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Improvements in Signs and Symptoms During Hospitalization for Acute Heart Failure Follow Different Patterns and Depend on the Measurement Scales Used: An International, Prospective Registry to Evaluate the Evolution of Measures of Disease Severity in Acute Heart Failure (MEASURE-AHF)

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Abstract

Background—The natural evolution of signs and symptoms during acute heart failure (AHF) is poorly characterized.

Methods and Results—We followed a prospective international cohort of 182 patients hospitalized with AHF. Patient-reported dyspnea and general well-being (GWB) were measured daily using 7-tier Likert (−3 to +3) and visual analog scales (VAS, 0–100). Physician assessments were also recorded daily. Mean age was 69 years and 68% had ejection fraction <40%. Likert measures of dyspnea initially improved rapidly (day 1, 0.22; day 2, 1.31; $P < .001$) with no significant improvement thereafter (day 7, 1.51; day 2 versus 7 $P = .16$). In contrast, VAS measure of dyspnea improved throughout hospitalization (day 1, 50.1; day 2, 64.7; day 7, 83.2; day 1 versus 2 $P < .001$, day 2 versus 7 $P < .001$). Symptoms of dyspnea and GWB tracked closely (correlation $r = .813$, $P < .001$). Physical signs resolved more completely than did symptoms (eg,

from day 1 to discharge/day 7, absence of edema increased from 33% to 72% of patients, whereas significant improvements in dyspnea increased from 27% to 52% of patients; $P < .001$).

Conclusions—Changes in patient-reported symptoms and physician-assessed signs followed different patterns during an AHF episode and are influenced by the measurement scales used. Multiple clinical measures should be considered in discharge decisions and evaluation of AHF therapies.

Keywords

Congestive heart failure; exacerbation; dyspnea; physical examination; treatment outcome; end point determination

Acute heart failure (AHF) is one of the most common and costly medical conditions. It accounts for more than 1 million hospitalizations annually in the United States.¹ Despite this high prevalence, the development of new therapies for AHF has lagged behind that of other comparable cardiovascular disorders, such as chronic heart failure or acute coronary syndromes.^{2–4} Consequently, neither routine therapy for AHF nor the subsequent risk of death have changed significantly over the past 30 years.^{5,6}

One barrier to successful therapeutic development in this area has been a lack of validated end points for AHF studies. Previous studies have focused on a wide variety of surrogate and clinical end points including hemodynamics,⁷ arrhythmias,⁸ biomarkers,⁹ dyspnea scores,¹⁰ total days of hospitalization,^{11,12} or a composite of clinical end points during follow-up.^{13–16} Although these end points address potentially important aspects of the AHF syndrome, none of them capture the totality of AHF care, in which clinicians are simultaneously concerned about relief of symptoms, resolution of signs, length of stay, and short- and long-term safety. In addition, few, if any, currently approved agents for the treatment of AHF have been definitively shown in prospective randomized trials to improve longer term clinical outcomes.¹⁷ Full assessment of intermediate- and long-term clinical end points requires large study cohort sizes that are not feasible under most circumstances. Consequently, trials of new therapies for AHF, particularly in early phases, are likely to rely on short-term surrogate end points or limited clinical assessments.^{4,18}

Furthermore, no clear guidelines exist for what metrics should be used to ascertain when AHF has adequately resolved to warrant discharge from inpatient care.^{3,19} Thus decision-making about the timing of discharge in patients admitted with AHF relies on subjective criteria that vary widely among physicians.

The purpose of the International, Prospective Registry to Evaluate the Evolution of Measures of Disease Severity in Acute Heart Failure (MEASURE-AHF) was to prospectively examine a series of possible AHF end points that would reflect the clinical realities of AHF care and encompass multiple domains of the AHF syndrome. Existing AHF registries lack sufficient detail to fully describe the short-term evolution of AHF while in hospital,²⁰ and completed trials in AHF do not adequately represent the general AHF population. Our overall goals were to prospectively describe the natural course of signs and symptoms during hospitalization for AHF and how changes in readily accessible end point measures correlated with each other over time.

Methods

Within the context of designing a clinical trial program for the development of a novel adenosine-A₁ receptor antagonist (rolophylline),²¹ we conceived this independent registry with the primary aim of defining a clinically valid end point for evaluating the efficacy of

AHF therapies used to promote diuresis. Specifically, MEASURE was an international multicenter prospective observational study to observe from admission to the earlier of 7 days or discharge serial changes in measures of disease severity in patients admitted for AHF and volume overload.

Participants

AHF patients were identified between November 2005 and September 2006 at 7 centers in 4 countries: Duke University Medical Center, Durham, NC, USA; Moses Cone Hospital, Greensboro, NC, USA; Columbia University Medical Center, New York, NY, USA; University Hospital, Attikon, Greece; Barzilai Medical Center, Ashkelon, Israel; Istituto Clinico Humanitas, Rozzano, Italy; and Section of Cardiology, University of Brescia, Italy. A deidentified log of all AHF patients presenting to each institution during the enrollment period was collected with basic baseline data. These AHF patients were eligible for enrollment in the study if they were admitted to the hospital within the last 24 hours because of signs or symptoms of heart failure requiring intravenous diuretic therapy, were 18 years of age or older, and were willing to consent. Exclusion criteria were: need for intravenous inotropes; mechanical ventilation (including noninvasive ventilation); mechanical support (intra-aortic balloon pump, ventricular assist device); severe pulmonary disease or known pulmonary hypertension (>50 mm Hg); severe known renal impairment (defined by serum creatinine >3.0 mg/dL or need for hemofiltration or hemo-dialysis); significant aortic stenosis or mitral stenosis; acute major coronary syndromes within 2 weeks defined as ST-elevation myocardial infarction or troponin T >0.4 ng/mL or troponin I >1.5 ng/mL; AHF from significant arrhythmias (ventricular tachycardia, bradyarrhythmias with ventricular rate <45 /min, atrial fibrillation/flutter with a ventricular response >130 /min); acute myocarditis; hypertrophic cardiomyopathy; restrictive or constrictive cardiomyopathy; congenital heart disease; hepatic impairment (total bilirubin >3 mg/dL); and non-cardiac pulmonary edema, including suspected sepsis. These exclusion criteria were designed to recruit a registry population with typical decompensated AHF representative of patients evaluated in recent and ongoing trials of novel AHF therapies. The study was approved by the Institutional Review Boards of all participating centers.

The sample size of the study was derived from considerations related to survey design and the particular focus of the study on obtaining estimates of changes in measures of disease severity in patients admitted for AHF over time. A prespecified goal sample size of 200 patients was calculated to provide 93% probability of obtaining 95% confidence limits that are within ± 0.15 standard deviations of the mean.

Data Collection

A standard cardiovascular history and physical examination was performed at enrollment by an investigating cardiologist. Baseline New York Heart Association (NYHA) functional class was defined by asking patients to describe their symptoms and functional level 1 month before admission. Medical charts were reviewed for additional baseline information. Standardized patient-reported symptom scales, physical examination, and review of routine laboratories were performed daily while the patient was hospitalized until discharge or hospital day 7, whichever came first. Scales were largely selected based on prior use in existing large trials of AHF therapies. Patients were asked to describe current dyspnea status and general well-being using 2 separate symptom scales: (1) 7-tier Likert scales (-3 = markedly worse, -2 = moderately worse, -1 = mildly worse, 0 = unchanged, up to 3 = markedly better),^{10,22,23} and (2) 100-point visual analog scales (VAS, from 0 = "worst you can imagine" to 100 = "best you can imagine," with labeled hash marks at increments of 5).²³ Likert scales and VAS were determined by having patients use a writing instrument to physically circle on a preprinted piece of paper which part of the scale corresponded to their

current level of symptoms. Study personnel were instructed to read symptom scale instructions verbatim to patients and not to guide the patients in their responses. Physician-assessed symptoms were recorded using 4-tier Likert scales. Orthopnea was assessed by asking the physician, "Observe patient in the lowest recumbent position for up to 15 minutes to determine the minimum number of pillows required to obtain/ maintain comfort while supine: 0 = comfortable with no pillow (minimal elevation of head); 1 = comfortable with no less than 1 pillow (~10 cm of head elevation); 2 = comfortable with no less than 2 pillows (~20 cm of head elevation); and 3 = comfortable with head no less than at 30 degrees of elevation." Dyspnea was assessed similarly by asking the physician to "Query the patient as to the extent of dyspnea noted over the preceding 1 to 3 hours: 0 = no exertional dyspnea (NYHA Class I equivalent); 1 = mild exertional dyspnea (climbing stairs, NYHA Class II equivalent); 2 = moderate exertional dyspnea (walking, NYHA Class III equivalent); and 3 = severe exertional dyspnea, occurring at rest (NYHA Class IV)." Data were collected daily by study personnel on a case report form. To limit interobserver variability for each patient, the same physician was expected to administer questions and perform physical assessments. Follow-up at 60 days was obtained by a telephone call. Manual checks of data validity were performed by site investigators.

Data Analysis

Descriptive statistics including means and standard deviations for continuous variables and percentages for categorical variables are presented for the baseline characteristics and in-hospital measures. Creatinine clearance was calculated using the Cockcroft-Gault formula.^{24,25} Because daily measures collected during hospitalization progressively represented smaller numbers of sicker patients, summary statistics of signs and symptoms over time carried forward the last known value for patients discharged to home. Weight loss was calculated from baseline value to last recorded observation. Physician-elicited and patient-reported symptoms were transformed to a common scale by dividing each observed value by the outcome's range. Mean transformed values with 95% confidence intervals are presented. Comparison of the various transformed scales was performed using a repeated measures concordance correlation coefficient. SAS version 9.1 was used to perform all analyses (SAS Institute, Inc, Cary, NC, USA).

Results

Baseline Characteristics

A total of 182 patients were enrolled: 62 in Italy, 62 in the United States, 30 in Israel, and 28 in Greece. Table 1 summarizes key baseline characteristics collected for study subjects. The cohort was primarily white and male, with a mix of ischemic and nonischemic cardiomyopathy. Significant systolic dysfunction (left ventricular ejection fraction <40%) was observed in 68% of patients. Less than a quarter of patients had implanted cardioverter defibrillators or cardiac resynchronization therapy. Most patients were classified as having NYHA Class II or III symptoms 1 month before admission, which likely reflected the exclusion of patients requiring more advanced therapies such as inotropes. Renal function was impaired in a significant number of patients, despite exclusion criteria eliminating severe renal dysfunction (creatinine clearance <50 mL/min in 44% of patients). International differences were observed. In comparison to the overall cohort, study subjects recruited from sites in the United States tended to be younger (mean age 64.5 years), racial minority (black race 40.3%), and have nonischemic etiology for heart failure (48.4%).

Evolution of Patient-Reported Symptoms Over Time, Likert Versus VAS

In AHF patients on standard therapy, symptoms of dyspnea improved in the majority of patients. By hospital day 2, 58% of patients graded their dyspnea as improved from

admission using the Likert scale, whereas only 19% said their symptoms were worse compared with admission. As assessed by the Likert scale, the majority of improvement in dyspnea occurred early. Likert measures of dyspnea improved rapidly within the first 2 days of hospitalization (day 1, 0.22; day 2, 1.31; $P < .001$) with no significant improvement thereafter (day 7, 1.51; day 2 versus 7 $P = .16$). In contrast, the VAS measure of dyspnea improved continually throughout hospitalization (day 1, 50.1; day 2, 64.7; day 7, 83.2; day 1 versus 2 $P < .001$, day 2 versus 7 $P < .001$). Figure 1 visually demonstrates the temporal differences in dyspnea resolution between Likert and VAS.

General well-being (GWB) scores closely mirrored the changes in dyspnea, both in terms of amount and rates of change over time (Table 2; Fig. 2, 3). Correlation between dyspnea and GWB Likert scales during hospitalization was statistically robust ($r = .813$, $P < .001$). Likert scores for GWB again showed rapid initial improvement, reaching a plateau after day 2, whereas VAS GWB scores had a more continuous improvement over the entire course of the hospitalization.

Evolution of Physician-Assessed Symptoms Over Time

Orthopnea and dyspnea on exertion (evaluated by physician assessments) also improved during hospitalization. Using 4-tier Likert scales, orthopnea improved in 31% of patients between admission and day 2, whereas in 3% it worsened. Dyspnea on exertion improved in 24% of patients, whereas in 2% it worsened. Improvements in dyspnea on exertion continued past 2 days such that it was absent in the majority of patients at final assessment (Table 2). Conversely, orthopnea remained in the majority of patients by discharge or 7 days despite similar early improvements (Table 2). Visually improvement continued up until day 5 for orthopnea, whereas dyspnea on exertion was significantly improved across each day throughout the study (Fig. 1). Using transformed scales to allow for visual comparison, improvements in physician-assessed dyspnea on exertion and orthopnea more closely matched VAS measures of patient-reported symptoms than Likert measures.

Evolution of Physical Signs Over Time

Signs of volume overload (edema and rales) showed a higher degree of complete resolution by last measure when compared with the patient-reported symptoms (Table 2). Edema on admission was absent in only a third of patients, but by discharge or day 7 was gone in 72%. The change in rales was more pronounced with only 20% of patients free of rales at admission, but 82% free of rales at last measure; this was despite only 40% of patients being free of rales at day 2. These changes in signs largely mirror the changes in physician-reported symptoms and differ from changes in patient-reported symptoms particularly as recorded using Likert scales.

Urine output was initially brisk the first 2 days of hospitalization. After 2 days, for those patients remaining hospitalized, observed urine output progressively diminished (Fig. 4). Weight loss corresponded well with urine output. The majority of patients lost weight (Fig. 5), but these losses were minor in the majority of patients (<3 kg). Changes in symptom and physical exam measures did not appear to correlate well with changes in weight during admission (Table 2).

Clinical Outcomes

For the index hospitalization, patients had a median length of stay of 9.2 days (interquartile range 4–10). Follow-up at 60 days was complete in 100% of patients. Repeat admission occurred in 48 (26%) patients. Mortality at 60 days from admission was documented in 11 (6%) patients (Table 2).

Discussion

Using comprehensive daily assessments of a wide range of clinical metrics during hospitalization for AHF, we were able to better characterize the natural course of signs and symptoms and how changes in readily accessible end point measures correlated with each other over time. We found that dyspnea and GWB symptoms measures tracked relatively closely with one another throughout hospitalization for AHF. Additionally, the instrument selected to characterize these symptom data had a significant effect on the reported course of resolution during hospitalization; tiered Likert expressions of symptoms improved rapidly in the first 48 hours and then plateaued, whereas VAS measures of the same symptoms improved continually throughout hospitalization. Physical signs resolved more completely than did symptom measures by discharge. These data represent the first attempt to describe the natural course of signs and symptoms, and their relative progression, during hospitalization with usual care among a broad-based international population of AHF patients.

The resolution of dyspnea has been emphasized over other clinical measures by the US Food and Drug Administration and European Medicines Agency as a key end point in efficacy trials of AHF therapies.⁴ A recent consensus statement has proposed a standardized “Provocative Dyspnea Assessment,” which employs sequential dyspnea provocation as measured using a 5-tier Likert scale.²⁶ We found that the choice of scale appeared to have significant bearing on reported symptom change over time. The 0 to 100 VAS had a relatively gradual continuous progressive rate of change that better mirrored changes in more objective physical signs of volume overload. Symptom measures, when assessed by the 7-tier Likert scale, did not parallel these other measures as closely. This insight is valuable as recent large AHF trials have relied on the 5- and 7-tier Likert scales of dyspnea (identical to that used here) as a co-primary end point, and not surprisingly have shown early large improvements in dyspnea for the various trial arms regardless of randomization status.^{10,22}

Physical signs ultimately showed greater resolution during hospitalization in comparison to all symptom measures. The relative objectivity of signs and the correlation of discharge with improvements in these signs suggest a link between clinical AHF physiology and findings on physical examination. Thus early-phase trials of AHF therapies that incorporate physician-assessed symptoms and physical signs into composite assessments rather than relying on patient-reported dyspnea alone could potentially have better correlation with important longer term treatment effects. Additionally, emphasizing physician-assessed measures of disease improvement in decisions regarding hospital discharge may potentially decrease readmission rates in the sickest patients and accelerate discharge in the healthiest. However, the potential use of physician-assessed subjective measures for the determination of trial end points has obvious potential problems. Patient symptoms, unlike physician measures, are in and of themselves meaningful to patients—decreases in dyspnea should improve quality of life. Physical exam measures of volume overload can have significant inter- and intraobserver variability.²⁷ Subjective physician assessments are often influenced by other more objective data available to physicians (eg, laboratory values, echocardiographic results). And unless adequately double-blinded in clinical trials, physicians may bias their assessments to favor one therapy over another. Considerable regulatory discussion has considered these issues and ultimately dismissed such physician-assessed measures to date.¹⁸ Our data do not refute those concerns, but do raise the question as to whether favoring patient-reported symptoms alone is appropriate. Ultimately, the current study is not able to answer which short-term measures are ideal due to its small size and limited follow-up of hard outcomes; only very large clinical studies specifically designed to evaluate rehospitalization and mortality (ie, Acute Study of Clinical

Effectiveness of Nesiritide in Decompensated Heart Failure) can provide reliable insight into the link between short-term surrogate end points and relevant clinical outcomes.

Overall, the description of signs and symptoms presented here confirm and refine prior data on the clinical course of AHF. Randomized clinical trials have previously shown that the majority of patients presenting with AHF have rapid improvement in symptoms after hospitalization and initiation of therapy.^{7,10,15–17,22,23} Prior AHF trials, while generally detailed in their data collection, have been limited by the narrow patient population enrolled and by the atypical attention enrolled subjects receive during their care. Large existing registries have also generally showed rapid improvement in signs and symptoms.²⁰ However, these registries lack some of the detail and follow-up necessary to fully evaluate the true nature of signs and symptoms progression. Neither prior registries nor completed trials have been specifically designed to prospectively address the progression of signs and symptoms in AHF. Thus we feel the data in this unique study enhance understanding of the evolution of AHF manifestations. The international diversity of the cohort also captures some of the cultural reporting biases and regional treatment differences that may affect evolution of reported symptoms and signs.

The design of this study does not specifically address why patient-reported symptoms resolve in a pattern different than physical signs. We speculate that a number of factors are involved. Placebo effects of medical therapy are common, variable, and have actually increased over time among American patients.^{28,29} Patients may naturally try to reassure and please their care providers in the early stages of AHF hospitalization by agreeing that treatment is helpful. Conversely, physicians may tailor their subjective reports to meet the more objective findings they have available. Consequently, subjective physician assessments may be linked to improvements in vital signs and laboratory values. Physician-reported signs may also be influenced to correspond with overall care decisions such as hospital discharge. Thus it is not surprising that physicians report that rales and edema largely resolve around the time of discharge.

The implications of these findings are particularly important for future design of AHF trials evaluating potential therapeutics. The potential for significant placebo effect in the measure of dyspnea is particularly central to the field of AHF research. The history of randomized placebo-controlled clinical trials of therapeutic agents for AHF is marked by failure to show differences in the primary end points. Milrinone, levosimendan, nesiritide, tolvaptan, tezosentan, ultrafiltration, and even tailored therapy have all had marginal effects on the clinical end points chosen, and consequently have failed to significantly transform the care of AHF.^{10–12,14,16,22,23} However, reliance on short-term hemodynamic and symptom-related data in the assessment of therapeutic efficacy in AHF management has not necessarily correlated with improvements in clinical outcome measures at days to months from randomization. Nesiritide was approved based on its short-term reduction in patient-reported dyspnea and wedge pressure. Yet, significant concerns now exist about the safety and clinical efficacy of this agent.^{30,31} The data reported here indicate that patient-reported symptom improvements may not be an adequate end point in isolation; attention to resolution of signs or other surrogate markers may offer important information about disease progression.

On the other hand, subjective factors such as anxiety may directly contribute to AHF worsening through multiple mechanisms like increased blood pressure and tachycardia. An early improvement in symptoms may have a beneficial effect on the evolution of an AHF episode. This may be more important in patients with acute pulmonary edema than in patients admitted for subacute decompensation of chronic heart failure, the latter in whom progressive fluid retention generally dominates the clinical picture.

This study has a number of limitations. Missing data from loss to follow-up was minimal. However, by study design, data collection on symptom and sign progression was truncated at the time of discharge. Because the most stable and rapidly improving patients were discharged after a short stay, summary statistics for symptoms and signs over time progressively reflected a smaller and smaller subset of relatively sicker patients. Analyses were adjusted to account for missing data using the following approaches: (1) last known results were carried forward in some analyses, (2) a comparative summary of first to last known values was created, and (3) restricted time interval summary statistics were created. Although the registry enrolled patients from around the world, this cohort is biased toward white males from developed countries. Blood pressure was also lower than that seen in some broad AHF registries and length of stay was slightly increased, which may represent the more academic focus of enrolling centers. Otherwise, despite the exclusion criteria designed to recruit a targeted registry population with typical decompensated AHF and volume overload, the MEASURE population closely matched existing cross-sectional surveys of AHF patients in the US.^{20,32} Finally, although associations of various signs and symptoms with each other are provided in detail, data on the relationship between changes in these signs and symptoms and objective hard clinical outcomes (ie, rehospitalization and mortality) were not possible because of the relatively small size of the cohort.

Conclusion

Changes in patient-reported symptoms and physician-assessed signs followed different patterns during an AHF episode. Furthermore, choice of measurement instrument had an affect on the course of symptoms during hospitalization. Although use of the 7-tier Likert scale for dyspnea has become a commonly accepted tool for assessment of short-term improvement in AHF, these data suggest that both physician-assessed measures and VAS-scored symptoms should be considered as well in clinical decisions regarding discharge and in research evaluating the efficacy of AHF therapies.

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Fig. 1. Mean patient-reported dyspnea scores measured by both the visual analog (VAS) and Likert scales over time compared with physician-elicited orthopnea and dyspnea on exertion measures on transformed scales.

Fig. 2.
Patient-reported dyspnea and general well-being scores on visual analog scale.

Fig. 3.
Patient-reported dyspnea and general well-being scores on transformed Likert scale.

Fig. 4.
Change in mean weight and urine output over time ($\pm$ SD).

Fig. 5.
Distribution of change in weight from admission to last reported.

Table 1

Characteristics of Enrolled Patients at Admission

Characteristic, mean (SD)	Total n = 182
Age at admission, y	69.0 (13.4)
Male	66.9
Race	
White	81.9
Black	13.7
Other	1.5
History of diabetes mellitus	49.5
History of hypertension	64.3
History of hyperlipidemia	58.8
History of stroke (beyond 2 y)	13.7
History of PVD	16.5
History of smoking	24.7
History of malignancy	8.2
History of depression	12.1
History of dementia	2.7
History of atrial fibrillation	41.2
History of pacemaker	22.0
History of biventricular pacemaker	12.6
History of AICD	23.1
History of ischemic heart disease	61.0
History of MI	45.6
History of CABG	28.0
History of PCI	23.1
History of stable angina	22.0
SBP, mm Hg	129.5 (32.0)
HR, beats/min	85.7 (24.7)
Weight, kg	85.5 (21.7)
Height, cm	169.5 (10.8)
Initial BNP, pg/mL	540.1 (535.6)
Initial NT-proBNP, pg/mL	2374.0 (9600.1)
Initial creatinine, mg/dL	1.5 (0.7)
EF, %	34.4 (15.0)
NYHA Class, 1 month before admission	
I	4.7
II	26.5
III	55.3
IV	13.5

Values presented as mean (SD) or percentage.

BNP, b-type natriuretic peptide; PVD, peripheral vascular disease; AICD, automatic implantable cardioverter defibrillator; MI, myocardial infarction; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; HR, heart rate; EF, ejection fraction; NYHA, New York Heart Association.

Table 2

Changes in Symptoms and Signs During the Hospital Course and Clinical Outcomes, With Subgroup Analysis by Presence or Absences of Weight Loss

Outcome, n (%)	Total n = 182	Weight Loss n = 127	Weight Gain or No Change n = 31	P Value [‡]
Dyspnea, moderately or markedly improved [*]				
Day 1	47 (26.6)	31 (24.4)	9 (29.0)	.5956
Day 2	74 (45.1)	46 (39.3)	11 (52.4)	.2629
Day 3	64 (46.0)	39 (37.1)	6 (42.9)	.6788
Last reported	74 (52.1)	59 (46.5)	23 (74.2)	.0056
General well-being, moderately or markedly improved [*]				
Day 1	44 (24.9)	30 (24.0)	9 (31.0)	.4326
Day 2	70 (42.9)	50 (44.6)	9 (45.0)	.9764
Day 3	57 (41.6)	36 (36.4)	4 (28.6)	.5682
Last reported	69 (48.6)	56 (46.7)	19 (63.3)	.1025
Orthopnea, none [§]				
Day 1	24 (13.4)	15 (12.1)	8 (25.8)	.0548
Day 2	38 (23.0)	25 (22.3)	11 (52.4)	.0044
Day 3	36 (25.9)	28 (28.0)	5 (35.7)	.5511
Last reported	60 (42.3)	56 (46.7)	12 (38.7)	.4273
Dyspnea on exertion, none or mild [§]				
Day 1	36 (20.2)	20 (16.1)	9 (30.0)	.0812
Day 2	52 (31.5)	27 (23.9)	10 (47.6)	.0255
Day 3	43 (30.7)	24 (23.5)	7 (50.0)	.0358
Last reported	85 (58.6)	69 (57.0)	17 (54.8)	.8266
Edema, none [†]				
Day 1	59 (33.0)	40 (32.3)	11 (35.5)	.7324
Day 2	76 (44.4)	51 (43.6)	11 (52.4)	.4558
Day 3	82 (56.2)	56 (53.3)	7 (50.0)	.8144
Last reported	106 (71.6)	95 (75.4)	16 (51.6)	.0091
Rales, none [†]				
Day 1	36 (19.9)	22 (17.5)	8 (25.8)	.2897
Day 2	68 (39.9)	37 (31.6)	10 (47.6)	.1544
Day 3	78 (53.4)	54 (51.4)	8 (57.1)	.6877
Last reported	121 (81.8)	97 (77.0)	19 (61.3)	.0747
Length of hospital stay, no., days				
Mean (SD)	9.2 (8.2)	9.9 (7.7)	8.3 (10)	.0365
Median (25th–75th)	7 (4.0–10.0)	8 (5.0–11.0)	5 (3.0–8.0)	
Mortality at 60 days, no. (%)	11 (6)			
In-hospital mortality, no. (%)	9 (5)			

* Patient-reported symptom.

[§]Physician-elicited symptom.

[†]Physician-assessed sign.

[‡]A chi-square test was used to test categorical variables, whereas a *t*-test is used for continuous variables.