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Magnitude of and Prognostic Factors Associated With 1-Year Mortality After Hospital Discharge for Acute Decompensated Heart Failure Based on Ejection Fraction Findings

Andrew H. Coles
University of Massachusetts Medical School

Et al.

ORIGINAL RESEARCH

Magnitude of and Prognostic Factors Associated With 1-Year Mortality After Hospital Discharge for Acute Decompensated Heart Failure Based on Ejection Fraction Findings

Andrew H. Coles, PhD; Mayra Tisminetzky, MD, PhD; Jorge Yarzebski, MD, MPH; Darleen Lessard, MS; Joel M. Gore, MD; Chad E. Darling, MD; Robert J. Goldberg, PhD

***Background*—**Limited data exist about the magnitude of and the factors associated with prognosis within 1 year for patients discharged from the hospital after acute decompensated heart failure. Data are particularly limited from the more generalizable perspective of a population-based investigation and should be further stratified according to currently recommended ejection fraction (EF) findings.

***Methods and Results*—**The hospital medical records of residents of the Worcester, Massachusetts, metropolitan area who were discharged after acute decompensated heart failure from all 11 medical centers in central Massachusetts during 1995, 2000, 2002, 2004, and 2006 were reviewed. The average age of the 4025 study patients was 75 years, 93% were white, and 44% were men. Of these, 35% (n=1414) had reduced EF (≤40%), 13% (n=521) had borderline preserved EF (41–49%), and 52% (n=2090) had preserved EF (≥50%); at 1 year after discharge, death rates were 34%, 30%, and 29%, respectively (*P*=0.03). Older age, a history of chronic obstructive pulmonary disease, systolic blood pressure findings <150 mm Hg on admission, and hyponatremia were important predictors of 1-year mortality for all study patients, whereas several comorbidities and physiological factors were differentially associated with 1-year death rates in patients with reduced, borderline preserved, and preserved EF.

***Conclusions*—**This population-based study highlights the need for further contemporary research into the characteristics, treatment practices, natural history, and long-term outcomes of patients with acute decompensated heart failure and varying EF findings and reinforces ongoing discussions about whether different treatment guidelines may be needed for these patients to design more personalized treatment plans. **(*J Am Heart Assoc*. 2015;4:e002303 doi: 10.1161/JAHA.115.002303)**

Key Words: acute heart failure • ejection fraction findings • population-based study

Acute decompensated heart failure (ADHF) is a worldwide epidemic that affects nearly 1 million US adults and results in considerable morbidity, functional disability, and mortality.[1] To better understand and characterize the epidemiology of this increasingly prevalent clinical syndrome, a classification schema for heart failure (HF) has been recently created based on ejection fraction (EF) findings.[2] The 2013 American Heart Association/American College of Cardiology (AHA/ACC) guidelines characterized 3 EF strata as preserved EF (pEF; ≥50%), reduced EF (rEF; ≤40%), and borderline preserved EF (BpEF; 41–49%).[2] This new classification schema was recommended because several research groups had used different EF cutoffs for differentiating patients with pEF from those with rEF findings, producing varying study results and difficulties in interpretation and extrapolation.

Prior epidemiological studies have identified a number of important prognostic factors associated with poor long-term outcomes for patients with ADHF including advanced age, male sex, hyponatremia, lower systolic blood pressure, poorer kidney function, and several comorbid conditions.[3–12] Many of these earlier studies examined the role of various prognostic factors in patients with HF that had not further been stratified according to EF findings, and among those that did,[11,13–17] none used the 2013 AHA/ACC guidelines recommending specific EF cut points.[2] Furthermore, few data exist on the prognosis or the factors associated with poor long-term prognosis for patients with BpEF values, especially from the

From the Program in Gene Function and Expression (A.H.C.), Departments of Quantitative Health Sciences (M.T., J.Y., D.L., R.J.G.), Medicine (J.M.G.), and Emergency Medicine (C.E.D.), University of Massachusetts Medical School, Worcester, MA.

Correspondence to: Robert J. Goldberg, PhD, Division of Epidemiology of Chronic Diseases and Vulnerable Populations, Department of Quantitative Health Sciences, University of Massachusetts Medical School, 55 Lake Avenue North, Worcester, MA 01655. E-mail: robert.goldberg@umassmed.edu

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more generalizable perspective of a population-based investigation.

The main objectives of the present communitywide study were to describe the factors that influence all-cause mortality during the first year after hospital discharge among patients with ADHF who were further categorized by currently recommended EF strata and cut points and by age. A secondary study objective was to describe differences in the medications prescribed and the procedures received at the time of hospital discharge for patients who survived the first year after hospital discharge in comparison with those who died. Data from the population-based Worcester Heart Failure Study were used for this investigation.[18–21]

Methods

Study Population

The study population consisted of adult residents of the Worcester, Massachusetts, metropolitan area (2010 census estimate of 518 000) who survived hospitalization for ADHF at all 11 central Massachusetts medical centers during the 5 study years of 1995, 2000, 2002, 2004, and 2006 and who had undergone an echocardiogram during the acute index hospitalization (n=4025). These study years were chosen based on grant funding availability.

Details of the Worcester Heart Failure Study have been described previously.[18–21] In brief, trained nurses and physicians reviewed the medical records of patients with primary and/or secondary International Classification of Diseases, 9th Revision (ICD-9), discharge diagnoses consistent with the possible presence of HF (ICD-9 code 428). In addition, the hospital medical records of patients with discharge diagnoses of hypertensive heart and renal disease, acute cor pulmonale, cardiomyopathy, pulmonary congestion, acute lung edema, and respiratory abnormalities were reviewed to identify hospitalized residents of central Massachusetts who may have had new-onset ADHF. The Framingham criteria (presence of 2 major criteria or the presence of 1 major and 2 minor criteria) were used to confirm the diagnosis of HF.[22]

All doubtful or questionable cases of ADHF were initially reviewed by the principal investigator in conjunction with the project coordinator and then by the senior cardiologist and internist panel. Doubtful or questionable cases of ADHF were defined as those in which there was uncertainty as to whether HF had occurred during the admission of interest, and only definite cases of ADHF were included in this investigation. Excluded from the study were patients with a principal diagnosis of acute myocardial infarction (ICD-9 codes 410.0 to 410.99), cases of HF secondary to a surgical procedure (eg, coronary artery bypass grafting) or to fluid overload (eg, during hemodialysis), and all medical records with a principal diagnosis of chest pain (eg, ICD-9 code 786.5). This study was approved by the institutional review board at the University of Massachusetts Medical School. Informed consent was waived.

Data Collection

Patient demographic characteristics (eg, age, sex), medical history (eg, diabetes, hypertension, stroke), clinical characteristics, and laboratory test results (eg, serum sodium, blood urea nitrogen [BUN]) were collected from the review of inpatient medical records. Although we collected information about kidney function through the measurement of the estimated serum glomerular filtration rate and BUN findings, these measures are highly correlated, and BUN findings have been shown to be more predictive of adverse events in patients with ADHF than estimated glomerular filtration rate findings.[23] Consequently, we presented data only on serum BUN findings.

All EF measurements were ascertained by results from a transthoracic echocardiogram during each patient's index hospitalization for ADHF. The rEF was defined as a patient with ADHF who had an EF value $\leq$40%, pEF was defined as an EF value $\geq$50%, and BpEF was classified as being present in patients with an EF value between 41% and 49%. These 3 cut points were chosen based on currently recommended 2013 AHA/ACC guidelines.[2]

Physicians' progress notes and daily medication logs were reviewed for prescription of selected medications and medication classes at the time of hospital discharge, including angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), aldosterone inhibitors, aspirin, beta blockers, calcium channel blockers, digoxin, diuretics, lipid-lowering agents, and nitrates. Postdischarge survival status for all confirmed cases of ADHF was obtained by the review of medical records at all participating medical centers for further hospitalizations or medical care contacts and review of Social Security Death Index and statewide death certificates. Follow-up of all patient cohorts was through calendar year 2011.

Data Analysis

We examined differences in the characteristics of patients in the 3 mutually exclusive EF strata using ANOVA and χ^2 tests for continuous and discrete variables, respectively. A life table analysis was performed to estimate postdischarge death rates including patients with varying duration of follow-up. Cox proportional hazards regression models were used to examine the association between various prognostic factors and 1-year postdischarge mortality, further stratified according to EF findings. This time point was chosen for analysis

because of the particularly high death rates experienced by patients with ADHF after discharge from the hospital. The factors chosen for inclusion in the regression models were based on established predictors of mortality in the published literature and differences between the EF groups at baseline, defined as $P<0.05$. We did not control for the receipt of cardiac medications during the index hospitalization because of the potential for confounding by treatment indication, difficulties in interpretation, and lack of more detailed information about the timing of therapy administration relative to the onset of ADHF. The Committee for the Protection of Human Subjects in Research at the University of Massachusetts Medical School approved this study.

Results

Study Population Characteristics

During the 5 years under study, a total of 4025 residents of central Massachusetts were discharged from all 11 Worcester metropolitan medical centers after ADHF and had echocardiography results available during their index hospitalization. The average age of this population was approximately 75 years, the majority of patients were white, and 56% were women. In this population, 35% (n=1414) of patients were considered to have rEF (EF ≤40%), 13% (n=521) had BpEF (EF 41–49%), and 52% (n=2090) were classified as having pEF (EF ≥50%).

Postdischarge Survival

Overall, 34% (n=474) of the patients with rEF, 30% (n=157) of the patients with BpEF, and 29% (n=614) of the patients with pEF died during the first year after hospital discharge for ADHF ($P=0.03$). The median survival times were 2.4, 2.3, and 2.7 years after hospital discharge for patients with rEF, BpEF, and pEF, respectively. There was an important decline in the proportion of patients who died during the first year under study (1995) compared with the most recent year under investigation (2006) among those with rEF (41% in 1995 versus 24% in 2006) and pEF (35% versus 26%) but not among those with BpEF (28% versus 30%) (Figure).

Characteristics of Deceased Patients

We examined the differences in the characteristics of patients who died compared with those who survived the first year after hospital discharge in the 3 EF strata. Patients who died were significantly older (79 versus 74 years), were more likely to be white (96% versus 92%), had a longer stay in the hospital (7.9 versus 6.0 days), and were more likely to have been diagnosed previously with chronic obstructive pulmonary disease (COPD; 37.1% versus 29.5%), atrial fibrillation (43.1% versus 32.3%), and HF (68.0% versus 57.2%). In addition, patients who died within the first year after hospital discharge had significantly lower average blood pressures (diastolic 71.9 versus 78.4 mm Hg; systolic 138.3 versus 148.8 mm Hg) but significantly higher BUN levels (37.9 versus 28.4 mg/dL).

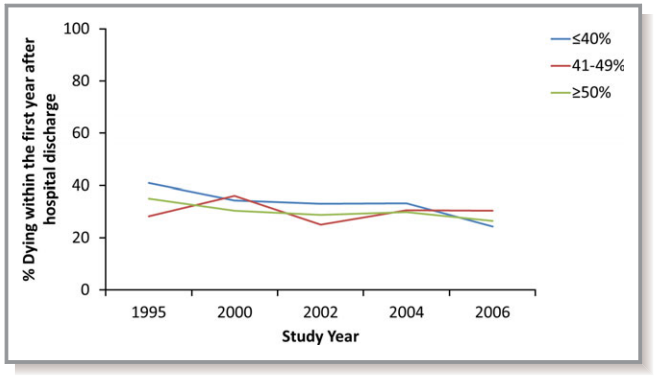

Figure. Trends in 1-year postdischarge mortality according to ejection fraction findings.

In terms of the specific EF strata, patients with rEF who died within 1 year after hospital discharge were more likely to have been previously diagnosed with chronic kidney disease, peripheral vascular disease, and coronary heart disease (Table 1). In addition, these patients had lower serum sodium and hematocrit findings at the time of hospital admission but higher BUN values. Patients with BpEF who died were more likely to have been previously diagnosed with atrial fibrillation and HF than those who survived this period and had higher BUN findings. Patients with pEF that died during this high-risk period were more likely to have a history of either chronic kidney disease or peripheral vascular disease, were less likely to have a history of hypertension, and had lower serum hematocrit findings but higher BUN levels at the time of hospital admission than those who survived the first year after hospital discharge for ADHF. The vast majority of patients with ADHF were admitted to the 3 major teaching and community hospitals in central Massachusetts.

Hospital Medication Use by EF Strata

Prescribing patterns of selected discharge medications for patients with ADHF further stratified according to EF findings were evaluated, with several between-group differences noted. Patients with pEF were less likely to have been prescribed ACEIs and ARBs (72% for patients with rEF, 56% for patients with BpEF, and 44% for patients with pEF) and digoxin (56%, 36%, and 22%, respectively) at the time of hospital discharge for ADHF ($P<0.01$). Patients with pEF, however, were significantly more likely to have been prescribed calcium channel blockers at the time of hospital discharge than either

Table 1. Characteristics of Patients With Acute Decompensated Heart Failure After Hospital Discharge According to Ejection Fraction Findings and 1-Year Survival Status

	rEF (EF ≤40%)		BpEF (EF=41–49%)		pEF (EF ≥50%)	
Demographics	Alive (n=940)	Dead (n=474)	Alive (n=364)	Dead (n=157)	Alive (n=1476)	Dead (n=614)
Age (mean, y)	71.4	77.1**	74.4	80.0**	75.7	79.6**
<65, n (%)	245 (26.1)	64 (13.5)	66 (18.1)	7 (4.5)	260 (17.6)	55 (9.0)*
65 to 74	247 (26.3)	85 (17.9)	87 (23.9)	30 (19.1)	288 (19.5)	98 (16.0)*
75 to 84	317 (33.7)	200 (42.2)	144 (39.6)	69 (44.0)*	561 (38.0)	232 (37.9)*
≥85	131 (13.9)	125 (26.4)	67 (18.4)	51 (32.5)*	367 (24.9)*	228 (37.2)*
Male, n (%)	564 (60.0)	274 (57.8)	164 (45.1)	74 (47.1)	490 (33.2)	203 (33.1)
White, n (%)	845 (89.9)	451 (95.2)**	334 (91.8)	151 (96.2)	1362 (92.3)	590 (96.1)*
Length of stay (mean, days)	6.2	7.4**	5.9	7.6*	5.9	8.9**
Teaching hospital	835 (88.8)	443 (93.5)**	327 (89.8)	137 (87.3)	1323 (89.6)	544 (88.6)
Comorbidities, n (%)						
Atrial fibrillation	312 (33.2)	187 (39.5)*	111 (30.5)	69 (44.0)*	492 (33.3)	282 (45.9)**
Cancer	146 (15.5)	112 (23.6)*	88 (24.2)	43 (27.4)	275 (18.6)	164 (26.7)*
Chronic kidney disease	217 (23.1)	186 (39.2)**	87 (23.9)	49 (31.2)	306 (20.7)	182 (29.6)**
COPD	242 (25.7)	148 (31.2)*	107 (29.4)	66 (42.0)*	492 (33.3)	234 (38.1)*
Coronary heart disease	497 (52.9)	308 (65.0)**	191 (52.5)	95 (60.5)	658 (44.6)	279 (45.4)
Diabetes	353 (37.6)	191 (40.3)	144 (39.6)	71 (45.2)	529 (35.8)	205 (33.4)
Heart failure	578 (61.5)	356 (75.1)**	199 (54.7)	105 (66.9)*	816 (55.3)	380 (61.9)*
Hypertension	632 (67.2)	324 (68.4)	274 (75.3)	109 (69.4)	1110 (75.2)	425 (69.2)*
Liver disease/failure	31 (3.3)	15 (3.2)	10 (2.8)	6 (3.8)	38 (2.6)	19 (3.1)
Peripheral vascular disease	154 (16.4)	132 (27.9)**	90 (24.7)	33 (21.0)	278 (18.8)	135 (22.0)**
Stroke	108 (11.5)	68 (14.4)	50 (13.7)	30 (19.1)	175 (11.9)	80 (13.0)
Laboratory and physiologic variables, mean±SD						
Blood urea nitrogen, mg/dL	27.7±18.2	42.3±24.6**	30.0±19.6	36.0±21.7*	27.5±17.4	35.4±22.6**
Diastolic blood pressure, mm Hg	81.4±19.4	72.2±18.1**	78.6±18.7	72.7±17.1*	75.1±19.2	70.8±19.7**
Glucose, mg/dL	158.5±68.7	153.2±64.9	161.9±75.5	158.8±70.1	153.9±65.6	149.9±62.7
Hematocrit (%)	38.1±6.5	36.4±6.4**	36.1±6.3	35.3±6.4	36.4±13.1	34.7±6.2*
Sodium, mEq/L	137.9±5.4	136.9±5.0*	137.9±4.2	137.7±4.9	137.8±5.0	137.3±7.2
Systolic blood pressure, mm Hg	144.2±30.0	130.1 ±28.4**	151.9±32.9	142.3±29.3*	150.4±31.8	142.4±32.1**
Total cholesterol, mg/dL	158.1±42.9	148.6±39.2	157.6±38.8	145.2±44.3	158.5±42.6	152.5±46.2

ACEIs indicates angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; BpEF, borderline preserved ejection fraction; COPD, chronic obstructive pulmonary disease; EF, ejection fraction; pEF, preserved ejection fraction; rEF, reduced ejection fraction.
*P<0.05.
**P<0.001.

of the other EF comparison groups (13% for rEF, 28% for BpEF, and 33% for pEF; P<0.01).

We examined possible differences in the medications prescribed at hospital discharge for patients who survived the first year after discharge in comparison to those who died, further stratified according to EF findings (Table 2). Patients with rEF who died during this period were significantly less likely to have been prescribed ACEIs or ARBs, aldosterone inhibitors, aspirin, beta blockers, and lipid-lowering agents than those who survived but were more likely to have been prescribed nitrate therapy (Table 2). Patients with BpEF who died were significantly less likely to have been prescribed aspirin, beta blockers, lipid-lowering agents, and nitrates but were more likely to have been prescribed digoxin than those who survived the first year after hospital discharge. Patients with pEF who died were significantly less likely to have been prescribed ACEIs or ARBs, aspirin, beta blockers, and lipid-lowering agents but were more likely to have been

Table 2. Hospital Discharge Medications and Procedures According to Ejection Fraction Findings and 1-Year Survival Status

	rEF (EF ≤40%)		BpEF (EF=41–49%)		pEF (EF ≥50%)	
Medication, n (%)	Alive (n=940)	Dead (n=474)	Alive (n=364)	Dead (n=157)	Alive (n=1476)	Dead (n=614)
ACEIs/ARBs	724 (77.0)	292 (61.6)*	212 (58.2)	82 (52.2)	692 (46.9)	226 (36.8)*
Aldosterone inhibitors	110 (11.7)	39 (8.2)*	19 (5.2)	4 (2.6)	63 (4.3)	20 (3.3)
Aspirin	555 (59.0)	236 (49.8)*	191 (52.5)	71 (45.2)**	749 (50.8)	240 (39.1)*
Beta blockers	597 (63.5)	230 (48.5)*	231 (63.5)	77 (49.0)*	855 (57.9)	300 (48.9)*
Calcium channel blockers	128 (13.6)	55 (11.6)	104 (28.6)	42 (26.8)	474 (32.1)	214 (34.9)
Digoxin	523 (55.6)	262 (55.3)	123 (33.8)	65 (41.4)**	289 (19.6)	161 (26.2)*
Diuretics	785 (83.5)	405 (85.4)	295 (81.0)	130 (82.8)	1131 (76.6)	455 (74.1)
Lipid-lowering agents	360 (38.3)	115 (24.3)*	121 (33.2)	41 (26.1)**	515 (34.9)	127 (20.7)*
Nitrates	271 (28.8)	157 (33.1)**	122 (33.5)	52 (33.1)*	322 (21.8)	131 (21.3)
Procedures, n (%)						
Dialysis	21 (2.2)	25 (5.3)**	13 (3.6)	4 (2.6)	30 (2.0)	14 (2.3)
ICD	85 (9.0)	32 (6.8)	15 (4.1)	4 (2.6)	21 (1.4)	13 (2.1)
CRT	2 (0.2)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Combination medications (ACEIs/ARBs, beta blockers, aldosterone antagonists)						
0	76 (8.1)	104 (21.9)*	64 (17.6)	43 (27.4)*	344 (23.3)	199 (32.4)*
Any 1	377 (40.1)	197 (41.6)	149 (40.9)	65 (41.4)	677 (45.9)	287 (46.7)
≥2	487 (51.8)	173 (36.5)	151 (41.5)	49 (31.2)	455 (30.8)	128 (20.9)
Combination medications (digoxin, diuretics, nitrates)						
None or any 1	383 (40.7)	180 (38.0)**	189 (51.9)	70 (44.6)	1029 (69.7)	415 (67.6)
Any 2	410 (43.6)	200 (42.2)	135 (37.1)	70 (44.6)	384 (26.0)	164 (26.7)
All 3	147 (15.6)	94 (19.8)	40 (11.0)	17 (10.8)	63 (4.3)	35 (5.7)

BpEF indicates borderline preserved ejection fraction; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator; pEF, preserved ejection fraction; rEF, reduced ejection fraction.
*$P<0.05$.
**$P<0.001$.

prescribed digoxin than patients who survived this period (Table 2).

Patients who died during this 1-year period were also more likely not to have been prescribed any cardiac medication (ACEIs or ARBs, beta blockers, and aldosterone antagonists), regardless of EF strata (Table 2). Patients from all 3 EF strata who were prescribed >2 cardiac medications at the time of hospital discharge for ADHF were more likely to have survived the first year after hospital discharge than patients who had been prescribed fewer cardiac medications, and these trends were most evident for those with BpEF (Table 2). Few patients in each study group underwent dialysis or received implanted cardiac-support devices.

Factors Associated With 1-Year Mortality for Patients With ADHF by EF Strata

After adjusting for a number of important clinical and demographic variables, the 4 statistically significant factors that were associated with a greater risk for dying during the first year after hospital discharge across all 3 EF strata were advanced age, a history of previously diagnosed COPD, systolic blood pressure <150 mm Hg at the time of hospital admission, and serum sodium findings <135 mg/dL.

Among patients with rEF after multivariable adjustment, a history of peripheral vascular disease and elevated BUN levels were significantly associated with an increased risk of dying (Table 3). Among patients with BpEF, no additional factors were significantly associated with an increased risk of dying at 1 year. Among patients with pEF, a history of atrial fibrillation, absence of a history of hypertension, low hematocrit findings, and elevated BUN values at the time of hospital admission were associated with higher 1-year death rates after hospital discharge (Table 3). We also carried out an additional regression analysis in which we controlled for potential heterogeneity among participating medical centers and found no differences in the factors associated with 1-year death rates in the models with and without this variable (data not shown).

Table 3. Multivariable Adjusted HRs for Factors Associated With Mortality at 1 Year According to Ejection Fraction Findings

	rEF (EF ≤40%)		BpEF (EF 41–49%)		pEF (EF ≥50%)	
Parameter	HR	95% CI	HR	95% CI	HR	95% CI
Age, y						
<75	1.0		1.0		1.0	
75 to 84	1.55*	1.22, 1.96*	2.02*	1.29, 3.16*	1.44*	1.14, 1.80*
≥85	2.11*	1.62, 2.76*	3.20*	1.96, 5.22*	2.12*	1.67, 2.69*
White race	1.32	0.83, 2.10	1.44	0.58, 3.61	1.36	0.86, 2.16
Length of hospital stay, days	1.02*	1.01, 1.03*	1.03*	1.00, 1.05*	1.03*	1.03, 1.04*
Comorbidities						
Atrial fibrillation	0.90	0.74, 1.10	1.10	0.77, 1.58	1.37*	1.14, 1.63*
Chronic kidney disease	0.98	0.79, 1.23	1.20	0.78, 1.83	1.10	0.89, 1.36
COPD	1.28*	1.03, 1.58*	1.86*	1.29, 2.69*	1.20*	1.00, 1.44*
Coronary heart disease	1.08	0.87, 1.34	1.11	0.76, 1.62	0.97	0.81, 1.16
Heart failure	1.14	0.90, 1.45	1.31	0.88, 1.94	1.09	0.90, 1.32
Hypertension	0.88	0.71, 1.08	0.77	0.52, 1.13	0.77*	0.64, 0.93*
Peripheral vascular disease	1.31*	1.05, 1.64*	0.76	0.49, 1.19	1.04	0.84, 1.29
Stroke	1.19	0.90, 1.57	1.17	0.75, 1.82	1.01	0.78, 1.32
Laboratory and physiologic variables						
BUN, mg/dL						
<20	1.0		1.0		1.0	
20 to 39	1.80*	1.33, 2.44*	1.34	0.86, 2.10	1.26*	1.00, 1.57*
≥40	3.96*	2.85, 5.50*	1.52	0.92, 2.52	1.94*	1.50, 2.52*
Hematocrit (%)						
<30	1.0		1.0		1.0	
30 to 44	0.94	0.71, 1.25	0.89	0.57, 1.39	0.73*	0.59, 0.90*
≥45	0.86	0.56, 1.33	1.35	0.63, 2.89	0.67	0.42, 1.06
Serum sodium, mEq/L						
<135	1.0		1.0		1.0	
≥135	0.68*	0.54, 0.84*	0.64*	0.42, 0.99*	0.77*	0.63, 0.94*
Systolic blood pressure, mm Hg						
<150	1.0		1.0		1.0	
150 to 159	0.66*	0.45, 0.99*	0.54*	0.31, 0.95*	0.65*	0.47, 0.89*
≥160	0.69*	0.52, 0.93*	0.74	0.47, 1.15	0.85	0.68, 1.05

Controlling variables were age, race, hospital length of stay, previously diagnosed chronic lung disease, chronic kidney disease, hypertension, peripheral vascular disease, stroke, atrial fibrillation, coronary heart disease, heart failure, blood pressure findings, serum sodium, hematocrit, and BUN values at the time of hospital admission. BpEF indicates borderline preserved ejection fraction; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; pEF, preserved ejection fraction; rEF, reduced ejection fraction.
*Shows significant differences.

Impact of Age on Prognostic Factors That Affect All-Cause Mortality During the First Year After Hospital Discharge

Age is an established predictor of mortality for patients with ADHF and other serious chronic diseases, and we showed advanced age to be the most significant predictor of postdischarge mortality during the first year after discharge from the hospital in our regression analyses (Table 3). In our study population, 55% of patients with rEF, 65% of patients with BpEF, and 66% of patients with pEF were aged ≥75 years (Table 1). Consequently, we further divided patients in the 3 EF strata into 2 age groups, <75 and ≥75 years, for purposes of examining whether there

were differences in various prognostic factors between younger and older patients hospitalized with ADHF (Table 4).

The important prognostic factors that were significantly associated with an increased risk of dying during the first year after hospital discharge for ADHF for comparatively younger patients with rEF included a history of previously diagnosed stroke, systolic blood pressure findings <150 mm Hg on admission, hyponatremia, and elevated BUN levels (Table 4). Factors associated with an increased risk of dying during the first year after hospital discharge for those aged ≥75 years with rEF included a history of previously diagnosed COPD or peripheral vascular disease and those with elevated BUN levels (Table 4).

Table 4. HRs Associated With 1-Year Death Rates After Hospital Discharge According to Age and Ejection Fraction Findings

	rEF (EF ≤40%)				BpEF (EF 41–49%)				pEF (EF ≥50%)			
	<75 years		≥75 years		<75 years		≥75 years		<75 years		≥75 years	
Factor	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
White race	1.31	0.74, 2.34	1.43	0.63, 3.25	1.70	0.37, 7.74	1.09	0.34, 3.52	1.91*	1.01, 3.59*	0.86	0.44, 1.67
Comorbidities												
Atrial fibrillation	0.68	0.46, 1.01	1.00	0.79, 1.27	2.09	0.97, 4.50	0.99	0.66, 1.50	1.86*	1.29, 2.69*	1.27*	1.04, 1.56*
Chronic kidney disease	1.18	0.77, 1.81	0.86	0.66, 1.14	1.09	0.46, 2.59	1.33	0.80, 2.22	1.00	0.66, 1.54	1.14	0.89, 1.46
COPD	1.20	0.80, 1.80	1.37*	1.06, 1.76*	1.95	0.82, 4.65	1.63*	1.07, 2.47*	1.13	0.78, 1.62	1.14	0.93, 1.41
Coronary heart disease	1.20	0.81, 1.78	1.01	0.78, 1.31	1.66	0.64, 4.30	0.86	0.56, 1.32	1.03	0.71, 1.49	0.93	0.76, 1.15
Heart failure	1.20	0.78, 1.85	1.15	0.86, 1.54	1.07	0.43, 2.66	1.44	0.92, 2.25	1.28	0.87, 1.90	1.07	0.86, 1.33
Hypertension	0.74	0.51, 1.08	0.97	0.75, 1.26	0.49	0.22, 1.12	0.86	0.55, 1.36	0.89	0.61, 1.30	0.75*	0.60, 0.93*
Peripheral vascular disease	1.01	0.67, 1.54	1.46*	1.12, 1.92*	1.00	0.41, 2.43	0.69	0.40, 1.18	1.19	0.76, 1.84	0.98	0.77, 1.26
Stroke	1.70*	1.04, 2.79*	1.00	0.71, 1.39	0.57	0.18, 1.85	1.24	0.76, 2.03	1.20	0.72, 1.98	0.93	0.68, 1.26
Laboratory and physiologic variables												
BUN levels, mg/dL												
<20	1.0		1.0		1.0		1.0		1.0		1.0	
20 to 39	1.81*	1.09, 3.00*	1.64*	1.11, 2.42*	1.92	0.68, 5.46	1.25	0.75, 2.08	1.18	0.77, 1.80	1.39*	1.07, 1.82*
≥40	5.02*	2.92, 8.63*	3.28*	2.16, 4.98*	2.11	0.71, 6.31	1.31	0.72, 2.38	1.23	0.75, 2.02	2.34*	1.72, 3.18*
Hematocrit (%)												
<30	1.00		1.00		1.00		1.00		1.00		1.00	
30 to 44	0.80	0.49, 1.32	1.03	0.72, 1.48	2.58	0.90, 7.42	0.70	0.42, 1.16	0.56*	0.37, 0.83*	0.81	0.63, 1.05
≥45	0.78	0.36, 1.69	0.98	0.57, 1.67	3.57	0.55, 23.16	1.26	0.54, 2.94	0.33*	0.14, 0.80*	0.82	0.48, 1.41
Serum sodium, mEq/L												
<135	1.00		1.00		1.00		1.00		1.00		1.00	
≥135	0.54*	0.37, 0.80*	0.81	0.61, 1.07	0.22*	0.10, 0.51*	1.03	0.57, 1.86	0.65*	0.43, 0.98*	0.79	0.63, 1.00
Systolic blood pressure, mm Hg												
<150	1.00		1.00		1.00		1.00		1.00		1.00	
150 to 159	0.68	0.35, 1.32	0.64	0.39, 1.04	0.63	0.20, 1.93	0.47*	0.24, 0.91*	0.48*	0.25, 0.96*	0.73	0.51, 1.05
≥160	0.41*	0.22, 0.77*	0.78	0.56, 1.09	0.51	0.17, 1.49	0.76	0.46, 1.26	0.84	0.52, 1.37	0.86	0.67, 1.10

Controlling variables were age, race, hospital length of stay, previously diagnosed chronic lung disease, chronic kidney disease, hypertension, peripheral vascular disease, stroke, atrial fibrillation, coronary heart disease, heart failure, estimated glomerular filtration rate, blood pressure findings, serum sodium, hematocrit, and blood urea nitrogen values at the time of hospital admission. BpEF indicates borderline preserved ejection fraction; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; pEF, preserved ejection fraction; rEF, reduced ejection fraction.

*Shows significant differences.

The only statistically significant factor that was associated with an increased risk for dying during the first year after hospital discharge for younger patients with BpEF was lower serum sodium findings at the time of hospital admission (Table 4). For older patients with BpEF, a history of COPD was associated with an increased risk for dying, whereas systolic blood pressure <150 mm Hg at the time of hospital admission was associated with an increased risk of dying.

White race, a history of atrial fibrillation, systolic blood pressure <150 mm Hg, hyponatremia, and low hematocrit findings were significantly associated with an increased risk of dying for comparatively younger patients with pEF (Table 4). Among older patients with pEF, a history of hypertension was associated with a decreased risk of dying, whereas a history of atrial fibrillation was associated with an increased risk of dying; elevated serum BUN findings were associated with increased mortality during the first year after hospital discharge for older patients with pEF (Table 4).

Discussion

The results of this study of central Massachusetts residents who were hospitalized among all 11 metropolitan Worcester medical centers suggest that patients with ADHF who survived their acute index hospitalization had high 1-year postdischarge all-cause mortality rates. Patients with rEF experienced the highest total death rates, whereas patients with pEF experienced the highest postdischarge survival rates. Advanced age, previously diagnosed COPD, systolic blood pressure findings <150 mm Hg at the time of hospital admission, and hyponatremia were associated with poorer postdischarge prognosis across all EF strata. In contrast, several prognostic factors differed between the 3 EF groups in our univariate and multivariable adjusted analyses. When the study population was further stratified according to age, different prognostic factors were associated with postdischarge mortality in our 3 EF comparison groups.

Study Population Characteristics

Previously published observational studies and clinical trials have primarily examined differences in the demographic and clinical characteristics of patients with either pEF or rEF, with few describing the characteristics of patients with BpEF.[12,24–26] These studies found that HF patients with lower EF values had a higher burden of preexisting diseases, including coronary heart disease and renal failure, and were primarily male. Patients presenting with pEF findings were typically older and mostly female. Our study agreed with the previous literature for patients in these 2 EF strata; however, unlike prior studies, we included patients with BpEF values. Our findings suggest that patients with BpEF appear to represent an intermediate group with some of the characteristics of patients with pEF and rEF. These findings suggest that ADHF is a heterogeneous condition with distinct group characteristics for patients whose prognosis may differ and whose long-term management might need to be approached differently.

Post–Hospital Discharge Mortality

There have been conflicting published findings as to which EF strata have better long-term prognosis after patients develop ADHF.[11,13–17] In the present study, patients with pEF fared better over long-term follow-up than patients with either rEF or BpEF up to 2004. In 2006, patients with rEF fared better than patients with BpEF, and patients with pEF findings had the poorest survival of the 3 EF groups. This finding could be related to more effective medications being prescribed to patients with rEF, or it could be a chance finding resulting from the multiplicity of comparisons carried out.

Our findings of higher survival rates in patients with pEF are consistent with the observation that these patients typically have more noncardiovascular comorbidities than patients with rEF at the time of hospital admission for ADHF.[27] Nevertheless, there are no established treatments for patients with pEF, suggesting that their lower postdischarge mortality might be less a factor of how these patients are managed and more a function of the underlying pathophysiology associated with pEF. This is supported by the observation that ACEIs and ARBs and specific beta blockers have been shown to be beneficial in patients with rEF but not in those with pEF.[28] It is currently unknown whether these medications are as effective in patients with BpEF as they are for patients with rEF. Regardless of the mechanisms involved, and although all patients discharged from the hospital after ADHF experience high long-term death rates, more aggressive management, support, and monitoring strategies are needed, particularly for patients with rEF.

Medication Prescribing Patterns

We observed that patients within each EF stratum were equally likely to have been prescribed a beta blocker at the time of hospital discharge. In addition, patients with pEF had the highest odds of being prescribed a calcium channel blocker; however, evidence of the effectiveness of this medication to improve outcomes in this patient population is lacking.[29] Our findings also provide insight into differences in the medication-prescribing practices for patients who died over the long term compared with those who survived, although we did not examine these associations further, given the nonrandomized observational nature of this investigation and the potential for confounding by treatment indication.

Two observations stand out in our univariate analyses. First, an analysis showed that digoxin was prescribed at the time of hospital discharge to a greater extent for patients with BpEF and pEF who died. Definitive evidence for digoxin efficacy in HF comes from the Digitalis Investigation Group's randomized clinical trial, which showed that although this medication does not improve survival, it appears to be associated with a reduced risk of hospitalization.[30] The second observation was that patients from all 3 EF strata who were still alive 1 year after hospital discharge were treated with multiple cardiac medications at the time of hospital discharge. The prescription of multiple cardiac medications to patients who survived the high-risk first year after hospital discharge suggests that future research should examine which specific combinations of cardiac medications and effective dosages can enhance long-term survival of patients with ADHF, including those in differing EF strata.

Prognostic Factors Affecting Mortality During the First Year After Hospital Discharge

Prospective studies that have classified patients with HF into groups based on EF findings and examined predictors of mortality have typically assessed only 2 strata, namely, those with pEF and rEF findings.[11,13–17] Consistent with the previous literature, older age was associated with worse prognosis for patients across EF strata. In addition, a history of COPD and low systolic blood pressure and serum sodium findings on admission were associated with an increased risk of dying for patients in each EF stratum. Interestingly, we observed that a number of factors differentiated patients with pEF and rEF that might be important for enhanced disease management and lifestyle practices and/or heightened surveillance.

Further stratification of the EF groups by age had an important impact on the factors associated with long-term prognosis for patients in each EF stratum examined in the present study. Atrial fibrillation, peripheral vascular disease, chronic kidney disease, and COPD, which have been reported to be important prognostic factors in patients with ADHF,[24,26,31] appeared to have a differential impact based on EF stratum and baseline age. Future clinical trials should include older patients with different comorbidities to better understand the effects of age and selected comorbidities on the long-term prognosis of patients with ADHF, its various EF strata, and the enhanced management of this clinical syndrome and its various subtypes.

Discrepancies between the current findings and the previous literature with regard to variables affecting the long-term prognosis of patients with ADHF could be related to a number of factors including comparatively small numbers of women studied, use of clinical trial data, different HF diagnostic criteria, exclusion of patients with BpEF,[11] duration of follow-up, and specific EF strata used. Future studies should use the same EF strata as those proposed in the 2013 AHA/ACC guidelines[2] to ensure that studies can be adequately compared. Further work is needed to understand the impact of various chronic conditions and sociodemographic, psychosocial, and clinical factors on the overall mortality of patients with ADHF by currently recommended EF strata.

Study Strengths and Limitations

Our study has several strengths including its population-based design and inclusion of only validated cases of ADHF that occurred among adult patients of all ages from a well-defined and characterized large metropolitan area. In contrast, because this New England community is predominantly white, the generalizability of our findings to other races and ethnicities may be limited. In addition, more contemporary data are needed to extend the present findings. We did not collect information on patients' socioeconomic, psychosocial, or cognitive status or other factors that have been shown to affect long-term prognosis after ADHF; we also did not assess changes in various physiological factors or laboratory findings during each patient's index admission that may have been associated with reduced or increased risk of dying or the role of novel serum biomarkers. Only those patients who had echocardiograms done for clinical indications were included in the analysis, and a large percentage of patients in our surveillance study did not have an echocardiogram performed during the index hospitalization and were excluded from the present investigation. Finally, we had only a single EF measurement available from the index hospitalization for each patient. Because EF findings may change over time,[32] we cannot account for the impact of potentially changing EF values over time and how those changes may have affected the mortality profiles of at-risk patients.

Conclusions

Patients with ADHF experience high death rates after discharge from the hospital, regardless of EF findings. The highest postdischarge mortality rates were observed for patients with rEF. Prognostic factors associated with mortality during the first year after hospital discharge for ADHF differed among patients in the various EF strata, with advanced age having a large impact on which prognostic factors were important determinants of mortality. This study highlights the need for further research into the effectiveness of presently available treatments for patients with varying EF findings and reinforces ongoing discussions about different treatment guidelines that may be needed for patients with pEF, rEF, and BpEF to design more personalized treatment plans.

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Disclosures

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Magnitude of and Prognostic Factors Associated With 1–Year Mortality After Hospital Discharge for Acute Decompensated Heart Failure Based on Ejection Fraction Findings

Andrew H. Coles, Mayra Tisminetzky, Jorge Yarzebski, Darleen Lessard, Joel M. Gore, Chad E. Darling and Robert J. Goldberg

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