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Trajectory of Congestion Metrics by Ejection Fraction in Patients with Acute Heart Failure (From the Heart Failure Network)

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Abstract

Differences in the clinical course of congestion by underlying ejection fraction (EF) have not been well-characterized in acute heart failure (AHF). A *post-hoc* analysis was performed using pooled data from the DOSE-AHF, CARRESS-HF, and ROSE-AHF trials. All patients were admitted for a primary diagnosis of AHF. Patients were grouped as reduced EF 40%, borderline 40% < EF < 50%, or preserved EF ≥ 50%. Multivariable Cox regression analysis was used to assess the association between measures of congestion and the composite of unscheduled outpatient visits, rehospitalization, or death. Mean age was 68±13 years and 74% were male. Patients with a preserved EF were older, more likely to be female, less likely to have an ischemic etiology of HF, and had a higher prevalence of atrial fibrillation/flutter and chronic obstructive pulmonary disease. Compared to patients with a reduced EF, preserved EF patients had lower NT-proBNP levels at baseline (i.e. reduced: 5998 pg/mL [3009 pg/mL, 11414 pg/mL] vs. borderline: 4420 pg/mL [1740 pg/mL, 8057 pg/mL] vs. preserved: 3272 pg/mL [1687 pg/mL, 6536 pg/mL]) and experienced smaller changes during hospitalization. In general, there were few differences between EF groups in the clinical course of congestion as measured by signs and symptoms of HF, body weight change, and net fluid loss. After adjusting for potential confounders, a greater improvement in global visual analogue scale was associated with lower risk of unscheduled outpatient visits, rehospitalization, or death at day 60 (Hazard Ratio 0.94 per 10 mm increase, 95% Confidence Interval 0.89–0.995). This relationship did not differ by EF (p-value = 0.54). In conclusion, among patients hospitalized for AHF there were few differences in the in-hospital trajectory or prognostic value of routine markers of congestion by EF.

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Keywords

acute heart failure; ejection fraction; congestion; signs and symptoms; outcomes

INTRODUCTION

There are more than 1 million hospital admissions for heart failure (HF) annually in the U.S., accounting for the vast majority of the approximately \$40 billion spent on HF-related care each year.^{1,2} Although the prevalence of HF with a preserved EF is growing and expected to overtake HF with a reduced EF in terms of absolute numbers, HF with a preserved EF remains an incompletely understood clinical entity and there are currently no available disease-modifying therapies.^{3–8} Furthermore, AHF patients with a preserved EF experience a similarly poor in-hospital and post-discharge prognosis.⁴ The clinical course of congestion during hospitalization has not been comprehensively and longitudinally described by ejection fraction in a contemporary cohort.^{9,10} Thus, the objective of this *post-hoc* analysis of the National, Heart, Lung, and Blood Institute (NHLBI)-sponsored Heart Failure Network (HFN) database is to systematically characterize the clinical course of congestion in AHF patients with reduced vs. borderline vs. preserved systolic function.

METHODS

The study design and primary results of the Diuretic Optimization Strategies Evaluation in Acute Heart Failure (DOSE-AHF)^{11,12}, Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF)^{13,14}, and Renal Optimization Strategies Evaluation in Acute Heart Failure (ROSE-AHF)^{15,16} trials have been previously reported. All three trials were prospective, double-blinded, and randomized patients admitted for a primary diagnosis of AHF defined by the presence of at least one symptom and one sign of HF. Patients were grouped as reduced EF $\leq 40\%$, borderline $40\% < \text{EF} < 50\%$, or preserved EF $\geq 50\%$.^{17–19}

Study visits were performed during the index hospitalization at baseline, hour 24, and hour 48 in all three studies. The final time point for in-hospital data collection was at hour 72 in DOSE-AHF and ROSE-AHF and hour 96 in CARRESS-HF. Outliers in body weight change and NT-proBNP change less than the 1st percentile or greater than the 99th percentile were excluded.

The global well-being self-assessment (i.e. global VAS) was analyzed on a visual analog scale (VAS). Patients marked their global well-being on a 10 cm vertical line with the top labeled “best you have ever felt” and the bottom labeled “worst you have ever felt”. Similar methodology was used for the dyspnea self-assessment (i.e. dyspnea VAS), with labels of “I am not breathless at all” and “I am as breathless I have ever been”. The global VAS and dyspnea VAS were scored from 0 to 100 by measuring the distance in millimeters from the marked site to the bottom of the line. A simple “orthodema congestion score” was calculated by summing the individual components of orthopnea and edema.²⁰ Orthopnea was defined as “present” if the patient needed ≥ 2 pillows to breathe comfortably (i.e. 2 points) or “absent” if the patient needed < 2 pillows to breathe comfortably (i.e. 0 points). Edema in DOSE and CARRESS were categorized as none/trace (i.e. 0 points), moderate (i.e. 1 point),

or severe (i.e. 2 points). Edema in ROSE was categorized as 0/1+ (i.e. 0 points), 2+/3+ (i.e. 1 point), or 4+ (i.e. 2 points). The primary endpoint for the present analysis was the 60-day time-to-event composite of unscheduled outpatient visits, rehospitalization, or death.

Baseline clinical characteristics, surrogate markers of congestion, self-reported assessments, and outcomes were compared by EF. Adjusted Cox proportional hazards models were used to determine associations between baseline surrogate markers of congestion/self-reported assessments and the primary endpoint. A landmark analysis²¹ was used for the adjusted Cox proportional hazards models determine the associations between changes in surrogate markers of congestion/self-reported assessments from baseline to hour 72/96 and the primary endpoint.

RESULTS

A total of 732 patients (86%) enrolled in the DOSE-AHF, CARRESS-HF, and ROSE-AHF trials had a documented EF within one year prior to randomization. Patients were grouped as reduced EF 40% (n = 449), borderline 40% < EF < 50% (n = 53), or preserved EF 50% (n = 230) for Tables 1 and 2 and EF was treated as a continuous variable for Tables 3 and 4.

Study participants had a mean age was 68±13 years and 74% were male (Table 1). Ischemic heart disease was reported in 60% of patients and the median (25th, 75th) EF was 33% (20%, 54%). Patients with a preserved EF were more likely to be female and less likely to have an ischemic etiology of HF compared to patients with a reduced or borderline EF. In addition, preserved EF patients had a higher prevalence of medical comorbidities including afib/flutter and COPD. As expected, patients with reduced systolic function tended to have higher utilization of guideline-recommended medical therapies for HF with a reduced EF (i.e. ACEIs/ARBs, β-blockers, and aldosterone antagonists).

Baseline NT-proBNP differed markedly across EF groups. The median (25th, 75th) baseline NT-proBNP level was 5998 pg/mL (3009 pg/mL, 11414 pg/mL) for patients with a reduced EF, 4420 pg/mL (1740 pg/mL, 8057 pg/mL) for patients with a borderline EF, and 3272 pg/mL (1687 pg/mL, 6536 pg/mL) for patients with a preserved EF (p-value <0.01).

The clinical course of congestion was largely similar across EF groups, with the exception of NT-proBNP (p-value = 0.01). Patients with a reduced EF experienced a greater reduction in NT-proBNP concentration from baseline to 72/96 hours as compared to patients with a borderline or preserved EF (Figure 1). Relative reductions in NT-proBNP levels at 72/96 hours were also greater in patients with reduced EF. Although surrogate markers of clinical and hemodynamic congestion uniformly improved during hospitalization, there were no significant differences in the trajectory of signs and symptoms of HF (Figure 2), body weight change (Figure 3), or net fluid loss by EF (Figure 4).

The rate of unscheduled outpatient visits, rehospitalization, or death at day 60 for patients with reduced, borderline, and preserved EF, were, respectively, 44%, 50%, and 44%. After adjusting for potential confounders, no association between baseline dyspnea VAS, global VAS, NT-proBNP levels, or orthodema congestion score and the 60-day time-to-event composite of unscheduled outpatient visits, rehospitalization, or death could be detected

(Table 3). A differential association between the composite endpoint and any of the aforementioned baseline clinical variables by baseline EF could not be detected.

The change in surrogate markers of congestion from baseline to hour 72/96 was not associated with the primary endpoint with exception of global VAS (Table 4). Greater improvement in global VAS from baseline to 72/96 hours was associated with a reduced hazard of unscheduled outpatient visits, rehospitalization, or death at day 60 (Hazard Ratio [HR] 0.94 per 10 mm increase, 95% Confidence Interval [CI] 0.89–0.995; p-value = 0.03). While this relationship was present in pooled data, the relationship did not differ by EF (interaction p-value = 0.54).

DISCUSSION

In summary, this study found that among patients admitted for a primary diagnosis of AHF, patients with a preserved EF were older, more likely to be female, less likely to have an ischemic etiology of HF, and had a higher prevalence of afib/flutter and COPD. Although patients with a preserved EF had lower NT-proBNP levels at baseline and experienced smaller in-hospital changes compared to patients with a borderline or reduced EF, in general, there were few differences in the clinical trajectory of congestion metrics by EF as measured by signs and symptoms of HF, body weight change, and net fluid loss. After adjusting for potential confounders, improvement in global VAS was associated with a lower risk of cardiovascular (CV) morbidity and mortality. Associations could not be detected between baseline levels/changes in other surrogate markers of congestion and the primary endpoint.

It is notable that only 30% of the patients enrolled in the DOSE-AHF, CARRESS-HF, and ROSE-AHF trials had HF with a preserved EF (HFpEF) (i.e. defined as EF $\geq$ 50%). Hospital-based registry data suggest that the proportion of patients with HFpEF is growing and expected to overtake HF with a reduced EF (HFrEF) in terms of absolute numbers in the near future.³ This may be partially explained by the fact that the present study required patients to have a documented EF within the past year and patients with preserved systolic function may be less likely to have repeat assessments of EF. The study protocols also required an experienced clinician-investigator to prospectively diagnose AHF, which may be more challenging to confidently make, and less often coded for, without the concurrent finding of systolic dysfunction. Similarly, prior clinical trials in HFpEF which have traditionally struggled to enroll patients and exhibited tremendous geographic variation in clinical characteristics and outcomes.²² Moreover, our study validates the clinical characteristics of patients with HFpEF as older, more likely to be female, and with a higher prevalence of cardiac and non-cardiac comorbidities.^{3–5}

To the best of our knowledge, the present analysis offers the first longitudinal and comprehensive characterization of clinical congestion by EF during an index AHF hospitalization. Basic and translation models of AHF and clinical experience suggest that the pathophysiology of congestion is likely due to a combination of both a gradual absolute increase in intravascular volume as well as a rapid relative redistribution of fluid from capacitance vessels to the effective circulation.^{23,24} One might anticipate that patients admitted for AHF with a preserved EF would be more sensitive to changes in the effective

circulating volume primarily due to a rapid relative redistribution of fluid given the high prevalence of diastolic dysfunction/restrictive filling and increased arterial stiffening leading to abnormal ventricular-vascular coupling in HFpEF.^{25,26} However, this supposition is not supported by the present analysis, which found few systematic differences in the clinical course of congestion by EF. A notable exception was the in-hospital trajectory of NT-proBNP, which did differ significantly by EF. This finding has important implications for the design and conduct of clinical trials testing novel hemodynamic agents in AHF and a preserved EF. Patients admitted for AHF with a preserved EF should be expected to experience numerically smaller changes in NT-proBNP levels in response to therapy despite reporting comparable improvements in signs and symptoms of volume overload and other surrogate measures of congestion.

It is also noteworthy that, with the exception of the global VAS self-assessment, this study did not find associations between surrogate markers of congestion and the composite of unscheduled outpatient visits, rehospitalization, or death at day 60. Natriuretic peptides (i.e. BNP and NT-proBNP) are known to be the most powerful predictors of adverse events and in multiple studies have been shown to supersede clinical judgment in terms of prognostic potential.^{27,28} Thus, it is an unexpected finding that baseline and changes in NT-proBNP were not associated with the composite outcome across the spectrum of EF.^{29,30} While the reasons for this lack of association in the present study are unclear, potential explanations may relate to study power or comprehensive adjustment within multivariate models.

There are several limitations of the data that should be acknowledged. First, this study is a pooled analysis of three clinical trials employing similar, but not identical, inclusion/exclusion criteria and testing different decongestion strategies. However, the DOSE-AHF, CARRESS-HF, and ROSE-AHF trials required patients to be admitted for a primary diagnosis of AHF and confirmation was made at the point-of-care by experienced physician-investigators with clinical experience and research expertise in HF. Second, per study protocols, patients were enrolled within 24 hours of the first intravenous HF-related treatment. Patients likely experienced some degree of improvement in surrogate measures of congestion during the timeframe between initial presentation and enrollment, which would not be captured in these data. Third, the study protocols did not require a systematic process for weighing patients, which may have affected the reliability and reproducibility of weight changes over time. Fourth, dyspnea relief was assessed using a continuous VAS and while there is no universally agreed upon gold standard for measuring dyspnea, dyspnea relief results may have differed if different measurement instruments were used.

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Figure 1.

NT-proBNP levels by ejection fraction over time.

Note: Box extends to Q1 and Q3. Median displayed as horizontal line inside box. Mean displayed as a dot. The upper whisker reflects maximum value unless there are values more than 1.5 times the interquartile range above Q3, in which it reflects the third quartile plus 1.5 times the interquartile range. The lower whisker reflects minimum value unless there are values less than 1.5 times the interquartile range below Q1, in which it reflects the first quartile minus 1.5 times the interquartile range.

Abbreviations: NT-proBNP = amino terminal proBNP; EF = ejection fraction.

Figure 2.

“Orthodema” congestion score by ejection fraction shown as a percentage over time including baseline, hour 24, hour 48, and hour 72/96.

Note: “Orthodema” congestion score calculated by summation of orthopnea and edema scores.

Abbreviation: EF = ejection fraction.

Figure 3.

Weight change by ejection fraction over time.

Note: Box extends to Q1 and Q3. Median displayed as horizontal line inside box. Mean displayed as a dot. The upper whisker reflects maximum value unless there are values more than 1.5 times the interquartile range above Q3, in which it reflects the third quartile plus 1.5 times the interquartile range. The lower whisker reflects minimum value unless there are values less than 1.5 times the interquartile range below Q1, in which it reflects the first quartile minus 1.5 times the interquartile range.

Abbreviations: EF = ejection fraction.

Figure 4.

Net fluid loss by ejection fraction over time.

Note: Box extends to Q1 and Q3. Median displayed as horizontal line inside box. Mean displayed as a dot. The upper whisker reflects maximum value unless there are values more than 1.5 times the interquartile range above Q3, in which it reflects the third quartile plus 1.5 times the interquartile range. The lower whisker reflects minimum value unless there are values less than 1.5 times the interquartile range below Q1, in which it reflects the first quartile minus 1.5 times the interquartile range.

Abbreviations: EF = ejection fraction.

Table 1

Baseline clinical characteristics by ejection fraction.

Variable	40% (N=449)	Ejection Fraction 40% < X < 50% (N=53)	50% (N=230)	All Patients (N=732)	p-value
Age (years)	67 (58, 76)	69 (60, 78)	74 (64, 81)	69 (60, 78)	<0.01
Men	357 (80%)	41 (77%)	140 (61%)	538 (74%)	<0.01
Black	109 (24%)	12 (23%)	37(16%)	158 (22%)	0.12
White	325 (72%)	39 (74%)	188 (82%)	552 (75%)	
Other	15 (3%)	2 (4%)	5 (2%)	22 (3%)	
Body Mass Index (kg/m ²)	30 (26, 36)	34 (29, 40)	34 (28, 41)	32 (27, 38)	<0.01
Ejection Fraction (%)	23 (18, 30)	45 (45, 46)	56 (55, 63)	33 (20, 54)	<0.01
Heart Rate (bpm)	77 (68, 86)	75 (68, 81)	74 (65, 82)	75 (67, 85)	0.08
Systolic Blood Pressure (mmHg)	138 (135, 140)	139 (137, 141)	139.0 (136, 141)	138 (136, 141)	<0.001
Hospitalization for heart failure in last year	329 (74%)	37 (70%)	152 (67%)	518 (72%)	0.19
Ischemic etiology	281 (63%)	39 (74%)	116 (50%)	436 (60%)	0.01
Atrial fibrillation/flutter	232 (52%)	30 (57%)	148 (64%)	410 (56%)	0.01
Diabetes Mellitus	245 (55%)	39 (74%)	130 (57%)	414 (57%)	0.03
Chronic Obstructive Pulmonary Disease	114 (25%)	9 (17%)	76 (33%)	199 (27%)	0.02
NT-proBNP (pg/mL)	5989 (3009, 11414)	4420 (1740, 8057)	3272 (1687, 6536)	4503 (2315, 9882)	<0.01
Sodium (mg/L)	138 (135, 140)	139 (137, 141)	139 (136, 141)	138 (136, 141)	<0.01
Blood urea nitrogen (mg/dL)	38 (27, 53)	40 (25, 59)	39 (27, 56)	39 (27, 55)	0.85
Creatinine (mg/dL)	1.7 (1.4, 2.1)	1.9 (1.4, 2.3)	1.7 (1.3, 2.2)	1.7 (1.4, 2.2)	0.36
Angiotensin converting-enzyme inhibitor/Angiotensin receptor blocker	267 (60%)	23(43%)	90 (39%)	380 (52%)	<0.01
β-Blockers	385 (86%)	46 (87%)	167 (73%)	598 (82%)	<0.01
Aldosterone antagonist	136 (30%)	12 (23%)	50 (22%)	198 (27%)	0.04
Furosemide equivalent dose (mg/day)	80 (80, 160)	120 (80, 160)	80 (80, 160)	80 (80, 160)	0.56
Death, re-hospitalization, unscheduled outpatient visit occurring within 60 days	194/445 (44%)	25/50 (50%)	100/227 (44%)	319/722 (44%)	0.89

Note: Median (25th, 75th) display for continuous variables and frequencies (%) displayed for categorical variables. Unless otherwise stated, p-values obtained using Kruskal-Wallis test for continuous variables and Pearson chi-square for categorical variables.

Abbreviations: NT-proBNP = amino terminal proBNP

Table 2

Change in congestion metrics from baseline to 72/96 hours by ejection fraction.

Variable	Ejection Fraction			Overall p-value	p-value EF 1 vs 2	p-value EF 1 vs 3	p-value EF 2 vs 3
	40 N=449	40 < X < 50 N=53	50 N=230				
NT-proBNP (pg/mL)	-2051 (5287)	-673 (2808)	-1027 (3095)	0.01	0.05	0.01	0.63
Weight (lbs)	-8.4 (7.6)	-10.2 (7.6)	-8.0 (7.6)	0.13	0.12	0.54	0.07
Creatinine (mg/dL)	0.0 (0.4)	0.1 (0.5)	0.1 (0.4)	0.14	0.41	0.05	0.80
Net Fluid Loss (mL)	4964 (3540)	5796 (3607)	5118 (3341)	0.30	0.12	0.610	0.23

Note: Mean (SD) displayed.

Abbreviations: EF = ejection fraction; NT-proBNP = amino terminal proBNP; lbs = pounds.

Table 3

Adjusted ^[1] association between baseline congestion metrics and the 60-day time-to-event composite of death, rehospitalization, or unscheduled outpatient visits.

Baseline Congestion Metric	Hazard Ratio (95% CI) ^a	χ^2	p-value
Dyspnea Visual Analogue Scale ^[2]	1.00 (1.00, 1.004)	<0.01	0.99
Dyspnea Visual Analogue Scale * Ejection fraction interaction	NA	0.78	0.38
Global Visual Analogue Scale ^[3]	1.00 (0.99, 1.00)	0.01	0.75
Global Visual Analogue Scale * Ejection fraction interaction	NA	1.04	0.31
NT proBNP ^[4]	1.01 (0.99, 1.02)	1.24	0.26
NT proBNP * Ejection fraction interaction	NA	1.67	0.20
Orthodema Congestion Score ^[5]	1.08 (0.97, 1.21)	2.08	0.15
Orthodema Congestion Score * Ejection fraction	NA	2.06	0.15

^[1] Model adjusted for trial, age, gender, HR, SBP, sodium, serum creatinine, BUN, NT-proBNP, afib/flutter, DMII, COPD, β -blocker, ACEI/ARB, digoxin, and EF.

^[2] HR per 10 mm change in dyspnea VAS.

^[3] HR per 10 mm change in global VAS.

^[4] HR per 1000 pg/mL change in NT proBNP.

^[5] HR per 1 point change in orthoedema congestion score.

Abbreviations: NA = not applicable; HR = heart rate; SBP = systolic blood pressure; BUN = blood urea nitrogen; NT-proBNP = amino terminal proBNP; afib/flutter = atrial fibrillation/atrial flutter; DMII = diabetes mellitus type II; COPD = chronic obstructive pulmonary disease; ACEI = angiotensin converting-enzyme inhibitor; ARB = angiotensin receptor blocker; EF = ejection fraction; HR = hazard ratio.

Table 4

Adjusted ^[1] association between change in congestion metrics and the 60-day time-to-event composite of death, rehospitalization, or unscheduled outpatient visits.

Change in Congestion Metric (BL to hour 72/96)	Hazard Ratio (95% CI) [1]	χ^2	p-value
Dyspnea Visual Analogue Scale ^[2]	0.996 (0.990, 1.001)	2.06	0.15
Dyspnea Visual Analogue Scale * Ejection fraction interaction	NA	3.15	0.08
Global Visual Analogue Scale ^[3]	0.940 (0.890, 0.995)	4.60	0.03
Global Visual Analogue Scale * Ejection fraction interaction	NA	0.38	0.54
NT proBNP ^[4]	1.02 (0.99–1.06)	2.37	0.12
NT proBNP * Ejection fraction interaction	NA	0.19	0.66
Orthodema Congestion Score ^[5]	1.03 (0.92, 1.14)	0.22	0.64
Orthodema Congestion Score * Ejection fraction interaction	NA	2.29	0.13
Net Fluid Loss ^[6]	0.90 (0.75, 1.09)	1.16	0.28
Net Fluid Loss *Ejection fraction interaction	NA	0.24	0.62

^[1] Model adjusted for trial, age, gender, HR, SBP, sodium, serum creatinine, BUN, NT-proBNP, afib/flutter, DMII, COPD, β -blocker, ACEI/ARB, digoxin, EF, and congestion metrics at baseline.

^[2] HR per 10 mm change in dyspnea VAS.

^[3] HR per 10 mm change in global VAS.

^[4] HR per 1000 pg/mL change in NT-proBNP.

^[5] HR per 1 point change in orthoedema congestion score.

^[6] HR per 5000 mL change in net fluid loss.

Abbreviations: NA = not applicable; HR = heart rate; SBP = systolic blood pressure; BUN = blood urea nitrogen; NT-proBNP = amino terminal proBNP; afib/flutter = atrial fibrillation/atrial flutter; DMII = diabetes mellitus type II; COPD = chronic obstructive pulmonary disease; ACEI = angiotensin converting-enzyme inhibitor; ARB = angiotensin receptor blocker; EF = ejection fraction; HR = hazard ratio.