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Relation of Volume Overload to Clinical Outcomes in Acute Heart Failure (From ASCEND-HF)

Marat Fudim, MD¹, Kishan S. Parikh, MD¹, Allison Dunning, MS¹, Adam D. DeVore, MD¹, Robert J. Mentz, MD¹, Phillip J. Schulte, PhD², Paul W. Armstrong, MD³, Justin A. Ezekowitz, MBBCh, MSc³, W.H. Wilson Tang, MD⁴, John J.V. McMurray, MD⁵, Adriaan A. Voors, MD, PhD⁶, Mark H. Drazner, MD, MSc⁷, Christopher M. O'Connor, MD⁸, Adrian F. Hernandez, MD, MHS¹, Chetan B. Patel, MD¹

¹Duke Clinical Research Institute, Durham, NC ²Mayo Clinic, Rochester, MN ³Canadian VIGOUR Centre, University of Alberta, Edmonton, Alberta ⁴Department of Cardiology, Cleveland Clinic, Cleveland, OH ⁵BHF Cardiovascular Research Centre, University of Glasgow, UK ⁶Department of Cardiology, University Medical Center Groningen, the Netherlands ⁷Division of Cardiology, University of Texas Southwestern Medical Center, Dallas, TX ⁸Inova Heart and Vascular Institute, Falls Church, VA

Abstract

We aimed to study whether jugular venous distension (JVD) and peripheral edema were associated with worse outcomes in patients with acute heart failure in the ASCEND-HF trial. Of 7141 patients in ASCEND-HF, 7135 had complete data on baseline JVD and peripheral edema status. Patients were grouped according to baseline examination findings: 1) no JVD or peripheral edema; 2) JVD only; 3) peripheral edema only; 4) JVD and peripheral edema. We used unadjusted and adjusted logistic or Cox regression analyses to assess associations between groups and the outcomes of index length of stay (LOS), in-hospital mortality, 30- and 180-day all-cause mortality. Patients with peripheral edema (Groups 3 and 4) had higher body mass index, NT-proBNP and BNP values, and more comorbid disease, and reduced left ventricular ejection fraction (LVEF) compared with patients in Groups 1–2. The median (25th–75th) LOS for Groups 1–4 was 6 (4–9), 5 (4–8), 7 (4–11), and 6 days (4–10), respectively. For the 30-day and 180-day outcomes, adjusted analyses found no significant difference in risk for patients presenting with JVD only or peripheral edema only as compared with patients without evidence of JVD or peripheral edema ($p > 0.05$ for all). The presence of both JVD and peripheral edema was associated with an adjusted 24% increase in risk for all-cause mortality at 30 days, but no risk difference at 180 days. In conclusion, in patients with heart failure presenting to the hospital with dyspnea, the presence of peripheral edema is associated with a longer hospital LOS, but no difference in short and long term clinical outcomes when compared with patients without peripheral edema. The combination of peripheral edema and JVD identifies the highest risk cohort for poor clinical outcomes.

Corresponding Author: Marat Fudim, MD, Duke University Medical Center, Phone: (919) 668-7121, Fax: (919) 668-7078, marat.fudim@duke.edu.

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Keywords

Congestion; heart failure; jugular venous distention; peripheral edema

Acute and chronic heart failure (HF) states are characterized by resting or exercise induced dyspnea with presence or absence of signs of clinical congestion. The bedside examination is still critical in the assessment and monitoring of patients presenting with acute HF. Jugular venous distension (JVD) and peripheral edema have been reported to predict poor prognosis in patients with chronic HF^{1,2}. However, the relative prognostic value of these variables is unclear in patients with acute HF with dyspnea. Some evidence suggests that clinical examination findings could identify specific congestion phenotypes with a predominant central vascular or peripheral congestion component³⁻⁵. Using data from the acute HF population enrolled in the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) trial, we aimed to stratify dyspneic patients with HF by congestion phenotypes based on the presence or absence of JVD and peripheral edema, and to compare the in-hospital and postdischarge outcomes between the groups. We also explored whether nesiritide, an arterial vasodilator, is associated with improved outcomes in any of the HF groups.

METHODS

Briefly, ASCEND-HF was a global, randomized, double-blind, placebo-controlled trial designed to examine the short and long term efficacy and safety of nesiritide, a recombinant natriuretic peptide^{6,7}. A total of 7141 patients hospitalized for HF were enrolled and randomized to receive either nesiritide or placebo, in addition to standard therapy, within 24 hours of the first intravenous HF-related treatment.

Physical examinations were conducted at randomization and patients were grouped post-hoc into the following 4 categories of volume overload: (1) no JVD or peripheral edema; (2) JVD only; (3) peripheral edema only; and (4) both JVD and peripheral edema. JVD was classified by the presence or absence of JVD only. Peripheral edema was classified by the extent of the edema as no edema, ankle, shins, knees, and sacrum. Patients without information on JVD or peripheral edema at randomization were excluded from the analysis. The primary outcomes of interest were 30- and 180-day all-cause death and the combination of all-cause death or HF rehospitalization at 30 days only. Additional secondary endpoints included in-hospital mortality and length of stay (LOS) (time from randomization to discharge). Finally, we compared 2 quality of life assessments across the 4 groups. We used the EuroQOL 5 dimensions (EQ-5D) questionnaire⁸. The questionnaire has 2 components—a descriptive profile and a single-index visual analogue scale (VAS). The descriptive profile includes 5 dimensions (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression), and the VAS provides a global assessment of health status ranging from 0 (“worst imaginable health state”) to 100 (“best imaginable health state”).

All continuous variables are presented as medians and 25th, 75th percentiles; all categorical variables are presented as frequencies and percentages. Comparisons of baseline and discharge characteristics between HF groups were conducted using ANOVA or Kruskal-

Wallis tests for continuous variables and Chi-square or Fisher's exact tests for categorical variables. In-hospital mortality was compared using logistic regression analyses. Further, ANOVA models were used to compare the length of stay between the 4 groups. If a significant difference was found, then multiple comparisons using Tukey methods were conducted to determine differences in mean log length of stay between patients presenting with peripheral volume overload and patients without evidence of peripheral volume overload.

Cox regression models were used to determine the relationship between the 4 congestion groups and 180-day all-cause death. Logistic regression models were used to determine the relationship between the 4 congestion groups and 30-day all-cause death and 30-day combined death and readmission endpoints. Previously published adjustment models for 30-day and 180-day endpoints in the ASCEND-HF trial were available and used for these analyses⁹. Imputed datasets were used for the Cox and logistic regression analyses conducted on 30- and 180-day endpoints, in which missing values for all baseline variables included in the selection models were imputed. In addition to these imputed variables, brain natriuretic peptide (BNP) was an a priori determined covariate. In ASCEND-HF, measurements of BNP varied by site (BNP vs. NT-proBNP); therefore, patients had 1 of 2 measurements for BNP that were on different scales and unable to be converted and combined. In order to combine these BNP measures into 1 variable to be used in analysis, we standardized each of the 2 BNP measurement types and then combined the standardized values into 1 BNP variable for use in adjusted analyses. There was also missing data for the outcomes measures that could not be imputed.

Interaction between nesiritide treatment and peripheral volume overload group in relation to the combination of 30-day all-cause mortality and HF rehospitalization was assessed in an unadjusted logistic regression. The model included main effects for treatment (nesiritide vs. placebo), peripheral volume overload group, and the interaction effect between the 2 variables. All analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC). A two-tailed $P < 0.05$ was considered statistically significant.

Scios Inc., now Johnson & Johnson, provided financial and material support for ASCEND-HF. The authors take responsibility for the manuscript's integrity and had complete control and authority over its preparation and the decision to publish.

RESULTS

The ASCEND-HF cohort included 7141 patients. Six patients were excluded due to missing physical assessment at baseline. The remaining 7135 patients were categorized into the following 4 congestion groups: (1) no JVD or peripheral edema ($n=1096$); (2) JVD only ($n=714$); (3) peripheral edema only ($n=2036$); and (4) both JVD and peripheral edema ($n=3289$).

At baseline, patients with peripheral edema (with or without JVD) were more commonly white and had more comorbidities compared with those without peripheral edema (Table 1). Patients with peripheral edema were more likely to be taking guideline-directed medical

therapy, including beta blockers, angiotensin converting enzyme (ACE) inhibitors, and diuretics. Patients with JVD only had the lowest left ventricular ejection fraction and patients with JVD with or without peripheral edema had worse clinical signs of intravascular congestion such as orthopnea and pulmonary rales. Additionally, patients with JVD had higher BNP values and worse renal function on admission. Patients with JVD and peripheral edema at discharge continued to have worse renal function with higher rates of beta blocker and diuretic use (Supplemental Table 1). Measures of QOL at discharge indicated a lower rating on the EQ-5D (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression) for patients with JVD and peripheral edema, despite similar global QOL as measured by VAS across all 4 groups.

Of the 7135 patients included in the final analysis, 151 (2%) experienced in-hospital mortality. The highest in-hospital mortality was seen in patients with both JVD and peripheral edema (n=90 [2.7%]) (Supplemental Table 2). In unadjusted analyses, odds ratios (ORs) determined that patients with both JVD and peripheral edema were significantly more likely to experience in-hospital mortality (OR 1.79, 95% confidence interval [CI] 1.06–3.01; p=0.0298), but this trend did not hold after adjustment (OR 1.17, 95% CI 0.67–2.03; p=0.59). The overall median hospital length of stay was 6 days. Patients with peripheral edema only had the longest median length of stay (7 days), while patients with JVD only had the shortest median length of stay (5 days) (p<0.001).

Of the 7135 patients in our analysis, 686 (10%) experienced primary the endpoint of the combination of 30-day all-cause death or HF rehospitalization; 273 (4%) experienced the endpoint of 30-day all-cause death; and 1036 (15%) experience the endpoint of 180-day all-cause death (Figure 1 and Table 2). For the primary endpoint of combined 30-day all-cause death or HF rehospitalization, adjusted analyses found no significant difference in risk for patients presenting with JVD only or peripheral edema only as compared with patients without evidence of JVD or peripheral edema (p=0.48 and p=0.14, respectively). However, adjusted logistic regression analyses found that patients presenting with both JVD and peripheral edema had a significantly increased risk of 30-day all-cause death or HF rehospitalization compared with patients without evidence of peripheral volume overload (OR 1.25, 95% CI 1.08–1.43; p=0.002) (Table 3). In adjusted analyses for the endpoint of 30-day all-cause death, only patients presenting with both JVD and peripheral edema showed significant (borderline) increased risk compared with patients without evidence of peripheral volume overload (OR 1.24, 95% CI 1.00–1.54; p=0.050). Finally, for the endpoint of 180-day all-cause death, patients with JVD and peripheral edema were at increased risk compared with patients without edema or JVD (unadjusted HR 1.26, 95% CI 1.04–1.51; p=0.018) (Figure 2). This association with 180-day all-cause death was no longer present after adjustment (Table 3). Unadjusted analyses are presented in Supplemental Table 3.

There was no association between nesiritide treatment and congestion phenotype in relation to the combination of 30-day outcome (interaction p=0.42).

DISCUSSION

There were 4 major findings from our analysis of the largest clinical trial population with acute HF. First, the majority (75%) of patients hospitalized with acute dyspnea had at least some degree of peripheral edema, while a minority (10%) presented with JVD without signs of extravascular fluid accumulation. In 15% of cases, patients were hospitalized for acute HF without signs of central or peripheral congestion. Second, while patients with peripheral edema alone have longer hospital length of stay, when compared with patients with JVD alone, the 2 groups have comparable in-hospital, 30-day and 180-day outcomes. Third, patients with signs of peripheral and central congestion have a significantly higher rate of 30-day combined all-cause death or HF rehospitalization. Fourth, treatment with the vasodilator nesiritide was not associated with differential outcomes in any of the groups tested.

The bedside examination is critical in the assessment of and initial decision making for patients presenting with acute or chronic HF¹⁰. In patients with acute and chronic HF, central (JVD)¹¹ and peripheral congestion (edema)^{1, 2, 5, 12} have been reported to predict poor prognosis. While it is well accepted that the extent of fluid volume congestion is closely associated with clinical outcomes^{13–15}, the concept of fluid and salt overload as the primary driver of cardiac decompensation with resting or exercise-induced dyspnea has been challenged^{3, 4}. Notably, about 50% of patients gain only minor weight (<2 pounds or <2 kg based on the study) in the days prior to a hospitalization^{16, 17}. In a previous analysis of the ASCEND-HF trial, 26% of patients had no weight loss (+/-1 kg change) and 8% actually experienced weight gain (>1 kg) during hospitalization¹⁸. Finally, an increase in central filling pressures^{19, 20} occurs in many cases in the absence of weight gain or total body volume increase^{15, 21}, suggesting a complimentary contribution of volume redistribution to the mechanism of cardiac decompensation^{22, 23}.

Patients with acute and chronic HF have been previously classified as “puffers” and “bloaters”^{5, 24, 25}. A typical “bloater” presents with signs of fluid retention, weight gain, peripheral edema, and renal impairment. These patients are characterized by more advanced right ventricular dysfunction and pulmonary hypertension²⁶. On the contrary, the classic “puffers” have exercise-induced dyspnea in the absence of objective findings of fluid retention. Their predominant mode of decompensation appears to be redistribution of fluid from the periphery and abdominal compartment to the central compartment as a result of impaired vascular compliance and increased systemic vascular resistance^{3, 27}. For that reason, this congestion phenotype is sometimes referred to as “vascular phenotype.” Arguably “puffers” are more likely to show signs of central vascular congestion (JVD) without peripheral edema. It has been suggested that patients with HF and preserved ejection fraction (HFpEF) might be overrepresented among “puffers” given that HFpEF is known to be especially fluid sensitive and those with HFpEF are prone to developing exercise induced symptoms with minimal fluid retention²⁸. Our analysis does not appear to support the notion that “puffers” are more commonly associated with preserved LVEF, given comparably low mean LVEF in patients with peripheral edema alone and JVD alone.

In our study, patients with JVD alone and peripheral edema had distinct phenotypes. Presence of peripheral edema was associated with longer hospital length of stay compared with patients with JVD alone, but the short and long term clinical outcomes did not differ between the groups. Whether the presence of JVD and peripheral edema represents differing pathophysiologies or the same congestive process on a continuum, the combined presence of central vascular and peripheral congestion identified an advanced phenotype, likely with more severe biventricular impairment, which was associated with significantly worse 30-day outcomes. Our findings are in concordance with previous analyses of chronic HF populations^{1, 2}. Similarly, a greater extent of congestion upon discharge has been associated with poor clinical outcomes, suggesting that congestion phenotypes are linked to outcomes irrespective of timing during a HF hospitalization²⁹.

Patients with a more preload- and afterload-sensitive physiology and a component of volume redistribution (“puffers”) could be more responsive to vasodilator therapy. These patients may infer less benefit from volume removal given only minor-to-no fluid overload on presentation to the hospital for dyspnea^{3, 27, 28}. This concept did not seem to hold up in a retrospective analysis of the RELAX-AHF trial testing the direct vasodilator serelaxin. Serelaxin had no benefit in patients with acute HF with no or only minor peripheral edema (“puffers”), but had more absolute benefit in patients with overt peripheral edema on presentation to the hospital⁵. The drug nesiritide tested in ASCEND-HF, a natriuretic peptide with primary vasodilator properties, did not appear to have any association with better outcomes compared with placebo in any of the groups tested. Previous work suggested that the physiology underlying the vascular phenotype is primarily based on an increased venous vascular tone, causing decreased vascular compliance of the peripheral and abdominal vascular beds. Thus, neuromodulatory agents (renin-angiotensin blockers) and venodilators (nitrates) have been proposed as preferential drug choices to affect physiology in patients with elevated filling pressures without significant volume gain³⁻⁵. The predominant arterio-dilatory properties of agents such as serelaxin (48 h) and nesiritide (24–168 h) or the short exposure to them could explain a lack of therapeutic effectiveness in the vascular phenotype/puffers. Whether a more nuanced classification of congestion (congestion scores) can provide more insight into different congestion phenotypes needs to be further explored. At the same time, we need to test the best approach to the safe management of fluid overload in acute and chronic HF.

We acknowledge that there are limitations to the assessment of volume overload based on clinical examination parameters such as presence of JVD, peripheral edema, orthopnea, and an S3 and positive hepatojugular^{30, 31}. Most notably, these limitations apply to many other commonly accepted markers of congestion measures such as increases in body weight^{17, 32}, natriuretic peptides^{17, 33}, and even invasive hemodynamic measurements^{34, 35}, all of which have modest sensitivity and specificity to assess a patient’s intra- and extravascular volume status. Nevertheless, physical examination findings retain a strong prognostic value for short and long term clinical outcomes.

In patients with HF presenting to the hospital with dyspnea, the presence of peripheral edema is associated with a longer hospital length to stay, but no difference in short and long term clinical outcomes when compared with patients without peripheral edema. The

combination of peripheral edema and JVD identifies the highest risk cohort for poor clinical outcomes. Use of an arterial vasodilator, nesiritide, does not appear to be associated with improved outcomes in any of the studied groups.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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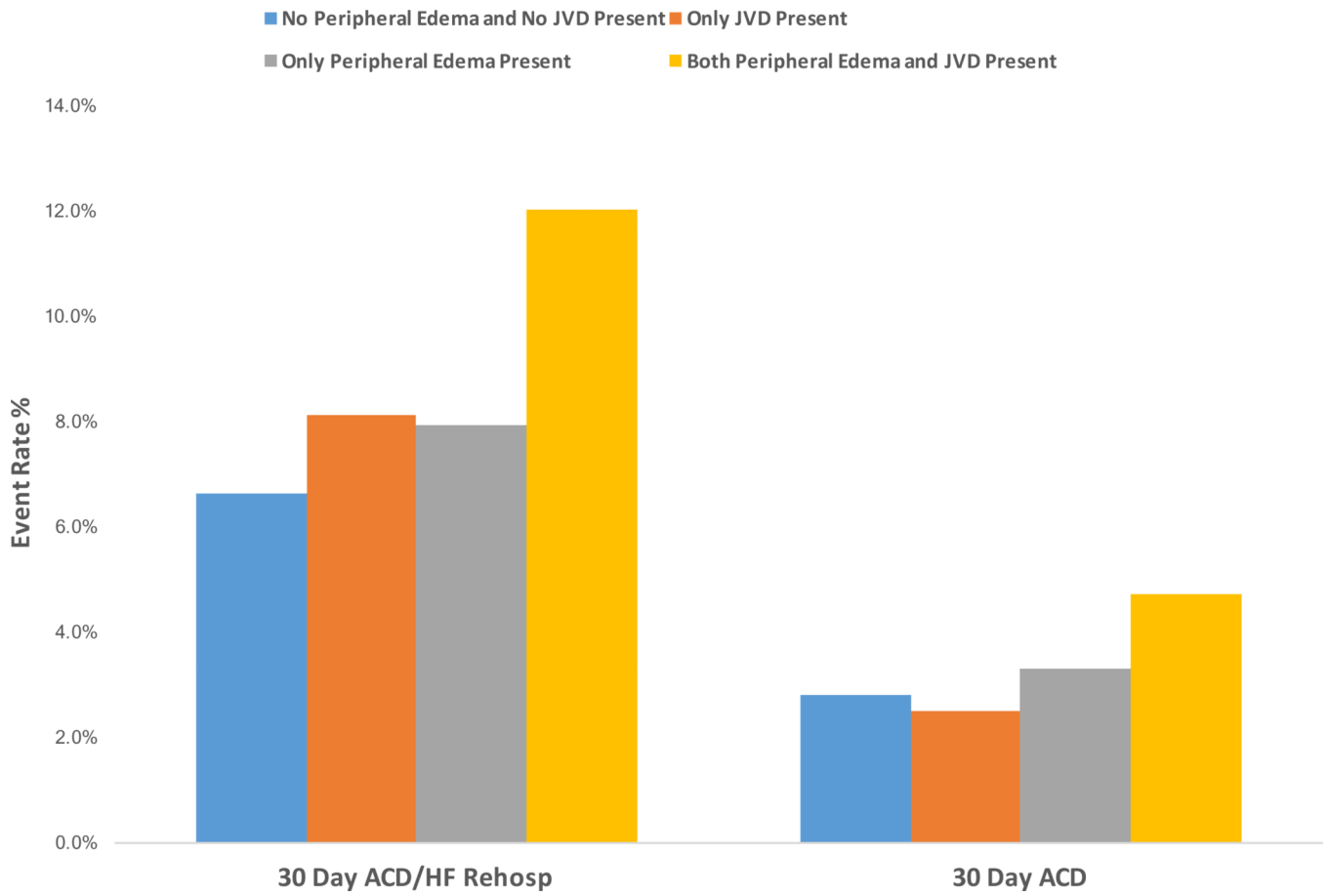


Figure 1. 30-day event rate (%) for all-cause death and heart failure hospitalization by congestion group. ACD=all-cause death, HF=heart failure, JVD=jugular venous distension

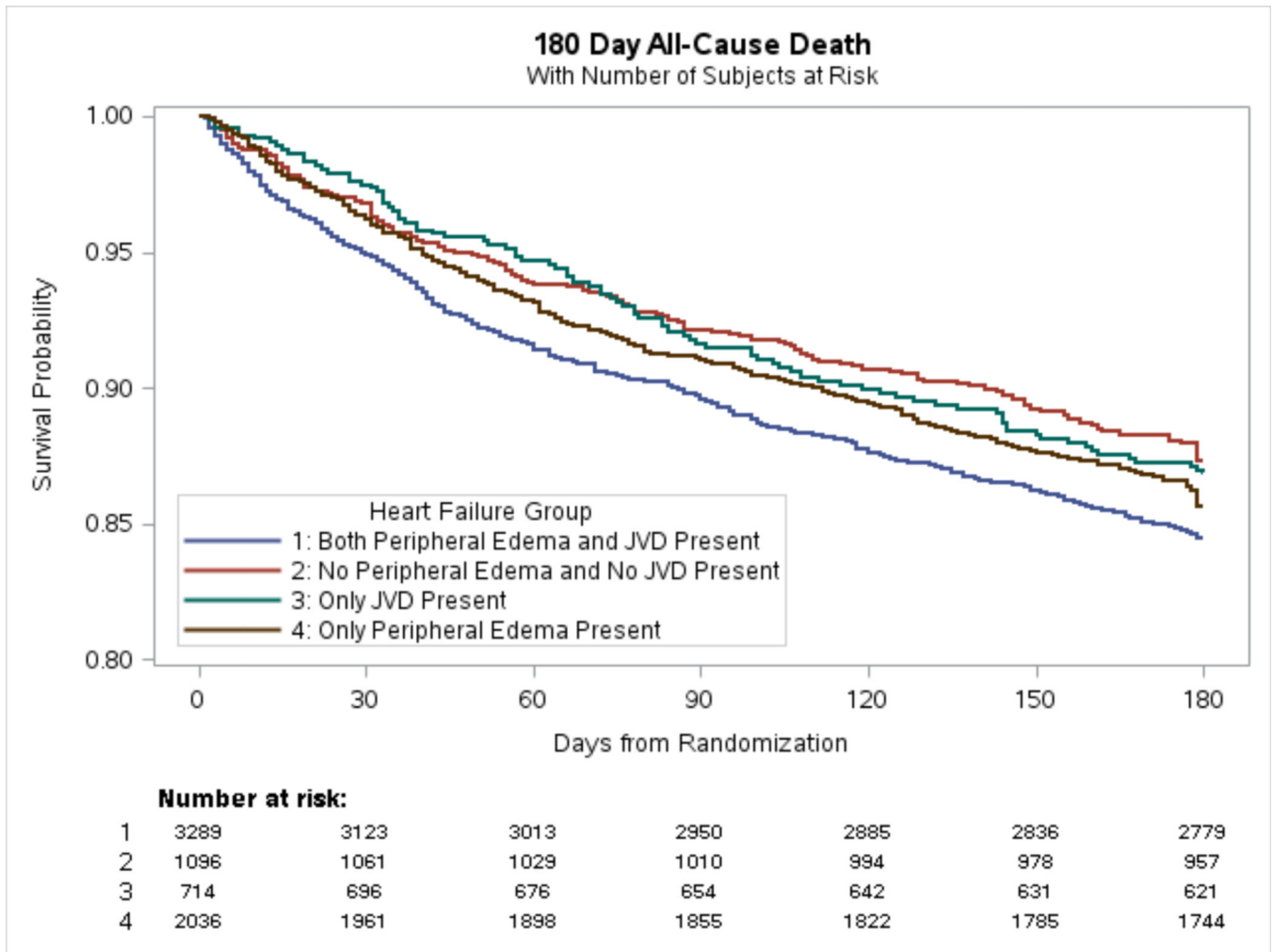


Figure 2. 180-day all-cause mortality. Only significant relationship in unadjusted analysis group 1 vs 2 [HR 1.3 (1.0–1.5), p=0.02]. JVD=jugular venous distension

Table 1.

Patient characteristics at acute HF presentation by congestion group

Characteristic	No JVP or Peripheral Edema (N=1096)	JVP Only (N=714)	Peripheral Edema Only (N=2036)	Both JVP and Peripheral Edema (N=3289)	P-Value
Age (years)	65 (55, 76)	64 (53, 73)	69 (59, 77)	66 (56, 76)	<.001
Female	391 (35.7%)	248 (34.7%)	714 (35.1%)	1088 (33.1%)	0.300
White	482 (44.0%)	318 (44.5%)	1467 (72.1%)	1717 (52.2%)	
Black	74 (6.8%)	90 (12.6%)	235 (11.5%)	678 (20.6%)	
Asian	528 (48.2%)	267 (37.4%)	286 (14.0%)	685 (20.8%)	
Other	12 (1.1%)	39 (5.5%)	48 (2.4%)	208 (6.3%)	
Baseline BMI (kg/m ²)	24.5 (21.9, 28.1)	24.7 (21.5, 29.1)	29.6 (25.5, 35.1)	28.2 (24.2, 33.1)	<.001
LVEF (%)	28 (21, 35)	25 (20, 34)	30 (22, 40)	28 (20, 35)	<.001
Orthopnea	667 (61.0%)	537 (75.3%)	1470 (72.3%)	2806 (85.4%)	<.001
Rales >1/3 lung fields	503 (45.9%)	387 (54.2%)	963 (47.3%)	1880 (57.2%)	<.001
NYHA classification					<.001
I	46 (4.2%)	23 (3.2%)	66 (3.2%)	120 (3.6%)	
II	200 (18.2%)	101 (14.1%)	358 (17.6%)	439 (13.3%)	
III	405 (37.0%)	269 (37.7%)	724 (35.6%)	1454 (44.2%)	
IV	306 (27.9%)	210 (29.4%)	419 (20.6%)	748 (22.7%)	
Baseline SBP (mm Hg)	122 (110, 139)	120 (110, 135)	127 (113, 140)	122 (110, 139)	<.001
Prior MI	384 (35.0%)	258 (36.1%)	712 (35.0%)	1133 (34.4%)	0.853
Prior AF/Flutter	313 (28.6%)	204 (28.6%)	875 (43.0%)	1280 (38.9%)	<.001
Hypertension by history	689 (62.9%)	440 (61.6%)	1539 (75.6%)	2478 (75.3%)	<.001
Prior diabetes mellitus	380 (34.7%)	259 (36.3%)	866 (42.5%)	1538 (46.8%)	<.001
Prior cerebrovascular disease	92 (8.4%)	82 (11.5%)	252 (12.4%)	415 (12.6%)	0.002
Prior PAD	83 (7.6%)	60 (8.4%)	226 (11.1%)	371 (11.3%)	<.001
ACE inhibitor or ARB	619 (56.5%)	419 (58.8%)	1274 (62.6%)	2024 (61.5%)	0.005
Beta blockers	556 (50.8%)	393 (55.1%)	1243 (61.1%)	1964 (59.7%)	<.001
MRAs (aldosterone antagonists)	272 (24.8%)	194 (27.2%)	604 (29.7%)	922 (28.0%)	0.037
Calcium antagonists	116 (10.6%)	79 (11.1%)	296 (14.5%)	432 (13.1%)	0.006
Loop diuretics	562 (51.4%)	408 (57.1%)	1332 (65.5%)	2235 (68.0%)	<.001
Baseline creatinine (mg/dL)	1.2 (1.0, 1.4)	1.2 (1.0, 1.5)	1.2 (1.0, 1.5)	1.3 (1.0, 1.7)	<.001
Baseline BUN (mg/dL)	22 (17, 33)	25 (18, 38)	24 (18, 37)	27 (19, 42)	<.001
Baseline sodium (mmol/L)	139 (136, 141)	138 (136, 141)	139 (136, 142)	139 (136, 141)	<.001
Baseline BNP (pg/mL)	1029 (541, 2130)	921 (417, 1586)	907 (558, 1592)	1067 (572, 1953)	<.001
Baseline NT-proBNP (pg/mL)	3694 (1690, 7781)	4842 (2456, 8973)	3909 (1875, 8004)	5150 (2490, 10745)	<.001
ACE inhibitor or ARB	619 (56.5%)	419 (58.8%)	1274 (62.6%)	2024 (61.5%)	0.005
Beta blockers	556 (50.8%)	393 (55.1%)	1243 (61.1%)	1964 (59.7%)	<.001

Characteristic	No JVP or Peripheral Edema (N=1096)	JVP Only (N=714)	Peripheral Edema Only (N=2036)	Both JVP and Peripheral Edema (N=3289)	P-Value
MRA (aldosterone antagonists)	272 (24.8%)	194 (27.2%)	604 (29.7%)	922 (28.0%)	0.037
Calcium antagonists	116 (10.6%)	79 (11.1%)	296 (14.5%)	432 (13.1%)	0.006
Loop diuretics	562 (51.4%)	408 (57.1%)	1332 (65.5%)	2235 (68.0%)	<.001

Variables expressed as median (25th, 75th) percentile or no. (%) if continuous or categorical, respectively, unless otherwise specified. P value

ACE=angiotensin converting enzyme; AF=atrial fibrillation; ARB=angiotensin receptor blocker; BMI=body mass index; BNP=brain natriuretic peptide; BUN=blood urea nitrogen; JVP=jugular venous pressure; LVEF=left ventricular ejection fraction; MI=myocardial infarction; MRA=mineralocorticoid receptor antagonist; NYHA=New York Heart Association; PAD=peripheral artery disease; SBP=systolic blood pressure.

Table 2.

Distribution of events by congestion groups

Group	30-Day All-cause Death/ HF Rehospitalization	30-Day All-cause Death	180-Day All-cause Death
No JVP or peripheral edema	72 (6.6%)	31 (2.8%)	139 (12.7%)
JVP only	58 (8.1%)	18 (2.5%)	94 (13.2%)
Peripheral edema only	160 (7.9%)	68 (3.3%)	292 (14.3%)
Both JVP and peripheral edema	396 (12.0%)	156 (4.7%)	511 (15.5%)

HF = heart failure; JVP=jugular venous pressure.

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Table 3.

Adjusted survival analysis for 30- and 180-day all-cause death endpoints

Group Comparison	30 Day All-Cause Death*		30-Day All-Cause Death/ HF Rehospitalization*		180-Day All-Cause Death*	
	OR (95% CI)	P-Value	OR (95% CI)	P-Value	HR (95% CI)	P-Value
Group 2 vs. Group 1	0.87 (0.60–1.27)	0.477	1.08 (0.87–1.36)	0.482	0.92 (0.69–1.22)	0.5578
Group 3 vs. Group 1	0.94 (0.73–1.22)	0.652	0.88 (0.74–1.07)	0.139	1.03 (0.83–1.28)	0.7734
Group 4 vs. Group 1	1.24 (1.00–1.54)	0.050	1.25 (1.08–1.43)	0.002	1.05 (0.86–1.29)	0.6225

Group 1 = No JVP or peripheral edema; Group 2 = JVP only; Group 3 = Peripheral edema only; Group 4 = Both JVP and peripheral edema.

* Adjusted for age, baseline BUN (log), cerebrovascular disease, baseline creatinine (log), depression, dyspnea, prior HF hospitalization is past year, baseline sodium, baseline SBP, chronic renal disease, and BNP (standardized).

CI=confidence interval; HR=hazard ratio; OR=odds ratio