JACC: HEART FAILURE
VOL. 4, NO. 6, 2016

ISSN 2213-1779/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jchf.2016.02.017

Precipitating Clinical Factors, Heart Failure Characterization, and Outcomes in Patients Hospitalized With Heart Failure With Reduced, Borderline, and Preserved Ejection Fraction

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ABSTRACT

OBJECTIVES This study assessed the comparative frequency of precipitating clinical factors leading to hospitalization among heart failure (HF) patients with reduced, borderline, and preserved ejection fraction (EF)

BACKGROUND There are few data assessing the comparative frequency of clinical factors leading to HF among hospitalized among patients with reduced, borderline, and preserved EF.

METHODS We analyzed the factors potentially contributing to HF hospitalization among 99,825 HF admissions from 305 hospitals in the Get With The Guidelines-HF (GWTG-HF) database between January 2005 and September 2013 and assessed their association with length of stay and in-hospital mortality.

RESULTS Mean patient age was 72.6 ± 14.2 years, 49% were female, and mean EF was 39.3 ± 17.2%. Common factors included pneumonia/respiratory process (28.2%), arrhythmia (21.7%), medication noncompliance (15.8%), worsening renal failure (14.7%), and uncontrolled hypertension (14.5%). In patients with borderline EF (EF 40% to 49%), pneumonia was associated with longer hospital stay, whereas dietary and medication noncompliance were associated with reduced length of stay. In patients with preserved EF (EF ≥50% or qualitative assessment of normal or mild dysfunction), pneumonia, weight gain, and worsening renal function were independently associated with longer lengths of stay. Worsening renal function and pneumonia were independently associated with higher in-hospital mortality in all HF groups, and acute pulmonary edema was associated with higher mortality in reduced EF. Dietary noncompliance (14.7%) was associated with reduced mortality for all groups but reached statistical significance in the subgroups of reduced (odds ratio [OR]: 0.65; 95% confidence interval [CI]: 0.46 to 0.91) and preserved systolic function (OR: 0.52; 95% CI: 0.33 to 0.83). Patients presenting with ischemia had a higher mortality rate (OR: 1.31; 95% CI: 1.02 to 1.69; and 1.72; 95% CI: 1.27 to 2.33, respectively, in the 2 groups).

CONCLUSIONS Potential precipitating factors among patients hospitalized with HF vary by EF group and are independently associated with clinical outcomes. (J Am Coll Cardiol HF 2016;4:464–72) © 2016 by the American College of Cardiology Foundation.

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Manuscript received September 15, 2015; revised manuscript received February 5, 2016, accepted February 7, 2016.

Heart failure (HF) is a major cause of morbidity and mortality (1), and its incidence, prevalence, and financial burdens continue to rise. Heart failure is also the leading cause of hospitalizations among elderly U.S. adults. Several precipitating clinical factors have been identified that may contribute to HF hospitalizations (2–7). These include arrhythmia, myocardial ischemia, pneumonia, hypertension, worsening renal failure, and dietary or medication noncompliance. Similarly, there are a number of HF signs and symptoms that are used to characterize HF at presentation, including acute pulmonary edema, dizziness/syncope, dyspnea, implantable cardioverter-defibrillator (ICD) shock, pulmonary congestion, volume overload/weight gain, or worsening fatigue. However, there is a dearth of studies assessing the frequency with which these factors are present in patients hospitalized for HF with reduced ejection fraction (HFrEF) (3–7) but no studies, to our knowledge, assessing the frequency of presentation of these factors in patients with HF and borderline or preserved EF. In addition, there are limited data to determine whether these clinical factors are associated with clinical outcomes. Prior studies are limited by relatively small study groups investigated at single centers or with tight inclusion criteria (3–7). Studies assessing large representative populations of patients in various subgroups of HF are critical for providing insight into the factors and HF characterizations that precipitate HF hospitalizations. The Get With The Guidelines-HF (GWTG-HF) program is a registry and performance improvement program for patients hospitalized for HF that prospectively tracks several performance measurements and other quality of care indicators for hospitalized patients with HF (8,9). This study sought to determine the frequency at which various precipitating factors and HF characterizations contributing to HF hospitalization are identified in patients hospitalized with HF and to improve the understanding of whether and to what extent these factors influence clinical outcomes, including hospital length of stay and in-hospital mortality in patients with reduced, borderline, and preserved EF.

METHODS

DATA COLLECTION. The GWTG-HF program is a national, prospective, observational, and ongoing voluntary data collection and continuous quality improvement initiative (8,9). Hospitalized adults are enrolled in the registry when an episode of new or worsening HF occurs as the primary reason for admission or with significant HF symptoms that developed during hospitalization in which HF was the primary discharge diagnosis. Hospitals from all census regions of the United States, including teaching and nonteaching, rural and urban, and large and small hospitals, are represented in the database.

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An online interactive case report form (Outcome Sciences, Inc., Cambridge, Massachusetts) is used by participating institutions to submit clinical information about consecutively eligible patients to the GWTG-HF database, in compliance with Joint Commission and Centers for Medicare and Medicaid standards. Outcome Sciences, Inc., is the data collection coordination center for the American Heart Association/American Stroke Association GWTG programs. Standardized definitions are used to abstract clinic data. Demographic and clinical characteristics, medical history, previous treatments, contraindications to therapies, and outcomes are among the variables collected. Reported data are checked to ensure they are complete and that completeness and accuracy of data quality are monitored. The GWTG protocol is reviewed and approved by institutional review boards. A waiver of informed consent is granted for sites under the common rule because data were used primarily at the local site for quality improvement. The data analysis center is the Duke Clinical Research Institute. Data are monitored for completeness and accuracy, and aggregate deidentified data are analyzed for research purposes.

STUDY POPULATION. The cohort was divided into those subjects with reduced EF (EF <40% or, if EF was missing, qualitative assessment of moderate to severe dysfunction), patients with borderline systolic function (40% ≤ EF <50%) and those with preserved EF (EF ≥50% or, if EF was missing, qualitative assessment of normal or mild dysfunction). We excluded patients without a documented EF.

OUTCOME MEASURES. Each hospital selected the presence or absence of individual precipitating factors using dedicated fields, which was based on the clinical judgment of local providers. Hospital lengths of stay (number of days from admission to discharge) and in-hospital deaths were assessed.

STATISTICAL ANALYSIS. Baseline characteristics were compared between groups by using the Pearson chi-square test for categorical variables and the Kruskal-Wallis test for continuous variables. Categorical variables were reported as percentages, and continuous variables were reported as mean ± SD and median (interquartile range) values. Multivariate

ABBREVIATIONS AND ACRONYMS

CI = confidence interval
EF = ejection fraction
HF = heart failure
HFrEF = heart failure with reduced ejection fraction
ICD = implantable cardioverter-defibrillator
OR = odds ratio

logistic regression was performed for each factor individually using the generalized estimating equations method to adjust for clustering within hospitals to determine whether comorbid factors independently influenced each outcome. We dichotomized length of stay to compare length of stay >4 days versus lengths of stay <4 days, as 4 days was the median length of stay. The model adjusted for patient characteristics and medical history (age, race, sex, insurance, admission systolic blood pressure, heart rate, sodium, blood urea nitrogen [BUN], history of anemia, stroke, diabetes, chronic obstructive pulmonary disease, hypertension, hyperlipidemia, atrial fibrillation/flutter, peripheral vascular disease, renal failure, smoking status, and cause of HF) and hospital characteristics (region, number of beds, rural vs. urban, academic status). If a patient had missing medical history, it was imputed to no. Missing values for all other categorical variables were imputed to the most frequent category, and missing values for continuous variables were imputed to the median. Missing hospital characteristics were not imputed, and patients without these data were excluded from multivariate models. A p value of <0.05 was considered significant for all test results. All analyses were performed using SAS version 9.3 software (SAS Institute, Inc., Cary, North Carolina). The authors are solely responsible for the design and conduct of this study, including all analyses, drafting, and editing, and its final contents.

RESULTS

BASELINE CHARACTERISTICS. After we excluded patients with missing EF (n = 3,167 subjects from 5 sites), the final study population consisted of 99,825 patients hospitalized with a diagnosis of HF from 305 hospitals between January 2005 and September 2013. Of those, 48,950 patients (49.0%) had reduced EF, 12,819 patients (12.8%) had borderline EF, and 38,056 patients (38.1%) had preserved EF. Baseline characteristics of the overall population stratified by these groups are presented in Table 1. The overall population was an average 73 ± 14 years of age, with a slightly younger age distribution observed in patients with reduced EF (average 70 ± 15 years of age), compared with patients with borderline EF (74 ± 13 years of age) and patients with preserved left ventricular EF (76 ± 13 years of age). Race/ethnicity was white in 70%, with the remainder of the population consisting of black (19%), Hispanic (8%), and other (3%). There were also approximately equal proportions of females and males in the overall population (49% vs. 51%, respectively). Relative to the other groups, patients with borderline EF more frequently had comorbid diabetes, peripheral vascular disease, hyperlipidemia, renal insufficiency, dialysis, or history of ischemia. Patients with preserved EF more frequently had a history of cerebrovascular accident, depression, or hypertension. Finally, patients with reduced EF had a higher rate of prior myocardial infarction relative to the other groups.

PRECIPITATING FACTORS. One or more factors that might have precipitated HF admission were identified in 81% of patients. The frequencies of these individual factors are shown in Figure 1. Of the factors found, pneumonia/respiratory process (28.2%), arrhythmia (21.7%), medication noncompliance (15.8%), worsening renal failure (14.7%), and uncontrolled hypertension (14.5%) were identified as the most common in the cohort. Relative to the other groups, dietary and medication nonadherence were identified more often in patients with reduced EF (16.8% and 19.7%, respectively). Uncontrolled hypertension was more likely to be present in patients with borderline EF (16.4%) and pneumonia/respiratory process was more likely in patient with preserved EF (32.7%). Two or more factors were identified in 16,446 patients (26.7%), and 3 or more factors were identified in 4,964 patients (8.1%) (Figure 1).

HEART FAILURE CHARACTERIZATIONS

Patients most frequently presented with dyspnea (71.2%) and volume overload/weight gain (11.3%) (Table 2). Patients with reduced EF presented with dizziness (3.1%), ICD shock/sustained ventricular arrhythmia (0.5%), volume overload/weight gain (11.8%), and worsening fatigue (3.3%) more frequently than other groups. In contrast, patients with borderline EF presented with dyspnea (74.0%) more frequently than other groups.

OUTCOMES. The median hospital length of stay in the overall population and in each subgroup was 4 days (interquartile range: 25th to 75th; 3 to 7 days, respectively) (Table 3). Longer hospital stays (>4 days) in patients with reduced EF were observed in association with pneumonia (odds ratio [OR]: 1.30; 95% confidence interval [CI]: 1.22 to 1.40), volume overload/weight gain (OR: 1.32; 95% CI: 1.20 to 1.46), worsening renal failure (OR: 1.19; 95% CI: 1.08 to 1.30), arrhythmia (OR: 1.10; 95% CI: 1.02 to 1.18), and acute pulmonary edema (OR: 1.28; 95% CI: 1.05 to 1.57), whereas dyspnea was associated with a

TABLE 1 Baseline Characteristics in the Overall Population Stratified by Ejection Fraction

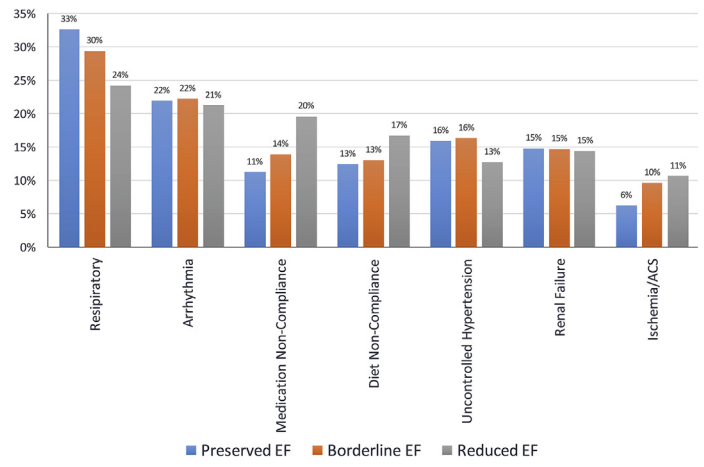
		Overall (N = 99,825)		Reduced Ejection Fraction (n = 48,950)		Borderline Ejection Fraction (n = 12,819)		Preserved Ejection Fraction (n = 38,056)		
	Level	N	%	n	%	n	%	n	%	p Value
Demographics										
Age,yrs	Median	99,825	75.00	48,950	72.00	12,819	77.00	38,056	78.00	<0.0001
	25th		63.00		60.00		66.00		68.00	
	75th		84.00		81.00		84.00		86.00	
	Mean		72.63		69.63		74.44		75.87	
	± SD		14.24		14.71		13.31		13.06	
	Minimum		18.00		18.00		19.00		18.00	
	Maximum		109.00		109.00		106.00		108.00	
Sex	Female	49,066	49.15	18,023	36.82	6262	48.85	24,781	65.12	<0.0001
	Male	50,759	50.85	30,927	63.18	6557	51.15	13,275	34.88	
Race	Other (includes unknown)	3,294	3.31	1,657	3.40	410	3.21	1,227	3.24	<0.0001
	Hispanic (any race)	7,676	7.72	4,090	8.39	1,021	8.00	2,565	6.76	
	Black	19,087	19.20	1,1571	23.74	1873	14.68	5,643	14.88	
	White	69,375	69.77	31,426	64.47	9,458	74.11	28,491	75.12	
Insurance status	No insurance/not documented	3726	3.95	2516	5.48	399	3.27	811	2.24	<0.0001
	Medicare	54,035	57.33	25,047	54.58	7,174	58.76	21,814	60.35	
	Medicaid	9,936	10.54	5,314	11.58	1,097	8.98	3,525	9.75	
	Other	26,549	28.17	13,012	28.36	3,540	28.99	9,997	27.66	
Medical history										
Anemia	Yes	23,827	23.87	9,265	18.93	3,464	27.02	11,098	29.16	<0.0001
Smoking	Yes	16,091	16.17	9,883	20.26	1,802	14.11	4,406	11.61	<0.0001
Atrial fibrillation	Yes	38,266	38.33	16,729	34.18	5,353	41.76	16,184	42.53	<0.0001
Atrial flutter	Yes	3,008	3.01	1,499	3.06	428	3.34	1,081	2.84	0.012
Coronary disease	Yes	54,726	54.82	28,567	58.36	7,677	59.89	18,482	48.57	<0.0001
COPD or asthma	Yes	35,424	35.49	15,593	31.85	4,670	36.43	15,161	39.84	<0.0001
CVA/TIA	Yes	16,479	16.51	7,759	15.85	2,192	17.10	6,528	17.15	<0.0001
Depression	Yes	12,538	12.56	5,346	10.92	1,649	12.86	5,543	14.57	<0.0001
Diabetes	Yes	46,821	46.90	21,763	44.46	6,430	50.16	18,628	48.95	<0.0001
Previous MI	Yes	24,575	24.62	14,972	30.59	3,264	25.46	6,339	16.66	<0.0001
Peripheral vascular disease	Yes	14,306	14.33	6,852	14.00	2,031	15.84	5,423	14.25	<0.0001
Prior heart failure	Yes	99,825	100.00	48,950	100.00	12,819	100.00	38,056	100.00	
Hyperlipidemia	Yes	52,119	52.21	25,954	53.02	6,925	54.02	19,240	50.56	<0.0001
Hypertension	Yes	80,558	80.70	38,062	77.76	10,535	82.18	31,961	83.98	<0.0001
Renal insufficiency (creatinine >2 mg/dl)	Yes	23,905	23.95	11,286	23.06	3,305	25.78	9,314	24.47	<0.0001
Dialysis	Yes	4,144	4.15	1,620	3.31	689	5.37	1,835	4.82	<0.0001
Ischemic history	Yes	61,596	61.70	32,432	66.26	8,596	67.06	20,568	54.05	<0.0001
Cause										
Ischemia	Yes	63,589	63.70	33,438	68.31	8,839	68.95	21,312	56.00	<0.0001
Nonischemic alcohol	Yes	1,937	4.37	1,476	7.72	158	2.96	303	1.53	<0.0001
Other nonischemic cause	Yes	9,990	22.55	4,082	21.34	1,225	22.91	4,683	23.62	<0.0001

COPD = chronic obstructive pulmonary disease; CVA = cerebrovascular accident; MI = myocardial infarction; TIA = transient ischemic attack.

decreased hospital length of stay in all EF subcategories of HF. Among patients with borderline EF, pneumonia was associated with longer hospital stay (OR: 1.31; 95% CI: 1.18 to 1.45), whereas dietary and medication noncompliance were associated with reduced length of stay. In patients with preserved EF, pneumonia, weight gain, and worsening renal function were independently associated with longer lengths of stay (Table 4).

There were 3,059 in-hospital deaths (3.1%) in the overall population during the study, with a slightly higher unadjusted death rate seen in the population with reduced EF (3.2%) versus in the population with borderline EF (2.6%) or in the population with

FIGURE 1 Precipitating Factors for Heart Failure Admission Are Shown for Different Levels of Left Ventricular Ejection Fraction



Patients with higher ejection fraction were more likely to have poorly controlled hypertension, less medication noncompliance, and ACS compared with those with reduced ejection fraction. ACS = acute coronary syndrome; EF = ejection faction.

preserved EF (3.0%) (Table 3). Dyspnea was associated with a reduced mortality rate in patients with reduced EF (OR: 0.78; 95% CI: 0.68 to 0.89) (Table 5). Dietary noncompliance also was associated with reduced mortality rate in the subgroups of reduced EF (OR: 0.65; 95% CI: 0.46 to 0.91) and preserved EF (OR: 0.52; 95% CI: 0.33 to 0.83), whereas patients presenting with ischemia had a higher mortality rate in the same subgroups (OR: 1.31; 95% CI: 1.02 to 1.69 and 1.72; 95% CI: 1.27 to 2.33, respectively). ICD shock and ventricular arrhythmia were also associated with a higher mortality rate (OR: 2.64; 95% CI: 1.73 to 4.02) in patients with reduced EF. Worsening fatigue was associated with higher mortality (OR: 1.49; 95% CI: 1.10 to 2.02), whereas weight gain/volume overload was associated with lower mortality (OR: 0.81; 95% CI: 0.67 to 0.99) with preserved EF HF. Worsening renal function and pneumonia were independently associated with higher in-hospital mortality in all HF EF groups and acute pulmonary edema was associated with higher mortality in reduced EF, whereas in certain subsets of HF, medication and dietary noncompliance were associated with lower in-hospital mortality.

DISCUSSION

This analysis from GWTG-HF demonstrates that among a large population of HF patients admitted to the hospital, 1 or more factors and HF characterizations were identified as contributing to the hospitalization and outcomes in most patients. This GWTG-HF study uniquely examined patients with reduced, borderline, and preserved EF. Of the factors that may have precipitated admission, pneumonia/respiratory process (28.2%), arrhythmia (21.7%), medication noncompliance (15.8%), worsening renal failure (14.7%), and uncontrolled hypertension (14.5%) were identified as most frequent. Patients most frequently presented with dyspnea (71.2%), which in turn was associated with a reduced mortality rate in patients with reduced systolic function. Dietary noncompliance was also associated with reduced mortality rate in the subgroups of reduced EF (OR: 0.65) and preserved EF (OR: 0.52), whereas patients presenting with ischemia had a higher mortality rate in the same subgroups (OR: 1.31 and 1.72, respectively). ICD shock and ventricular arrhythmia were also associated with a higher mortality rate (OR: 2.64) in patients with reduced EF.

TABLE 2 Prevalence of Heart Failure Characterizations

		Overall		Reduced Ejection Fraction		Borderline Ejection Fraction		Preserved Ejection Fraction		
		N	%	n	%	n	%	n	%	p Value
Acute pulmonary edema	Yes	2,265	2.27	1,067	2.18	306	2.39	892	2.34	0.17
Dizziness/syncope	Yes	2,596	2.60	1,511	3.09	267	2.08	818	2.15	<0.0001
Dyspnea	Yes	71,076	71.20	33,624	68.69	9,483	73.98	27,969	73.49	<0.0001
ICD shock/sustained ventricular arrhythmia	Yes	321	0.32	260	0.53	23	0.18	38	0.10	<0.0001
Pulmonary congestion	Yes	3,417	3.42	1,716	3.51	416	3.25	1,285	3.38	0.29
Volume overload/weight gain	Yes	11,238	11.26	5,753	11.75	1,280	9.99	4,205	11.05	<0.0001
Worsening fatigue	Yes	2,888	2.89	1,602	3.27	337	2.63	949	2.49	<0.0001
Count of HF characterizations	Any 1	93,801	93.97	45,533	93.02	12,112	94.48	36,156	95.01	<0.0001
	Zero	6,024	6.03	3,417	6.98	707	5.52	1,900	4.99	

HF = heart failure; ICD = implantable cardioverter-defibrillator.

TABLE 3 Summary of Outcomes by Ejection Fraction Groups

		Overall (N = 99,825)		Reduced Ejection Fraction (n = 48,950)		Borderline Ejection Fraction (n = 12,819)		Preserved Ejection Fraction (n = 38,056)		
	Level	N	%	n	%	n	%	n	%	p Value*
Length of stay†	Median	93,465	4.00	45,216	4.00	12,036	4.00	36,213	4.00	<0.0001
	25th		3.00		3.00		3.00		3.00	
	75th		7.00		7.00		7.00		7.00	
	Mean		5.77		5.67		5.69		5.92	
	± SD		6.92		7.26		6.62		6.56	
	Minimum		1.00		1.00		1.00		1.00	
	Maximum		362.00		362.00		311.00		307.00	
Length of stay >4 days	Yes	43,716	46.77	20,455	45.24	5610	46.61	17,651	48.74	<0.0001
In-hospital death	Yes	3,059	3.06	1,572	3.21	336	2.62	1,151	3.02	0.0020

*p values were calculated by comparing nonmissing row values only. †p values are based on Pearson chi-square test results for all categorical row variables.

Worsening fatigue was associated with higher mortality (OR: 1.49), whereas weight gain/volume overload was associated with lower mortality (OR: 0.81) in preserved EF HF. Longer hospital stay in patients with reduced EF was observed in association with pneumonia, volume overload/weight gain, worsening renal failure, arrhythmia, and acute pulmonary edema, whereas dyspnea was associated with a decreased hospital length of stay in all subcategories of HF. In patients with borderline EF, pneumonia was associated with longer hospital stay, whereas dietary and medication noncompliance were associated with reduced length of stay. In patients with preserved EF, pneumonia, weight gain, and worsening renal function were independently associated with longer lengths of stay. Worsening renal function and pneumonia were independently associated with higher in-hospital mortality in all HF groups, and acute pulmonary edema was associated with higher mortality in reduced EF HF, whereas in certain subsets of HF, medication and dietary noncompliance were associated with lower in-hospital mortality. These findings provide important insights into the factors that contribute to HF admissions and their association with outcomes and have important implications for the care of patients hospitalized with HF. It is important to note that the factors associated with reduced mortality (noncompliance with diet) are being compared with other factors among patients hospitalized. We could not evaluate the important question of whether dietary noncompliance increases hospitalization and mortality among outpatients.

Our data in some ways parallel findings from OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) (2). OPTIMIZE-HF also found similar precipitant factors associated with HF admissions and outcomes. Pneumonia and respiratory processes, arrhythmia, and uncontrolled hypertension were similarly identified as most frequently associated precipitants to HF admissions. The current study, however, also demonstrated that medication noncompliance and worsening renal failure were other frequent factors involved. Similar to our findings, pneumonia/respiratory processes and worsening renal function identified patients at significantly increased risk of greater lengths of stay in the OPTIMIZE-HF study. Other studies also demonstrate that worsening of renal function during HF hospitalization and HF patients with chronic obstructive pulmonary disease and pneumonia have an associated worse outcomes (10–12). However, we also identified longer hospital stays in patients with reduced EF in association with volume overload/weight gain, arrhythmia, and acute pulmonary edema, whereas dyspnea was actually associated with a decrease hospital length of stay in all EF subcategories of HF.

The frequency with which precipitating factors are associated with HF hospitalizations has been studied previously (3–7). The most commonly identified factors identified for HF exacerbations in 1 small single-center study of 435 patients identified acute chest pain (33%), respiratory tract infection (16%), uncontrolled hypertension (15%), and nonadherence to medications (15%) as most common (3). In another small study of 328 HF hospitalizations, the most common precipitating factors were arrhythmia (24%), infections (23%), poor adherence (15%), and angina (14%) (4). Another small study of 179 patients in Germany identified dietary sodium excess (43%), nonadherence to medications (24%), ischemia (13%), and

TABLE 4 Factors Associated With Length of Stay >4 Days From Individual Models

	Reduced Systolic Function						Borderline Systolic Function						Preserved Systolic Function					
	Unadjusted			Adjusted			Unadjusted			Adjusted			Unadjusted			Adjusted		
	OR	95% CI	p Value	OR	95% CI	p Value	OR	95% CI	p Value	OR	95% CI	p Value	OR	95% CI	p Value	OR	95% CI	p Value
Pneumonia/respiratory process	1.36	1.27–1.47	<0.0001	1.30	1.22–1.40	<0.0001	1.35	1.22–1.51	<0.0001	1.31	1.18–1.45	<0.0001	1.36	1.25–1.47	<0.0001	1.35	1.25–1.46	<0.0001
Volume overload/weight gain	1.41	1.24–1.60	<0.0001	1.32	1.20–1.46	<0.0001	1.18	1.06–1.33	0.0034	1.13	1.00–1.27	0.051	1.16	1.07–1.25	0.0002	1.10	1.02–1.19	0.014
Worsening renal failure	1.59	1.46–1.72	<0.0001	1.19	1.08–1.30	0.0002	1.38	1.21–1.57	<0.0001	1.12	0.97–1.31	0.12	1.40	1.30–1.52	<0.0001	1.15	1.05–1.25	0.0017
Arrhythmia	1.21	1.12–1.30	<0.0001	1.09	1.02–1.17	0.012	1.24	1.08–1.42	0.0019	1.12	0.98–1.28	0.10	1.08	1.02–1.16	0.016	1.00	0.93–1.07	0.94
Acute pulmonary edema	1.30	1.05–1.62	0.018	1.28	1.05–1.57	0.015	1.13	0.88–1.44	0.35	1.14	0.89–1.47	0.30	1.05	0.92–1.20	0.48	1.08	0.94–1.24	0.27
Dyspnea	0.89	0.83–0.96	0.0023	0.92	0.86–0.99	0.020	0.86	0.80–0.92	<0.0001	0.89	0.83–0.96	0.0032	0.90	0.85–0.95	0.0001	0.92	0.87–0.98	0.0045
Dietary noncompliance	0.84	0.76–0.92	0.0001	0.90	0.80–1.00	0.054	0.70	0.58–0.84	0.0002	0.72	0.58–0.88	0.0015	0.79	0.66–0.95	0.012	0.83	0.68–1.00	0.052
Uncontrolled hypertension	0.84	0.77–0.91	<0.0001	1.07	0.97–1.17	0.16	0.72	0.63–0.83	<0.0001	0.91	0.78–1.07	0.27	0.76	0.71–0.82	<0.0001	0.93	0.85–1.01	0.080
ICD shock/sustained ventricular arrhythmia	0.83	0.64–1.10	0.19	0.82	0.61–1.11	0.20	0.33	0.09–1.18	0.088	0.30	0.09–1.00	0.051	0.83	0.41–1.68	0.60	0.81	0.41–1.60	0.55
Medication noncompliance	0.84	0.75–0.93	0.0011	0.95	0.87–1.04	0.27	0.76	0.65–0.88	0.0002	0.86	0.75–0.99	0.032	0.82	0.74–0.90	<0.0001	0.92	0.84–1.00	0.049
Dizziness/syncope	1.05	0.96–1.16	0.25	1.05	0.96–1.15	0.30	0.90	0.65–1.24	0.50	0.88	0.62–1.24	0.47	0.98	0.86–1.12	0.73	0.99	0.87–1.13	0.90
Ischemia/ACS	1.04	0.89–1.22	0.59	1.03	0.91–1.17	0.63	0.96	0.80–1.15	0.67	1.00	0.82–1.21	0.98	0.89	0.75–1.07	0.22	0.90	0.77–1.06	0.20
Worsening fatigue	1.02	0.88–1.18	0.77	0.98	0.86–1.11	0.72	1.25	1.05–1.49	0.010	1.15	0.96–1.37	0.13	1.08	0.95–1.23	0.23	1.05	0.92–1.20	0.47
Pulmonary congestion	1.03	0.88–1.21	0.70	1.02	0.86–1.21	0.79	0.93	0.78–1.11	0.43	0.89	0.75–1.05	0.16	1.03	0.93–1.14	0.62	1.03	0.93–1.14	0.63

CI = confidence interval; ICD = implantable cardioverter-defibrillator; OR = odds ratio.

uncontrolled hypertension (8%) as most frequent (5). In a single-center study of 101 patients of low socioeconomic status, the most frequent precipitating factors were nonadherence to a low sodium diet, to medications, or to both (64%), uncontrolled hypertension (44%), and cardiac arrhythmia (29%) (6). In another study involving 768 patients with systolic HF, precipitating factors associated with worsening HF status included nonadherence to salt restriction (22%), pulmonary infections (20%), antiarrhythmic agents (15%), arrhythmia (13%), calcium channel blockers (13%), and inappropriate reductions in heart rate management (10%) (7). These studies are limited by their retrospective nature, small study populations from single centers, and inability to determine the cause or effect relationship of the precipitants for HF exacerbation (7). Selective enrollment criteria was also used in a double blind trial introducing potential patient selection bias, as patients received closer follow-up compared with the real-world setting.

Borderline patients were closer to the preserved EF group in terms of mean age and some comorbidities (anemia, atrial fibrillation, diabetes, hypertension, renal disease) but closer to reduced EF in ischemic cause of EF and length of stay. The prevalence of precipitating factors for the borderline group were more similar to those for the preserved EF group than to those for the low EF group, in which dizziness was more common and dyspnea was less common. However, the borderline group was intermediate in the prevalence of fatigue and arrhythmia between the preserved and reduced EF groups. Borderline EF patients were similar to reduced EF patients in certain associations with outcome (e.g., ischemia and fatigue with mortality). These data indicate that the borderline EF group was truly intermediate between preserved and reduced left ventricular EF groups.

The strengths of the present study include the fact that it investigated 99,825 HF admissions from 305 hospitals from all regions of the country, making it highly generalizable. The present study also investigated the relationship between factors that may have precipitated admission and clinical outcomes by EF group. Insight into how precipitants of HF hospitalization influence outcomes such as length of stay and mortality and whether these relationship are similar or different among EF groups may help guide management strategies for hospitalized patients with HF and assist with preventing HF rehospitalizations (13,14). HF guidelines recommend that patients hospitalized for HF undergo evaluation for precipitating factors and suggest that treatment of precipitating factors is an instrumental part of HF management

(14). This study provides further evidence supporting these guideline recommendations.

Heart failure patients with certain high-risk factors may benefit from closer monitoring and early intervention to prevent adverse outcomes. Optimizing patient education and disease management strategies may influence several of these precipitating factors, including dietary and medication nonadherence (13–15). Influenza and pneumococcal vaccinations may reduce adverse outcomes in HF patients (14), and the present study suggests that this is an important consideration because pneumonia/respiratory process was associated with longer hospital stay and greater mortality. Similarly, patients presenting with ischemia in the present study had a higher mortality rate in the group with reduced EF. Disease management in turn may therefore be improved with antiplatelets, statins, and possibly revascularization in certain patients (14,15). Strategies targeting identified precipitating factors that may or may not be associated with adverse outcomes should be part of a comprehensive management plan in HF patients to reduce hospitalizations and mortality. Future studies should focus on testing interventions targeting these contributing factors in the HF population.

STUDY LIMITATIONS. First, the lack of follow-up after discharge does not allow assessment of long-term outcomes. Second, data were collected by medical chart review and depend on the accuracy and completeness of documentation and abstraction. In addition, the ascertainment of a precipitating cause for decompensated HF was based on the clinical judgment of the local providers. The list of precipitating factors available to hospitals was not exhaustive, and it is important to consider less common precipitants, such as urinary retention (16). Given the observational nature of the study, unobserved variables may have confounded the results. Although the Generalized Estimating Equation (GEE) multivariate analyses adjusted for multiple baseline differences, residual measured and unmeasured confounding may influence these findings. Furthermore, although this is a registry-based study with an opportunity to study patients in real-world setting, data collection is dependent on voluntary participation of hospitals such that findings may not be generalizable to hospitals that differ in care patterns or patient characteristics. Due to the large number of comparisons, it is more likely that borderline significant differences would be observed by chance alone. Finally, because of the large number of patients in this study, small differences might lead to statistical significance but lack clinical relevance.

TABLE 5 Factors Associated With In-Hospital Mortality From Individual Models

	Reduced Systolic Function						Borderline Systolic Function						Preserved Systolic Function					
	Unadjusted			Adjusted			Unadjusted			Adjusted			Unadjusted			Adjusted		
Factor	OR	95% CI	p Value	OR	95% CI	p Value	OR	95% CI	p Value	OR	95% CI	p Value	OR	95% CI	p Value	OR	95% CI	p Value
Acute pulmonary edema	1.76	1.39–2.22	<0.0001	2.09	1.62–2.69	<0.0001	0.98	0.54–1.76	0.93	1.05	0.58–1.93	0.86	1.17	0.79–1.74	0.43	1.33	0.90–1.97	0.15
Worsening renal failure	2.87	2.41–3.42	<0.0001	1.62	1.33–1.96	<0.0001	2.08	1.52–2.84	<.0001	1.53	1.02–2.28	0.039	1.82	1.47–2.26	<0.0001	1.41	1.06–1.86	0.018
ICD shock/sustained ventricular arrhythmia	2.51	1.54–4.08	0.0002	2.63	1.73–4.02	<0.0001							1.80	0.40–8.03	0.44	1.98	0.43–9.02	0.38
Pneumonia/respiratory process	1.54	1.23–1.94	0.0002	1.52	1.22–1.89	0.0002	1.57	1.16–2.13	0.0033	1.48	1.05–2.10	0.025	1.63	1.37–1.92	<0.0001	1.61	1.36–1.91	<0.0001
Dyspnea	0.71	0.62–0.81	<0.0001	0.78	0.68–0.89	0.0003	0.75	0.58–0.97	0.029	0.83	0.64–1.08	0.16	0.82	0.71–0.94	0.0053	0.88	0.77–1.01	0.068
Dietary noncompliance	0.44	0.32–0.60	<0.0001	0.65	0.46–0.91	0.012	0.57	0.26–1.23	0.15	0.83	0.38–1.80	0.63	0.35	0.22–0.55	<0.0001	0.52	0.33–0.83	0.0058
Ischemia/ACS	1.41	1.05–1.91	0.023	1.31	1.01–1.69	0.038	0.97	0.58–1.63	0.91	1.17	0.73–1.88	0.51	1.67	1.23–2.27	0.0011	1.72	1.27–2.33	0.0005
Volume overload/ weight gain	0.95	0.79–1.16	0.62	0.84	0.70–1.01	0.058	1.05	0.76–1.44	0.78	0.99	0.71–1.40	0.97	0.85	0.69–1.05	0.13	0.81	0.67–0.99	0.041
Pulmonary congestion	1.20	0.87–1.63	0.26	1.26	0.90–1.74	0.17	1.67	1.02–2.71	0.040	1.54	0.95–2.48	0.079	1.21	0.80–1.82	0.37	1.24	0.82–1.87	0.31
Uncontrolled hypertension	0.47	0.34–0.64	<0.0001	1.16	0.86–1.57	0.33	0.54	0.33–0.89	0.017	1.15	0.61–2.18	0.67	0.41	0.30–0.55	<0.0001	0.81	0.61–1.07	0.14
Arrhythmia	1.32	1.16–1.51	<0.0001	1.07	0.91–1.26	0.42	1.61	1.24–2.08	0.0004	1.21	0.86–1.68	0.27	1.25	1.08–1.43	0.0019	1.04	0.89–1.21	0.65
Dizziness/syncope	1.16	0.87–1.54	0.30	1.10	0.85–1.41	0.47	1.10	0.60–2.02	0.75	1.07	0.55–2.06	0.84	1.11	0.69–1.77	0.67	1.07	0.69–1.68	0.75
Worsening fatigue	1.42	0.97–2.08	0.074	1.09	0.77–1.55	0.63	1.50	0.91–2.47	0.11	1.10	0.67–1.82	0.71	1.83	1.36–2.47	<0.0001	1.49	1.09–2.02	0.011
Medication noncompliance	0.55	0.39–0.79	0.0009	0.93	0.65–1.33	0.71	0.32	0.17–0.58	0.0002	0.52	0.27–0.98	0.043	0.36	0.26–0.51	<0.0001	0.55	0.40–0.76	0.0004

There were no occurrences of in-hospital mortality for subjects with ICD shock/sustained ventricular arrhythmia in the borderline ejection fraction group.
Abbreviations as in Table 4.

In addition, certain factors are associated with adverse in-hospital outcomes independent of other predictive variables among patients with reduced, borderline, and preserved EF. Heightened awareness of these factors, many of which are avoidable or modifiable, is important in optimizing HF management.

CONCLUSIONS

Identifiable factors that may have precipitated admission are common, and the frequency varies by EF group. In addition, certain factors are associated with adverse in-hospital outcomes independent of other predictive variables among patients with reduced, borderline, and preserved EF. Heightened awareness of these factors, many of which are avoidable or modifiable, is important in optimizing HF management.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Our study has several clinical implications. We identified several high-risk precipitating factors that varied for different groups of patients. Heart failure patients with high-risk factors may benefit from closer monitoring and early intervention to prevent adverse outcomes. For example, a comprehensive management plan for patients with HF should routinely look for the presence of precipitating factors to reduce hospitalizations and possibly mortality.

TRANSLATIONAL OUTLOOK: While our study identified precipitating factors, we did not test any interventions that directly addressed these factors. Future studies should focus on testing interventions that target these contributing factors in patients with HF. Such evaluations should examine factor interventions individually and also combined, as may occur through disease management or other types of comprehensive care structures.

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KEY WORDS heart failure, outcomes, precipitating factors