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Acute-onset heart failure and diabetes mellitus: A multicenter database analysis

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Abstract

Background: Literature regarding outcomes of acute Heart Failure with reduced Ejection Fraction (HFrEF) and acute Heart Failure with preserved Ejection Fraction (HFpEF) in patients with Diabetes Mellitus (DM) is still evolving.

Objective: To study clinical outcomes and all-cause mortality of acute HFrEF and acute HFpEF in DM patients.

Methods: Data from the National Emergency Department Sample (NEDS), which constitutes 20% of Emergency Departments (ED) within the United States (US), was analyzed for hospitalizations related to acute HF and DM using the International Classification of Diseases-10 (ICD-10) codes.

Results: Out of the total 1,479,716 adult acute HF encounters (mean age 69.7±14.9 years, 47.3% females) recorded for the years 2016-2018, 803,308 (54.3%) were acute HFrEF-related, with 317,517 (39.5%) DM-related, while 481,985 (32.5%) were acute HFpEF-related, with 195,945 (40.6%) DM-related. The HFrEF and HFpEF with DM group had higher multi-organ complications including NSTEMI, Acute Kidney Injury (AKI), and AKI requiring hemodialysis. However, the mortality for both HFrEF and HFpEF subgroups were higher compared to DM (5% vs 4.8% and 3.5% vs 3%, respectively, $p<0.001$). HFrEF with DM groups had higher cardiac procedures including stress test, coronary angiography, and PCI (29.9% vs 24.8%, 19% vs 15.4%, and7.6% vs 7%, respectively; $p<0.001$) compared to their counterparts. Similarly, HFpEF with DM groups also had higher cardiac interventions including stress test, coronary angiography, and PCI (19% vs 17.1%, 8.1% vs 7.1%, and 2.6% vs 2.1%, respectively; $p<0.001$) compared to their counterparts.

Conclusion: HFrEF and HFpEF complicated by DM did not show a significant worsening in mortality rates. Given higher ischemic evaluation associated with DM, we suggest more randomized trials to evaluate if procedures had any mortality benefits.

Keywords: Acute Heart Failure with Reduced Ejection Fraction (HFpEF); Acute Heart Failure with preserved Ejection Fraction (HFpEF); Diabetes Mellitus (DM); All-cause mortality; Percutaneous Coronary Intervention (PCI); Coronary Artery Bypass Grafting (CABG).

Introduction

Heart Failure (HF) and Diabetes Mellitus (DM) form a few of the major healthcare burdens in the United States (US) and worldwide. Patient with DM have a 2-fold increase in the risk of developing both variants of HF [1]. It is known that DM is associated with increased fatty acid use by the myocardium, decreased glucose use, increased myocardial oxygen consumption, and decreased cardiac efficiency [1]. According to the CDC, in 2018 there was a prevalence of 34.2 million American living with DM, causing an excess of $327 billion to the American Health system [2]. The National Health and Nutrition Examination Survey 2013-2016 reported that heart failure had a prevalence of 6.2 million patients in the United States, which was higher than 5.7 million for the years 2009-2012 [3,4]. For the year 2015, from amongst the top 10 causes of death in the United States, diabetes mellitus was the 7th and heart failure was the 9th leading etiology. These trends continued in subsequent years.

The ADVANCE trial (target HbA1c of 6.5%) showed that intensive glycemic control did not cause any reduction in macrovascular events [5]. Furthermore, the ACCORD trial showed that a target HbA1c of 6% had an increase in mortality by 22% [6]. A prospective study reported high rates of mortality and complications associated with acute Heart Failure with preserved Ejection Fraction (HFpEF) and acute Heart Failure with reduced Ejection Fraction (HFrEF); however, the studies were small [7]. The Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) study was done for patients who had new-onset heart failure exacerbation, or acute on chronic heart failure [8].

Data regarding the clinical complications, cardiovascular procedures and mortality outcomes in patients with acute HFpEF and acute HFrEF in conjunction with DM could provide information for improving outcomes. Therefore, we aimed to evaluate these factors for the years 2016-2018 from the National Emergency Department Sample (NEDS) database.

Methods

Study population and inclusion criteria

This is an observational cohort study of patients hospitalized for acute HF during the years 2016-2018 in the NEDS database. NEDS has records of patients who present to the emergency department. The information of patients who get admitted to inpatient services is retained for each emergency encounter. The NEDS constitutes an approximately 20% sample of hospital-owned Emergency Departments (ED) in the United States (US) [6]. Using a stratified, random sampling design, a sample of hospital-owned emergency departments from the United States participating in both the State Inpatient Databases (SID) and the State Emergency Department Databases (SEDD) was selected, and 100% of the ED visits the selected hospital-owned emergency departments were retained. Hospitals were included in the NEDS sample

based on geographic region (northeast, mid-west, west, or south), location (urban or rural), teaching status (teaching or non-teaching), ownership (public, private not for profit, private for-profit), and trauma center designation. A total of 950 emergency departments were included in the NEDS. From each selected EDs, all visits were included, which amounted to more than 33 million unweighted visits each year. Patients with age <18 years at the time of presentation were excluded from the study. The study was exempt from institutional review board evaluation however it was performed according to the ethical criteria set up by Healthcare Cost and Utilization Project (HCUP) [6].

Study definitions

Acute HF was defined by International Classification of Diseases-10 (ICD-10) codes of «I50.811», «I50.21», «I50.31», «I50.20», «I50.41» and «I50.40». Patients younger than 18 years (n=1,858) were excluded. Acute HF was further divided into acute HFpEF using ICD-10 code «I50.31" and acute HFrEF using ICD-10 codes «I50.21» and "I50.23». Based on the exclusion, 1,479,910 patients with acute HF were identified. Out of these, 480,157 were acute HFPEF and 462,613 were acute HFREF making a national prevalence of 32.4% and 31.3% respectively among acute HF hospitalizations. Data was verified for patients of chronic heart failure or acute on chronic HF using ICD-10 codes "I50.22», «I50.32», «I50.813», «I50.23», «I50.33», «I50.42», «I50.43», and «I50.42». No patients were identified using these codes which confirmed that only new-onset acute heart failure patients were included in the study. Details of ICD codes utilized to identify various complications are given in the supplementary file.

Patient and hospital characteristics

Baseline patient demographic characteristics (age, sex, insurance payer) were extracted. Diagnostic codes were used to identify hypertension, diabetes mellitus, hyperlipidemia, obesity, smoker, Peripheral Vascular Disease (PVD), chronic kidney disease, fluid or electrolyte imbalance, liver disease, chronic obstructive pulmonary disease, congenital heart disease, drug abuse, cancer, prior myocardial infarction, prior coronary artery bypass grafting, history of coronary artery disease, alcohol use, hemodialysis, hypothyroidism, smoking, and chronic obstructive pulmonary disease, were extracted using ICD-10 codes. Elixhauser comorbidity index codes were also used to extract comorbidities [7]. Cardiovascular procedures including Percutaneous Coronary Intervention (PCI, coronary artery bypass grafting (CABG), implantable defibrillator, Permanent Pacemaker (PPM), coronary angiography, and Mechanical Circulatory Support (MCS) were extracted using the CD-10 Procedural Classification System (PCS) codes (Supplementary file). We extracted complications associated with each sub-types of HF with and without DM. Complications included mortality, angina, Non-ST Elevated Myocardial Infarction (NSTEMI), ST-Elevated Myocardial Infarction (STEMI), Acute Kidney Injury (AKI), Ventricular Tachycardia/Fibrillation (VT/VF), intracardiac conduction block, cardiogenic shock, Pulmonary Embolism (PE), septic shock, and admission to Intensive Care Unit (ICU). All complications were generated using ICD-10 codes (supplementary file).

Outcomes

The primary outcome of the analysis was all-cause mortality during hospitalization for acute HFpEF

and HFrEF complicated by DM. We also evaluated clinical complications, 30-day readmission rates, and cardiac procedures performed among patients with acute HFpEF and acute HFrEF encounters associated with DM.

Statistical methods

Categorical variables were expressed as weighted values along with percentages and continuous variables were expressed as mean ± standard deviation if the variable was not skewed and as median with 25th and 75th percentiles otherwise. Descriptive statistics were performed for demographics and comorbidities which were stratified by the acute HFpEF and acute HFrEF and were compared with the rest of the population. We used the survey statistical method to perform a weighted analysis. Pearson's chi-square test was used to compare categorical variables and linear regression was used to compare continuous variables. We calculated mortality for acute HFpEF and acute HFRrEF. We extracted complications associated with acute HFpEF and HFrEF. The proportions were compared using the Chi-square test.

All analyses were weighted analyses. Statistical analysis was performed using STATA version 16.1 (College Station, Texas). All p values were 2-sided, with a significance threshold of $p<0.05$.

Results

Out of the total 1,479,716 acute HF patients (mean age 69.7±14.9 years, 47.3% females) were recorded in NEDS for the years 2016-2018, 803,308 (54.3%) had acute HFrEF while 481,985 (32.5%) had acute HFpEF (Figure 1).

When comparing the two major groups of HFrEF vs HFpEF, the prevalence of ischemic heart disease was higher among HFrEF 109,118 (13.6%) vs 38,783 (8.1%), also noticed higher PCI 88,859 (11.1%) vs 41,401 (8.6%) and higher CABG 83,812 (10.4%) vs 39,701 (8.2%) in the HFrEF group. The comparison has been provided in Table 1.

On subgroup analysis, 317,517 (39.5%) of the total acute HFrEF encounters were complicated by DM. The acute HFrEF with DM were males with a higher prevalence of hypertension, hyperlipidemia, prior history of MI, prior PCI, and prior CABG. Medicare was the primary payor across all groups. Baseline characteristics are provided in Table 1.

On subgroup analysis, 195,945 (40.6%) of the total acute HFpEF encounters were complicated by DM. Patients with acute HFpEF with DM were more likely to be elderly, females with a higher prevalence of hypertension, hyperlipidemia, prior stroke, and prior MI. Medicare was the primary payor across all groups. Baseline characteristics are provided in Table 2.

Clinical complications

The HFrEF with DM group had higher multi-organ complications including NSTEMI (14.6% vs 12.9%; p-value<0.001), Acute Kidney Injury (AKI) (29.3% vs 26.2%; p-value<0.001), AKI requiring hemo-

dialysis (10.5% vs 6.7%; p-value<0.001) when compared to HFrEF group only. Other fewer complications associated with acute HFREF are given in Table 3.

Similarly, the HFpEF with DM group had higher multi-organ complications including NSTEMI (8.4% vs 7.4%; p-value<0.001), Acute Kidney Injury (AKI) (33.1% vs 28.1%; p-value<0.001), AKI requiring hemodialysis (8.8% vs 5.5%; p-value<0.001) when compared to HFpEF group only. Other complications associated with acute HFpEF and DM are given in Table 4.

Mortality analysis

Out of 1,479,716 total acute onset HF encounters, the overall all-cause mortality was 55,403 (3.7%) during the hospitalizations. On subgroup analysis, the all-cause mortality for HFrEF only was higher as compared to HFrEF with DM (5% vs 4.8%; p<0.001) while the all-cause mortality for HFpEF only was higher as compared to HFpEF with DM (3.5% vs 3%; p<0.001).

Cardiac procedure analysis

HFrEF with DM groups had higher cardiac procedures including stress test, coronary angiography, and PCI (29.9% vs 24.8%, 19% vs 15.4%, and7.6% vs 7%, respectively; p<0.001) compared to their counterparts. Similarly, HFpEF with DM groups also had higher cardiac interventions including stress test, coronary angiography, and PCI (19% vs 17.1%, 8.1% vs 7.1%, and 2.6% vs 2.1%, respectively; p<0.001) compared to their counterparts. Other procedural data are presented in Supplementary Table 1 and Table 2.

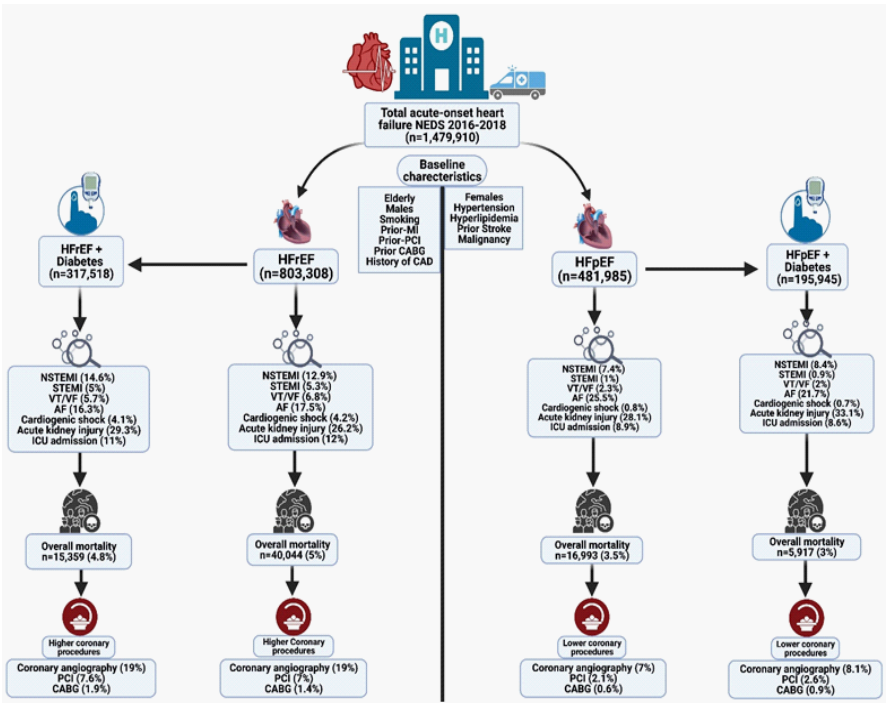

Figure 1: Graphic abstract, created with BioRender.com

Discussion

Metabolic alterations associated with DM have been recognized since the 1970s as a distinct pathway in the onset and progression of HF, independent of atherosclerotic cardiovascular disease [9-11]. Our study utilizes the multicenter database to retrospectively evaluate both subtypes of acute onset HF both alone and with DM. The most salient findings of our study were as follow: 1) Compared to patients with acute HFrEF or acute HFpEF alone, those with acute HFrEF or HFpEF with DM had significantly higher rates of AKI, AKI needing hemodialysis, and NSTEMI 2) Acute HFrEF or HFpEF with DM subgroups also exhibited higher rates of undergoing PCI or CABG 3) DM was not associated with worsening overall mortality in patients with both HFrEF and HFpEF and 4) HFrEF with and without DM was associated with more complications and worse outcomes than HFpEF with and without DM.

Acute heart failure with reduced ejection fraction and diabetes mellitus

This study added results to the controversial evidence available in literature about the impact of diabetes on complications and prognosis amongst patients admitted with acute HF. In our study, approximately one-third of patients hospitalized with HFrEF had diabetes. We observed a higher rate of AKI and AKI needing hemodialysis amongst patients who had HFrEF with diabetes compared to HFrEF alone. Kidneys in patients with DM are characterized by severe inflammation, athero- and arteriosclerosis, and glomerular damage. Thus, the kidneys are more prone to damage from ischemic injury during HFrEF exacerbations [12]. This endorsed the findings by others [13-16].

Hyperglycemia-accelerated atherosclerosis is the most common cause of HF in people with DM [17]. De Groote et. al evaluated 1,246 patients with left ventricular dysfunction and aimed to use diabetic status as a prognostic indicator in heart failure patients, finding DM to be an independent predictor of cardiovascular mortality in patients with ischemic heart disease compared to patients without ischemic heart disease (HR=1.43 [1.03;1.98] P=0.03 vs HR=0.46 [0.23;0.88], P=0.02) [18]. We found that HFrEF with DM was associated with higher rates of known ischemic heart disease, development of NSTEMI during the hospitalization, as well as increased rates undergoing PCI or CABG during the hospitalization.

We found improved mortality rates in patients with HFrEF with DM compared to HFrEF alone. This is analogous to the findings by others who reported a comparable prognosis in HFrEF with DM and HFrEF alone [17,19]. However, these finding contrasts previous studies. A retrospective Scottish population study found poorer prognostic outcomes after 1-year follow-up of patients with HF with DM compared to HF alone [20]. DIAMOND-CHF (Danish Investigations of Arrhythmia and Mortality on Dofetilide in Congestive Heart Failure) was a large Danish trial with >5,000 patients reporting higher 1-year mortality rates among patients with HF with DM than HF alone [21].

A potential reason for these discrepancies is a higher rate of undergoing PCI and CABG, procedures which are known to have mortality benefit, amongst the HFrEF with DM cohort compared to the HFrEF alone cohort. This is corroborated by our study as well, which finds HFrEF with DM group underwent more PCI and CABG than HFrEF alone.

Table 1: Baseline characteristics of Heart Failure with Reduced Ejection Fraction (HFrEF) only in comparison to HFrEF with Diabetes Miletus (DM).

Variables	HFrEF (n=803,308)	HFrEF + DM (n=317,518)	P value
Age, Years	68.8±14.9	72.7±13.9	<0.001
Female	326,676 (40.7%)	126,490 (39.8%)	<0.001
Male	476,632 (59.3%)	191,027 (60.2%)	<0.001
Medicare	504,281 (64.4%)	208,465 (67.4%)	<0.001
Medicaid	105,668 (13.5%)	39,317 (12.7%)	<0.001
Private Insurance	132,632 (16.9%)	48,556 (15.7%)	<0.001
Self-Pay	39,400 (5%)	12,838 (4.2%)	<0.001
Urban Hospital	749,247 (93.3%)	297,488 (93.7%)	0.002
Teaching Hospital	518,911 (64.6%)	207,202 (65.2%)	<0.001
Hypertension	642,901 (80%)	284,028 (89.4%)	<0.001
Hyperlipidemia	326,337 (40.6%)	163,413 (51.5%)	<0.001
Smoking	154,185 (19.2%)	50,745 (16%)	<0.001
Intravenous drug use	11,981 (1.5%)	3,351 (1.1%)	<0.001
History of Stroke	68,081 (8.5%)	31,672 (10%)	<0.001
Prior MI	109,118 (13.6%)	51,656 (16.3%)	<0.001
Prior PCI	88,859 (11.1%)	44,672 (14.1%)	<0.001
Prior CABG	83,812 (10.4%)	45.013 (14.2%)	<0.001
Family History of CAD	54,457 (6.8%)	20,729 (6.5%)	<0.001

MI: Myocardial Infarction; PCI: Percutaneous Coronary Intervention; CABG: Coronary Artery Bypass Grafting; CAD: Coronary Artery Disease.

Table 2: Baseline characteristics of Heart Failure with Preserved Ejection Fraction (HFpEF) only in comparison to HFpEF with Diabetes Miletus (DM).

Variables	HFpEF (n=481,985)	HFpEF + DM (n=195,945)	P value
Age, Years	68.5±13.6	71.7±13.3	<0.001
Female	287,297 (59.6%)	111,641 (57%)	<0.001
Male	194,688 (40.4%)	84,304 (43%)	<0.001
Medicare	369,329 (77.9%)	146,674 (76.3%)	<0.001
Medicaid	34,125 (7.2%)	16,230 (8.4%)	<0.001
Private Insurance	58,173 (12.3%)	24,604 (12.8%)	<0.001
Self-Pay	11,796 (2.5%)	4,700 (2.4%)	<0.001
Urban Hospital	454,229 (94.2%	184,667 (94.2%)	0.002
Teaching Hospital	287,761 (59.7%)	11,991 (60.2%)	<0.001
Hypertension	414,768 (86%)	181,666 (92.7%)	<0.001
Hyperlipidemia	214,021 (44.4%)	105,287 (53.7%)	<0.001
Smoking	63,324 (13.1%)	23,312 (11.9%)	<0.001
Intravenous drug use	5,604 (1.2%)	2,022 (1%)	<0.001
History of Stroke	46,893 (9.7%)	20,172 (10.3%)	<0.001
Prior MI	38,783 (8.1%)	18,620 (9.5%)	<0.001
Prior PCI	41,401 (8.6%)	20,843 (10.6%)	<0.001

Prior CABG	39,701 (8.2%)	20,555 (10.5%)	<0.001
Family History of CAD	27,355 (5.7%)	11,165 (5.7%)	<0.001

MI: Myocardial Infarction; PCI: Percutaneous Coronary Intervention; CABG: Coronary Artery Bypass Grafting; CAD: Coronary Artery Disease.

Table 3: Clinical complications associated with Heart Failure with Reduced Ejection Fraction (HFrEF) only in comparison to HFrEF with Diabetes Miletus (DM).

Complications	HFrEF (n=803,308)	HFrEF + DM (n=317,518)	P value
Mortality	40,044 (5%)	15,359 (4.8%)	<0.001
Atrial Fibrillation	140,747 (17.5%)	51,807 (16.3%)	<0.001
VT/VF	54,302 (6.8%)	18,080 (5.7%)	<0.001
NSTEMI	103,462 (12.9%)	46,365 (14.6%)	<0.001
STEMI	42,272 (5.3%)	15,808 (5%)	<0.001
Acute kidney Injury	210,245 (26.2%)	93,174 (29.3%)	<0.001
AKI needing Hemodialysis	53,734 (6.7%)	33,353 (10.5%)	<0.001
Cardiogenic Shock	33,818 (4.2%)	13,043 (4.1%)	<0.001
Pulmonary Embolism	28,087 (3.5%)	9,161 (2.9%)	<0.001
Infective Endocarditis	5,270 (0.6%)	1,571 (0.5%)	<0.001
Sepsis	87,176 (10.9%)	34,847 (11%)	<0.001
Septic Shock	32,731 (4.1%)	12,056 (3.8%)	<0.001
ICU admission	96, 150 (12%)	34,788 (11%)	<0.001
Mechanical Ventilation	69,112 (8.6%)	26,327 (8.3%)	<0.001

NSTEMI: Non-ST Elevated Myocardial Infarction, STEMI; ST-Elevated Myocardial Infarction, VT/VF: Ventricular Tachycardia/Fibrillation; ICU: Intensive Care Unit.

Table 4: Clinical complications associated with Heart Failure with Preserved Ejection Fraction (HFpEF) only in comparison to HFpEF with Diabetes Miletus (DM).

Complications	HFpEF (n=481,985)	HFpEF + DM (n=195,945)	P value
Mortality	16,993 (3.5%)	5,917 (3%)	<0.001
Atrial Fibrillation	122,975 (25.5%)	42,610 (21.7%)	<0.001
VT/VF	10,910 (2.3%)	3,906 (2%)	<0.001
NSTEMI	35,882 (7.4%)	16,429 (8.4%)	<0.001
STEMI	4,640 (1%)	1,816 (0.9%)	<0.001
Acute kidney Injury	135,590 (28.1%)	64,924 (33.1%)	<0.001
AKI needing Hemodialysis	26,539 (5.5%)	17,165 (8.8%)	<0.001
Cardiogenic Shock	4,019 (0.8%)	1,486 (0.7%)	<0.001
Pulmonary Embolism	16,146 (3.3%)	5,340 (2.7%)	<0.001
Infective Endocarditis	3,915 (0.8%)	1,192 (0.60%)	<0.001
Sepsis	58,821 (12.2%)	22,977 (11.7%)	<0.001
Septic Shock	14,827 (3.1%)	5,216 (2.7%)	<0.001
ICU admission	42,860 (8.9%)	16,797 (8.6%)	<0.001
Mechanical Ventilation	29,148 (6.1%)	12,531 (6.4%)	<0.001

NSTEMI: Non-ST Elevated Myocardial Infarction, STEMI; ST-Elevated Myocardial Infarction, VT/VF: Ventricular Tachycardia/Fibrillation; ICU: Intensive Care Unit.

Acute heart failure with preserved ejection fraction and diabetes mellitus

HFpEF is emerging as a significant clinical problem for patients with DM. Current data suggests that between 30% and 40% of patients with HFpEF have coexisting DM. The Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist Trial (TOPCAT) found that HFpEF with DM was associated with an increased risk for cardiovascular death [23]. In a post-hoc analysis from the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) study, HFpEF with diabetes was associated with a twofold increased risk of cardiovascular death or heart failure hospitalization [24]. Similarly, in the Irbesartan in Heart Failure with Preserved Ejection Fraction Trial (I-PRESERVE) study, HFpEF with DM had a 1.75-fold increased risk of cardiovascular death [25].

However, our study demonstrated that HFpEF with DM was not associated with a worse overall mortality. This again could be explained by higher rates of undergoing PCI and CABG amongst the HFpEF with DM cohort compared to the HFrEF alone cohort, highlighting survival benefits of early intervention amongst patients admitted for HFpEF.

Acute heart failure with reduced and preserved ejection fraction

The OPTIMIZE-HF registry reported mortality rates of (3.8%) in HFrEF which was similar to our study (4.4%) [8]. Gomez-Soto et al expanded on this data and found that acute HFrEF was associated with greater mortality rates compared to acute HFpEF patients amongst 267,231 patients in Spain ($p<0.05$) [26]. Our study validated this and found an increase in all-cause mortality in acute HFrEF patients compared to acute HFpEF (5.7% vs 3.5%, $P<.0001$).

High mortality among acute HFrEF is a multifactorial process: Patients with acute HFrEF have a higher comorbidity profile, higher rates of complications, and a higher number of ICU admissions compared to acute HFpEF patients (15% vs 8.9%, $P<.0001$) and exhibit higher rates of known ischemic cardiac events compared to patients with acute HFpEF, as has been validated previously [27-29].

Since the incidence of diabetes in HF patients is likely to further increase in the future, this will become a major health care problem with high morbidity and mortality as well as high costs for society [29]. Therefore, it is important to recognize diabetes in patients with HF. For that reason, more future clinical research is required for medical treatment and early coronary intervention on diabetics with HF.

Our study has multiple strengths. First, it represents the whole population of the United States. Secondly, a significant number of hospitalizations are recorded yearly for acute heart failure with significant mortality. This gives us rich epidemiological data that allows us to accurately compare subgroups with HF and DM as we have demonstrated. There are mortality benefits from screening tests for ischemic cardiomyopathy including stress tests and coronary angiography. However, the rates of undergoing stress tests and coronary angiography are dismal. This would suggest that there needs to be improvement in rates of procedures for cardiac ischemic work-up.

Study limitations

Our study has several limitations. First, this is a retrospective, observational study, and inference regarding causation should be made with caution as controlling for comorbidities is challenging. Also, we relied on reported ICD-10 codes to identify diagnoses to perform our analysis. The national emergency database is an administrative database that could be subject to inaccurate over-coding or underreporting of some comorbid diagnoses. There is also an absence of important information related to patients' physical examination, medications, and laboratory results. We could not evaluate the time to coronary interventions and ischemic work up. We could not take into consideration echocardiography or radiography. A significant number of acute new onset heart failure was recorded as non-specific which we could not classify under HFpEF and HFrEF. Also, there could be some chances of selection bias for procedures. However, NEDS and the codes used in this study have been applied in multiple clinical studies and can be considered a highly reliable database. Given the large cohort analyzed in this study this minimizes the limitation.

Conclusion

The present analysis shows that although DM was associated with higher rates of cardio-renal complications including AKI, AKI requiring HD, and NSTEMI within both subtypes of HF population studied. Also, the rate of the ischemic evaluation was relatively higher in DM with HF subgroups. More importantly, we found that the all-cause mortality rate was not higher in patients with DM within both subtypes of HF, which suggest importance of early intervention. Given higher cardiac procedures performed in patients with associated DM, more clinical trials will be needed to work on the hypothesis generated.

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Supplemental Table 1: Cardiovascular procedures performed among acute Heart Failure with Reduced Ejection Fraction (HFrEF) only in comparison to HFrEF with Diabetes Miletus (DM).

Interventions	HFrEF (n=803,308)	HFrEF + DM (n=317,518)	P-value
Stress test	199,220 (24.8%)	94,938 (29.9%)	<0.001
Coronary Angiography	123,710 (15.4%)	60,251 (19%)	<0.001
PCI	56,594 (7%)	24,030 (7.6%)	<0.001
CABG	11,450 (1.4%)	6,056 (1.9%)	<0.001
AICD	6,230 (0.8%)	2,152 (0.7%)	<0.001
PPM	5,506 (0.7%)	2,167 (0.7%)	<0.001
IABP	12,599 (1.6%)	5,475 (1.7%)	<0.001
PVAD	4,989 (0.6%)	2,164 (0.7%)	<0.001
ECMO	830 (0.1%)	263 (0.1%)	<0.001
Impella	4,654 (0.6%)	2,054 (0.6%)	<0.001

PPM: Permanent Pacemaker; AICD: Implantable Cardioverter Defibrillator; CABG: Coronary Artery Bypass Grafting; PCI: Percutaneous Coronary Intervention; MCS: Mechanical Circulatory Support.

Supplemental Table 2: Cardiovascular procedures performed among acute Heart Failure with Preserved Ejection Fraction (HFpEF) only in comparison to HFpEF with Diabetes Miletus (DM).

Interventions	HFpEF (n=481,985)	HFpEF + DM (n=195,945)	P-value
Stress test	82,420 (17.1%)	37,229 (19%)	
Coronary Angiography	33,749 (7%)	15,831 (8.1%)	<0.001
PCI	10,216 (2.1%)	5,159 (2.6%)	<0.001
CABG	3,033 (0.6%)	1,716 (0.9%)	<0.001
AICD	326 (0.1%)	140 (0.1%)	<0.001
PPM	6,610 (1.4%)	2,491 (1.3%)	<0.001
IABP	1,037 (0.2%)	432 (0.2%)	<0.001
PVAD	228 (0.04%)	88 (0.04%)	<0.001
ECMO	97 (0.02%)	35 (0.01%)	<0.001
Impella	199 (0.04%)	83 (0.04%)	<0.001

PPM: Permanent Pacemaker, AICD: Implantable Cardioverter Defibrillator; CABG: Coronary Artery Bypass Grafting; PCI: Percutaneous Coronary Intervention; MCS; Mechanical Circulatory Support.

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