined as a body mass index (BMI) >30 kg/m^2, calculated using patient's recorded weight and height on index admission. Model parameters included age, race, sex, obesity status, cocaine use, ejection fraction range, serum creatinine and hemoglobin level, clinic follow-up and medical co-morbidities including diabetes and hypertension. The primary outcome was time to readmission for HF as documented in the electronic medical record. Readmission was defined as presentation with symptoms and laboratory findings consistent with HF (dyspnea, asthenia, decreased exertional tolerance or evidence of fluid retention, elevated natriuretic peptide level) within 30 days post last hospital discharge for an HF admission.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation if following normal distribution or medians and interquartile range if not; normality was assessed through normality plots. Categorical variables were expressed as frequencies and percentages. Difference between groups for continuous variables was determined through the independent Student t-test; difference in categorical variables was assessed through χ^2. Univariate analysis to assess the unadjusted relationship between obesity and the study outcome was performed through Kaplan-Meier survival curves and log-rank testing. Survival time was calculated as time from hospital discharge day to date of readmission or last day of observation. The proportional hazards assumption was assessed using log-log plots. Multivariable analyses were performed through Cox regression with stepwise selection. The chunk test was performed to determine effect modification by cocaine of the association between obesity and the primary outcome using likelihood ratio to test significance of the interaction term. All analyses were carried out using SAS software, version 9.4 - 2013 (SAS Institute Inc., Cary, NC, USA).

Results

480 patients with HFrEF were identified and 219 were excluded due to volume overload for reasons other than HF, a history of CAD, life expectancy less than 30 days or missing data, leaving 261 subjects. The clinical characteristics of the study subjects are summarized in Table 1 under the appendix section.

The mean age for our population was 59±12.6 and 78% of the patients were male (Table 1). The prevalence of obesity was 43%. Thirty-two patients (12.3%) were readmitted within 30 days. Patients who were readmitted had a significantly lower BMI than those who were not readmitted (26.3±5.0 vs 30.5±8.1; p=0.002). For the entire study cohort, 19.2% were cocaine users. The number of cocaine users did not differ significantly between the obese and non-obese group.

Kaplan Meier survival estimates comparing obese and non-obese patients revealed that obesity was associated with a reduced risk of hospital readmission for HF post hospital discharge (p=0.025) – figure 1. The hazard for 30-day hospital readmission for non-obese patients was 2.4 times the hazard for obese patients (95% CI: 1.09 – 5.38) – table 2. A separate Kaplan Meier survival estimates comparing cocaine vs non-cocaine users showed increased risk of HF readmission among cocaine users (p=0.015) – figure 2. Univariate analysis showed cocaine users were 2.4 times more likely to be readmitted compared to non-cocaine users (95% CI: 1.16 – 4.97) – table 2.

We further assessed these findings through multivariate analysis by Cox regression with stepwise selection of model parameters. No significant interaction was found between obesity and cocaine use by the likelihood ratio test, so the interaction parameter was dropped, and a reduced model was used. After adjustment, obesity and a no-cocaine use status remained beneficial for HF prognosis in our study. In particular, the hazard for hospital readmission for subjects in the non-

obese group was more than double the hazard for those in the obese group (HR: 2.28, CI: 1.03 – 5.20) – table 3. Adjusted survival curve supports this finding with non-obese subjects having shorter time to readmission compared to obese patients – figure 3. The deleterious effect of cocaine use remained after adjustment for covariates (HR: 3.12, 95% CI: 1.42 – 6.86) – table 3. The results also revealed that for every 1 g/dl increase in hemoglobin, the likelihood of readmission was reduced by 18% (HR: 0.82, 95% CI: 0.71 – 0.98). Furthermore, for every 10 mmHg increase in systolic blood pressure, the hazard of rehospitalization was reduced by 14% (HR: 0.86, 95% CI: 0.75 – 0.97). We found no statistically significant effect of increasing age on the hazard of hospital readmission.

A sub-analysis of the combined effect of cocaine use and obese status on 30-day re-admission was performed by dividing the subjects into 4 categories namely – Non-obese/Cocaine (Group 1), Nonobese/No cocaine (Group 2), Obese/Cocaine (Group 3), Obese/No cocaine (Group 4) – table 4. Subjects in group 4 were used as the reference category for the Cox regression sub-group analysis, adjusting for covariates in the model. We found that subjects who were in the non-obese/cocaine group were more than 6 times as likely to be readmitted in 30-days post hospital discharge compared to subjects who are in the no cocaine/obese group (HR:6.45, 95% CI: 2.39 – 17.4) – table 4. This was also reflected in the adjusted survival curve that explored the interaction between the 2 variables – figure 4.

Discussion

The association between obesity and HF survival has been well studied, though its implications remain very contentious (33,34). A study by Mandviwala et al did find a protective effect of obesity on mortality among patients with HFpEF, but the opposite was the case with hospital readmission, as the authors reported that an increasing BMI independently increased the risk of HF rehospitalizations (35). Similarly, Zamora et al's study on obesity status and HF outcomes showed mixed results. They found a non-statistically significant association of obesity status and HF readmission among patients with Ischemic CM across the BMI spectrum, while the obesity paradox was significantly demonstrated among the cohort with non-ischemic CM (36). The latter is consistent with the findings of our study which focused on patients with non-ischemic CM. The varied conclusions from the several studies of the effect of obesity on HF outcome suggests that the etiology of HF might be a key factor in determining how and when the obesity paradox phenomenon can be applied (36).

In view of the increase in the number of illicit drug users in the US in recent years (26,27), studies that explore the varying cardiotoxic effect of cocaine to educate the public are imperative. While a vast literature on the association between cocaine use and cardiovascular diseases exists, studies on the prognostic implication of cocaine use specifically on patients known to have HF is scarce (37). Our study found cocaine use to be an independent predictor of HF readmissions, an association that was expected given prior reports of cocaine's adverse effect on general cardiovascular outcomes (38). Cocaine's deleterious effect on the heart is known to be enhanced by the presence of other toxic drugs (39), however, we found no study that has investigated the interaction of cocaine with other research proven predictors of cardiovascular outcomes. Though there was no modifying or confounding effect of cocaine use on the obesity paradox phenomenon,

our analysis revealed that patients who used cocaine and were non-obese had a higher rate of hospital readmission compared to patients who were obese and did not use cocaine. This finding implies the possibility of a negative additive effect of cocaine use and a non-obese status on HF outcomes.

It was not surprising that we found a reduced likelihood of hospital readmission with increasing hemoglobin level. Anemia in HF patients is multifactorial and could result from functional iron deficiency due to chronic inflammation, low erythropoietin production that occurs from cardio-renal syndrome and a tendency for bone marrow unresponsiveness (40,41). The resulting low hemoglobin leads to a significantly reduced oxygen carrying capacity of the blood, putting undue pressure on the heart to increase cardiac output. This can worsen the function of an already compromised left ventricle (40,41). Several studies have corroborated this association (42–44). The probability of HF hospitalization and mortality was found to be higher among HF patients with anemia compared to those without anemia across the HF spectrum in a large Swedish HF registry study (44). As was pointed out earlier, patients who are hypertensive are more tolerable to guideline directed medical therapy (GDMT) than patients who are of a lower blood pressure. Thus, patients with high blood pressure are likely to adhere to GDMT resulting in less likelihood of hospital readmission.

Implications and Recommendations

The beneficial effect of a high BMI in reducing re-admissions after a heart failure related hospitalization is not altered by active cocaine use. In addition, non-obese patients who are active cocaine users are at very high risk of being re-admitted in the short term. While our study found obesity status to be protective of HF readmission, the single-centric nature of the study precludes establishing definitive conclusion about causal association. We recommend more multi-center studies that evaluate potential mechanism that explains the obesity paradox phenomenon and its interaction with other readmission risk factors. Given that patients who are both non-obese and abuse cocaine have worse survival, these group of patients need to be followed more closely post discharge. Care team need to ensure that follow-up clinic appointments are kept, and that patients adhere to GDMT and optimal calorie intake. Enrolling such patients in post discharge transition of care with a community nurse navigator could be rewarding for the health system. The hematocrit level of HF patients admitted for exacerbation should be optimized prior to discharge; most guidelines recommend a hemoglobin level of 8 g/dl to reduce the workload on the heart. Since iron deficiency is one of the culprits of anemia in HF patients, experimental studies to test the beneficial effect of IV iron infusion in HF patients may be worthwhile.

Study Limitations

This is a retrospective chart review, which limits the available information regarding adherence to GDMT, frequency and route of cocaine use, and pre-HFrEF BMI. Moreover, anthropometric parameters used for analysis were those recorded on admission, and thus we assumed there were no changes in value of these parameters during admission. In addition, the use of other anthropometric measures of obesity like waist/hip ratio may yield a different outcome than using BMI. Since the study was limited to just one of the several New York City hospital corporation facilities, we could not ascertain if patients were readmitted to the other health system facilities. Also, death of a patient before readmission is a competing risk that was not adjusted for in this study. Finally, because it is not a randomize study, we are not able to draw definitive conclusions regarding association between variables.

Conclusion

In summary, a low BMI is independently associated with a higher likelihood of 30-day hospital readmission among patients with HFrEF. Furthermore, continued cocaine use potentiates the effect of a low BMI on the risk of readmission after an acute HF hospitalization. Treatment of patients with anemia and hypotension should be optimized prior to hospital discharge. Further multicenter studies are needed to corroborate these findings.

Appendix

Table 1. Baseline characteristics of patients by obesity status as defined by BMI.

Variable	All Patients (n = 261)	Obese (n = 113)	Non-Obese (n = 148)	P-value
Age (±SD), years	59 (±12.6)	56.3 (±11.6)	61 (±13)	***0.002****
Male Gender	204 (78.2%)	81 (71.7%)	123 (83.1%)	***0.03****
Race				***0.02****
AA	128 (49.1%)	62 (54.9%)	66 (44.6%)	
Hispanic	89 (34.1%)	27 (23.9%)	62 (41.9%)	
White	10 (3.8%)	6 (5.3%)	4 (2.7%)	
Others	34 (13%)	18 (15.9%)	16 (10.8%)	
BMI (±SD)	30 (±7.9),	37.2 (±6.5)	24.5 (±3.0)	***<0.001****
Diabetes	93 (35.6%)	53 (46.9%)	40 (27%)	***0.001****
Length of Stay (±SD)	4.6 (±4)	4.9 (±4.5)	4.5 (±3.8)	0.42
1 Week Follow-up	58 (22.2%)	24 (21.2%)	34 (23%)	0.76
Systolic BP (±SD)	144 (±29)	145 (±30)	143 (±27)	0.61
Ejection Fraction (%)				***0.03****
<25	142 (54%)	56 (49.6%)	86 (58.1%)	
25 - 34	81 (31.7%)	33 (29.2%)	48 (32.4%)	
35 - 40	38 (14.3%)	24 (21.2%)	14 (9.5%)	
Serum Creatinine (±SD)	1.42 (±0.95),	1.43 (±0.75)	1.42 (±1.08)	0.93
Hemoglobin (±SD)	12.4 (±2.05)	12.2 (±2.1)	12.4 (±2.0)	0.37
Cocaine Use	50 (19.2%)	21 (18.6%)	29 (19.6%)	0.88

Figure 1: Crude Curve of The Association Between Obese Status and Primary Outcome

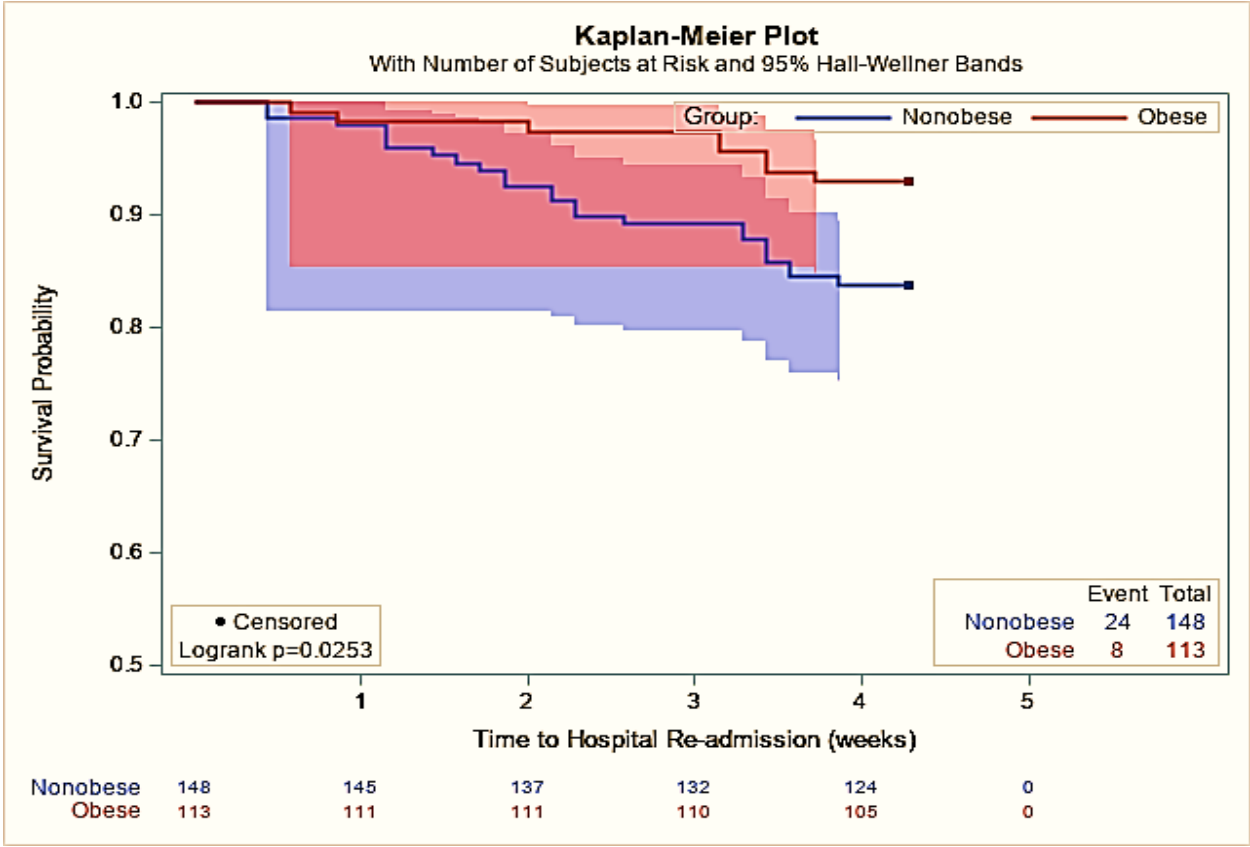


Table 2: Unadjusted Hazard Ratios of 30 days Readmission for HF

Parameter	HR	95% CI
Non-obese vs Obese status	2.42	1.09 – 5.38
Cocaine vs No cocaine	2.40	1.16 – 4.97
Age (per year)	1.02	0.99 – 1.05
LOS (per day)	0.88	0.75 – 1.02
SBP (per mmHg)	0.99	0.98 – 1.00
Hb (per g/dl)	0.89	0.76 – 1.03

*LOS – length of stay; SBP – systolic blood pressure on admission
*Hb - hemoglobin

Figure 2: Crude Curve of The Association Between Cocaine Use and Primary Outcome

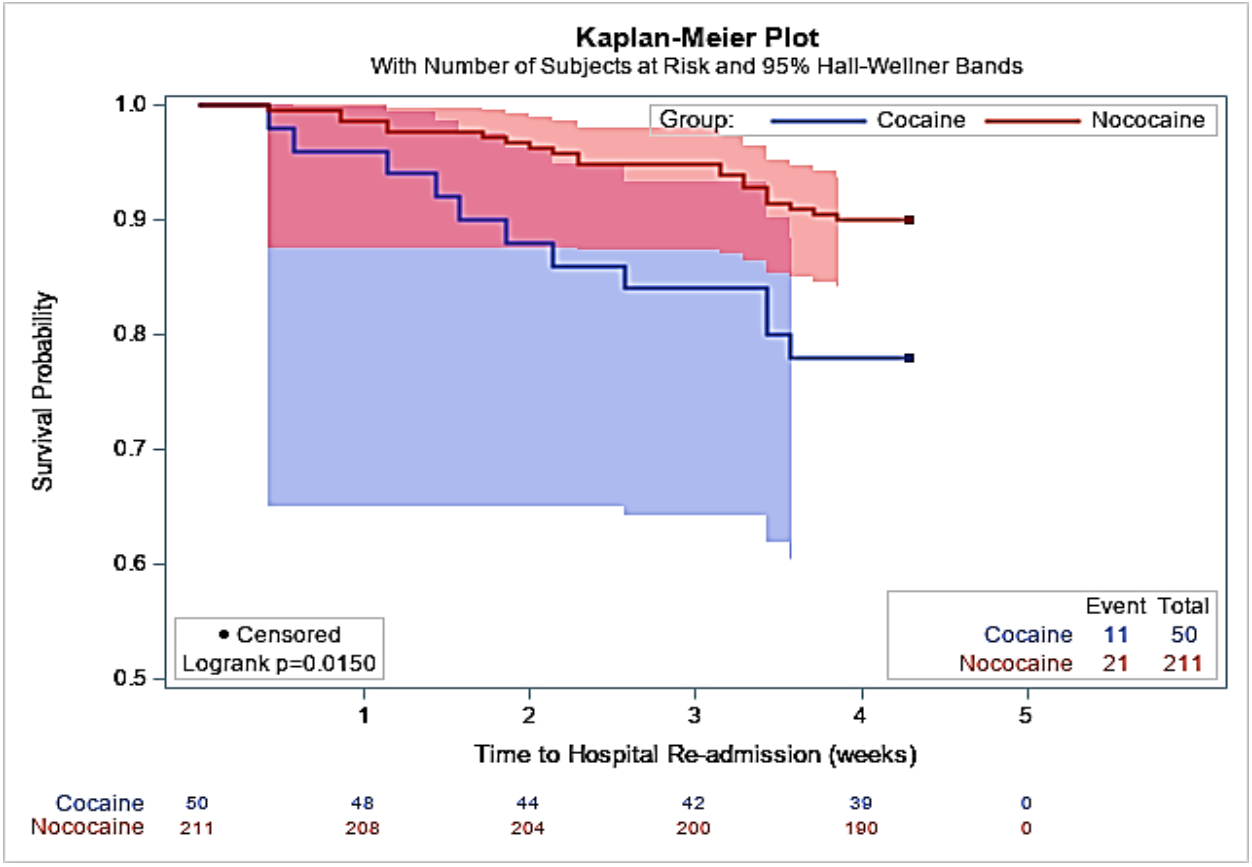


Table 3: Adjusted Hazard Ratio of 30 days Readmission for HF

Parameter	HR	95% CI
Non-Obese vs Obese status	2.28	1.03 – 5.20
Cocaine vs No cocaine use	3.12	1.42 – 6.86
Age (per 10 years)	1.30	0.98 – 1.84
LOS (per day)	0.86	0.73 – 1.00
SBP10 (per 10 mmHg)	0.86	0.75 – 0.97
Hb (per g/dl)	0.82	0.71 – 0.98

*LOS – length of stay; SBP – systolic blood pressure on admission
*Hb - hemoglobin

Figure 3: Adjusted Curve of The Association Between Obese Status and Primary Outcome

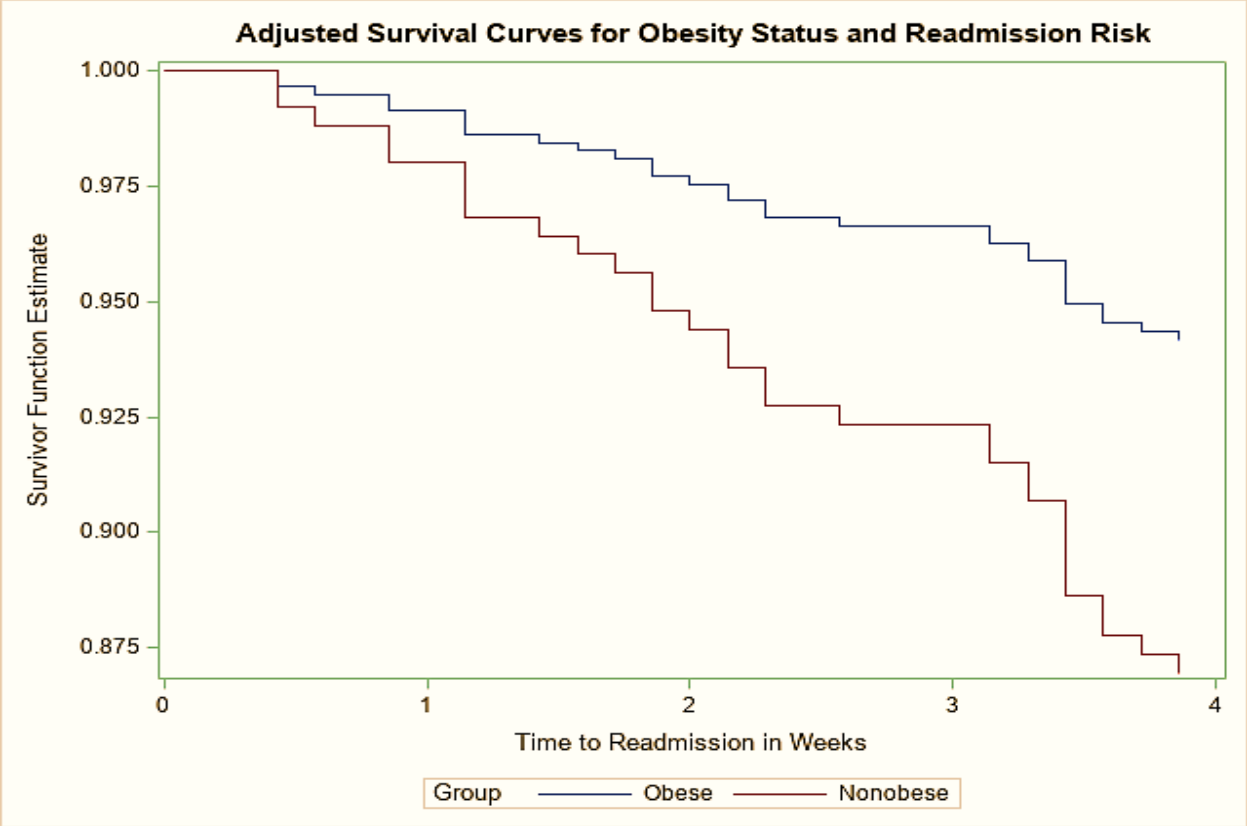
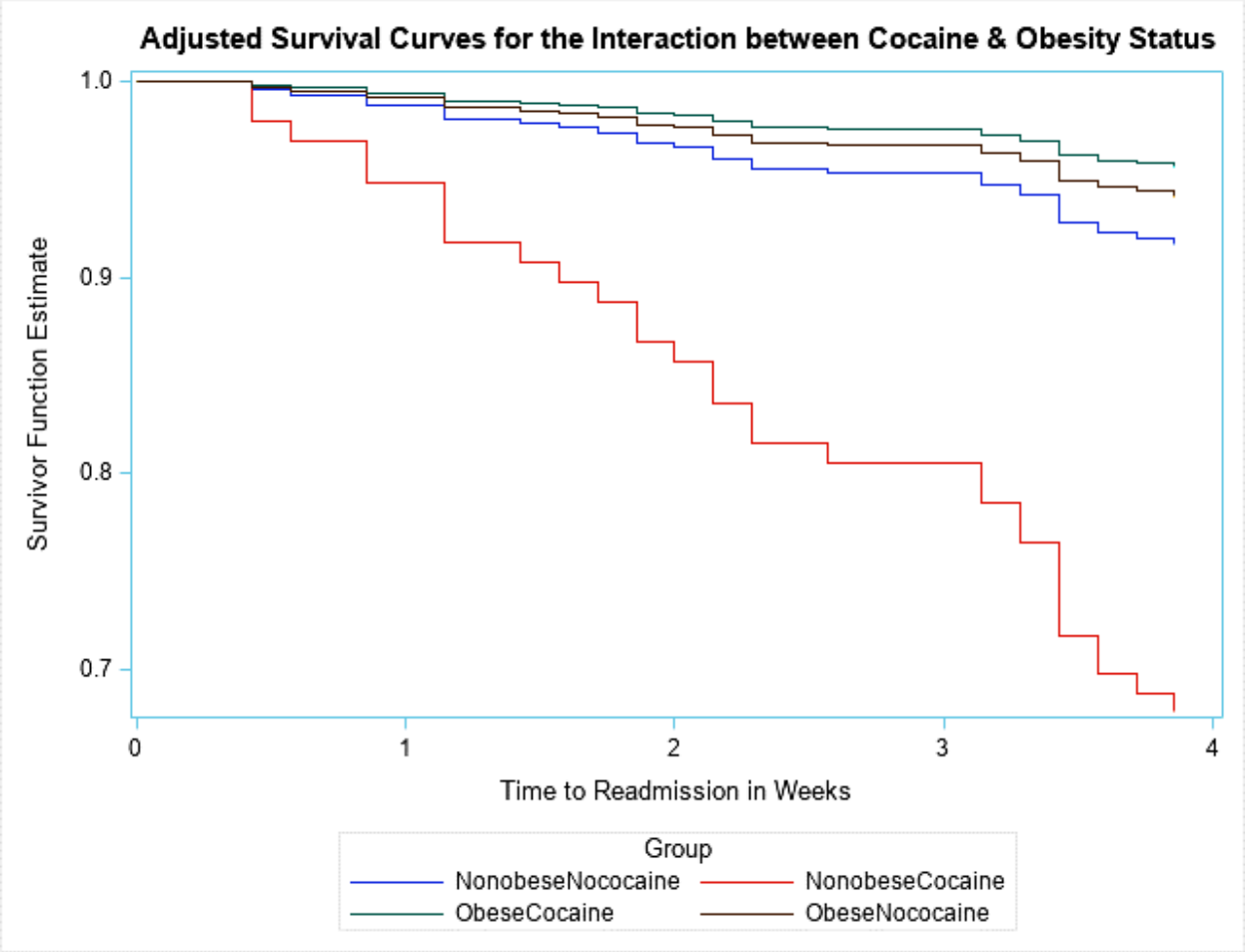


Table 4. Hazard Ratio of 30 days readmission combining Cocaine and Obesity Status*

Parameter	HR	95% CI
Obese/No cocaine	Ref.	-
Nonobese/Cocaine	6.45	2.39 – 17.41
Nonobese/No cocaine	1.44	0.57 – 3.64
Obese/Cocaine	0.74	0.09 – 6.24

*Adjusted for Age, Length of stay, systolic blood pressure and hemoglobin.

Figure 4:


Adjusted Survival Curves for the Interaction between Cocaine & Obesity Status
Survivor Function Estimate
1.0
0.9
0.8
0.7
0
1
2
3
4
Time to Readmission in Weeks
Group
NonobeseNococaine
NonobeseCocaine
ObeseCocaine
ObeseNococaine

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