The Burden of Congestion in Patients Hospitalized With Acute Decompensated Heart Failure

Lauren B. Cooper, MD, MHS[a,b,*], Steven J. Lippmann, PhD[b], Julia R. DiBello, PhD[c], Boris Gorsh, PharmD[d], Lesley H. Curtis, PhD[b], Vanja Sikirica, PharmD, MPH[e], Adrian F. Hernandez, MD, MHS[b], Dennis L. Sprecher, MD[f], Warren K. Laskey, MD, MPH[g], Rajnish Saini, MD[h], Gregg C. Fonarow, MD[i], and Bradley G. Hammill, DrPH[b]

Congestion is associated with adverse outcomes in heart failure (HF) patients. We characterized congestion in patients hospitalized for HF and examined the association between congestion severity at admission and postdischarge outcomes. Using the OPTIMIZE-HF registry linked to Medicare claims, we analyzed patients ≥65 years old hospitalized for HF from 2003 to 2004. Congestion severity was measured using a 15-point scale that scores dyspnea, orthopnea, fatigue, jugular venous pressure, rales, and edema. Patient characteristics and outcomes were described by congestion strata. Proportional hazards models were fit to examine associations between congestion and 1-year outcomes. Congestion scores for the 24,724 patients ranged from 0 to 14, with a median of 5 (Q1, Q3: 3, 7). At baseline, patients with the highest scores (≥7) had the highest rates of recent HF hospitalizations, EF ≤40%, and co-morbidities, including arrhythmias, diabetes mellitus, and renal insufficiency. Adjusting for patient characteristics, a 3-point congestion score increase was positively associated with mortality (hazard ratio [HR] 1.06, 95% confidence interval [CI] 1.03, 1.09), all-cause rehospitalization (HR 1.02, 95% CI 1.00, 1.04), and HF rehospitalization (HR 1.09, 95% CI 1.06, 1.12), but not emergency department visits (HR 0.99, 95% CI 0.97, 1.01). In conclusion, for patients hospitalized with HF, congestion was associated with rehospitalization and mortality. **(Am J Cardiol 2019;124:545−553)**

Congestion is the most common reason for hospital admission for patients with heart failure (HF) and affects all patients with HF regardless of ejection fraction, including those with reduced ejection fraction (HFrEF; EF <40%), mildly reduced ejection fraction (HFmrEF; EF 40% to 49%), and preserved ejection fraction (HFpEF; EF ≥50%).[1−3] Despite treatment, many patients achieve inadequate decongestion during hospitalization; those with persistent congestion have worse outcomes than those who achieve complete relief from congestion.[4−6] Therefore, accurate assessment of and treatment for congestion is important in all patients hospitalized with acute decompensated heart failure (ADHF). In addition to objective measures including hemodynamics, imaging, and biomarkers, patient reported signs and symptoms are essential in the assessment of congestion. Clinical congestion scores have been developed from clinical trial data for patients with HFrEF[4,6]; however, given the burden of congestion in ADHF, there is a need to further explore congestion outside of a clinical trial population and in patients regardless of ejection fraction. Using data from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) Registry linked to Medicare claims data, we characterized a real-world population of patients hospitalized for ADHF experiencing congestion and described their outcomes associated with the standard of care in the treatment of HF.

Methods

OPTIMIZE-HF was a multicenter registry of patients hospitalized with ADHF, with a primary or secondary diagnosis of systolic or diastolic HF, in the United States.[7] Overall, over 48,000 patients from 259 hospitals were enrolled in the registry between January 2003 and December 2004.[8] Each participating center had institutional review board approval for participation in the registry.

Medicare fee-for-service (FFS) standard analytic claims files were obtained from the Centers for Medicare and Medicaid Services. Inpatient facility claims, outpatient facility claims, noninstitutional/professional claims, and denominator files were used.

[a]Inova Heart and Vascular Institute, Falls Church, Virginia; [b]Duke University School of Medicine, Durham, North Carolina; [c]Merck, Center for Observational and Real World Evidence, North Wales, Pennsylvania; [d]Pfizer, Collegeville, Pennsylvania; [e]Pfizer, PHI Inflammation and Immunology, Collegeville, Pennsylvania; [f]BioView Consultants LLC., Blue Bell, Pennsylvania; [g]University of New Mexico School of Medicine, Albuquerque, New Mexico; [h]GlaxoSmithKline, Clinical Sciences, Collegeville, Pennsylvania; and [i]Ronald-Reagan-UCLA Medical Center, Los Angeles, California. Manuscript received March 4, 2019; revised manuscript received and accepted May 13, 2019.

Funding/Support: This project was supported by a research agreement (HO-15-16139) between Glaxo Smith Kline Pharmaceuticals Corporation (Wilmington, DE) and Duke University (Durham, NC).

See page 552 for disclosure information.

*Corresponding author: Tel: (703) 776-4001; fax: (703) 776-2797.

E-mail address: Lauren.Cooper@inova.org (L.B. Cooper).

0002-9149/© 2019 Elsevier Inc. All rights reserved.
https://doi.org/10.1016/j.amjcard.2019.05.030

The linkage of these data sources has been previously described.[9] Previous work has documented the comparability of the Medicare/OPTIMIZE-HF linked population to the larger Medicare FFS population.[10]

The study population included all OPTIMIZE-HF registry patients hospitalized between January 1, 2003 and December 31, 2004, who were aged 65 years and older and who had linked Medicare claims data. For patients with multiple registry hospitalizations linked to Medicare claims, only the earliest was included in the analysis and was referred to as the index hospitalization. Analyses excluded patients who left against medical advice from their index hospitalization (<0.5% of all patients) and patients who enrolled in a Medicare managed care plan during the 1-year study follow-up period (<2% of all patients)

Analyses of in-hospital outcomes included all patients. Analyses of postdischarge clinical outcomes were restricted to patients who were discharged alive from their index hospitalization.

The OPTIMIZE-HF registry included several components of congestion assessed at hospital admission including both patient-reported outcomes and objective physical exam findings: dyspnea at rest (yes/no), dyspnea on exertion (yes/no), orthopnea (yes/no), fatigue (yes/no), jugular venous pressures (JVP; yes/no and measurement in cm), rales (yes/no and location), and lower extremity edema (yes/no and severity). Patients with "Unknown" responses to the initial JVP, Rales, or Edema variables were imputed to a value of "No" for that variable and assigned 0 points for that component. JVP, rales, and lower extremity edema were also assessed at discharge. A congestion grading scale was created using these signs and symptoms of congestion (Table 1), similar to the grading scale for investigator-assessed signs and symptoms of congestion from the EVEREST trial in patients with HFrEF.[4] The study population was classified into 3 groups based on their total scores on signs and symptoms of congestion. Based on preliminary scoring, the following cut-points: 0 to 3, 4 to 6, 7 to 15, were designated, which divided the study population into 3 groups with approximately 25% each in the lowest and highest scoring groups and the remaining ~50% in the middle group. The underlying congestion signs and

Table 1
Congestion Grading score for OPTIMIZE-HF data, shown in comparison with Congestion Grading scale developed for the EVEREST Trial

	Points assigned			
Signs/symptoms	0	1	2	3
Dyspnea	*EVEREST* None — *OPTIMIZE-HF* No dyspnea	*EVEREST* Seldom	*EVEREST* Frequent — *OPTIMIZE-HF* Dyspnea on exertion	*EVEREST* Continuous — *OPTIMIZE-HF* Dyspnea at rest
Orthopnea	*EVEREST* None — *OPTIMIZE-HF* No orthopnea	*EVEREST* Seldom —	*EVEREST* Frequent — *OPTIMIZE-HF* Orthopnea	*EVEREST* Continuous
Fatigue	*EVEREST* None — *OPTIMIZE-HF* No fatigue	*EVEREST* Seldom	*EVEREST* Frequent — *OPTIMIZE-HF* Fatigue	*EVEREST* Continuous
JVD (cm H_2O)	*EVEREST* ≤6 cm — *OPTIMIZE-HF* JVP ≠ Yes* or ≤6 cm	*EVEREST* 6-9 cm — *OPTIMIZE-HF* 6-9 cm or unknown cm	*EVEREST* 10-15 cm — *OPTIMIZE-HF* 10-15 cm	*EVEREST* >15 cm — *OPTIMIZE-HF* >15 cm
Rales	*EVEREST* None — *OPTIMIZE-HF* Rales ≠ Yes*	*EVEREST* Bases — *OPTIMIZE-HF* Location <1/3 or unknown	*EVEREST* To <50% — *OPTIMIZE-HF* Location ≥1/3	*EVEREST* To >50%
Edema	*EVEREST* Absent/Trace — *OPTIMIZE-HF* Edema ≠ Yes* or Trace	*EVEREST* Slight — *OPTIMIZE-HF* 1+ or unknown†	*EVEREST* Moderate — *OPTIMIZE-HF* 2+	*EVEREST* Marked — *OPTIMIZE-HF* 3+ or 4+

Total score is the sum of points assigned to each sign/symptom.

* Patients with "Unknown" responses to the initial JVP, Rales, or Edema variables will be imputed to a value of "No" for that variable and assigned 0 points for that component from the EVEREST score.

† A small number of patients (~1092 or ~4% of the analysis population) were recorded as having edema (Edema = Yes) but the degree of edema was unknown. These were imputed to a degree of 1+ and assigned 1 point for the edema component of the EVEREST scale.

symptoms were well discriminated in these groupings with a distinct progression toward more severe symptoms in the higher congestion groups (Supplemental Table A).

In-hospital outcomes were ascertained using data from the OPTIMIZE-HF registry and the Medicare claims for the index hospitalization. Outcomes of interest associated with the index hospitalization included length of stay, mortality, and discharge disposition.

Postdischarge outcomes were ascertained using the linked Medicare claims and denominator files. Outcomes of interest within the 365-day postdischarge period included rehospitalization (all-cause and for HF), emergency department (ED) visits, and mortality. Hospitalization for HF was based on subsequent inpatient claims with a primary diagnosis of HF (ICD-9-CM diagnosis code 428.x, 402.x1, 404.x1, or 404.x3). ED visits were captured independent of whether or not they resulted in a hospitalization. Additionally, we ascertained Medicare payments associated with healthcare utilization. All payment values were adjusted to 2015 US dollars using the United States Consumer Price Index Medical Care component (Bureau of Labor Statistics, United States Department of Labor).

The baseline characteristics and in-hospital outcomes of the study population were described by congestion severity group, using proportions for categorical variables and means with standard deviations or medians with quartiles for continuous variables. Differences between groups were tested for using chi-square tests/Kruskal-Wallis tests for categorical variables and Wilcoxon rank-sum tests for continuous variables.

Most variables in OPTIMIZE-HF had low rates of missingness. For variables with <5% missingness, we imputed continuous variables to the overall median value, dichotomous variables to “no”, and categorical variables to the most frequent categorical value. For variables with >5% missingness, we treated the missing value as a separate category.

Survival analysis methods were used for time-to-event outcomes including mortality, first rehospitalization, or first ED visit after discharge from the index hospitalization. For patients who did not experience a particular outcome, a censoring date was defined as 365 days postdischarge. For rehospitalization and ED visits, death was treated as a competing risk and analyzed appropriately. For mortality, cumulative incidence at 30, 90, 180, and 365 days following discharge was calculated based on Kaplan-Meier estimates and assessed differences by congestion severity group using log-rank tests. For time to first rehospitalization and first ED visit, the cumulative incidence function was used to account for competing risk of death, to calculate incidence at 30, 90, 180, and 365 days and tested for group differences using Gray tests.[11,12]

For rehospitalizations and ED visits, which can occur more than once, event count variables for incidence at 30, 90, 180, and 365 days were created. Observed incidence was summarized by congestion severity group as mean event counts at each time point and tested for differences among groups using Kruskal-Wallis tests. To reduce the influence of outliers with high numbers of hospitalizations or ED visits, we Winsorized those counts to the 99th percentile for use in the regression models. Reported Medicare payments associated with healthcare utilization during the 365-day postdischarge period were summarized as medians with quartiles by congestion severity group.

Unadjusted and adjusted regression models were used to examine the association between congestion severity and each of the postdischarge outcomes at 365 days. Congestion severity score was examined both as a continuous variable and as a categorical variable, using the 3 groups previously described. For time-to-event outcomes, Cox proportional hazards regression models were used to estimate hazard ratios for the association between congestion severity and time to first event postdischarge from the index hospitalization. Negative binomial models were used for event counts. Differences in the estimated ratios between congestion severity groups were tested using the lowest severity group as the reference. In all models, the potential correlation of patients within hospitals was accounted for using a random intercept for hospital. Adjusted effects were estimated by controlling for the patient baseline characteristics listed in Table 2. The characteristics included were retained in all models. No automatic variable selection methods were employed.

In the main analyses, patients were scored based on congestion-related data collected at admission. JVP, rales, and edema were also collected at hospital discharge, although the discharge variables tend to have higher missingness than admission variables in the OPTIMIZE dataset. As a sensitivity analysis, patients discharged alive were scored using discharge congestion data. This sensitivity analysis was restricted to patients with nonmissing responses to all of the discharge congestion variables included in the congestion scale. Baseline characteristics of this subset of the study cohort were summarized. For these patients, scores derived using discharge data and admission data were compared. Agreement between the admission- and discharge-based scoring groups were calculated using the Stuart-Maxwell test, which is a generalized McNemar’s test for paired categorical data with >2 categories.[13,14] Agreement was also assessed by calculating the correlation coefficient between continuous forms of the admission- and discharge-based congestion severity measures. Differences reflected the ability of sites to alleviate or otherwise affect congestion. Models were rerun as previously described (postdischarge outcomes only) using the discharge-based scores in place of the admission-based scores.

Additional analyses were performed to evaluate differences in the associations between congestion severity and outcomes within specified subgroups. Subgroups were formed by ejection fraction (preserved vs reduced EF, as defined in Table 2), gender (male vs female), and age (65 to 74 vs ≥75 years). Differences were described in the observed outcomes by subgroup. Unadjusted and adjusted subgroup-specific estimates of the association between congestion severity and outcomes by including an interaction term for the interaction between the congestion severity group variables and the subgroup indicators were estimated. The interactions were modeled for each subgrouping individually; multi-way interactions were not considered.

All analyses were performed using SAS version 9.4 (SAS institute Inc, Cary, North Carolina). 95% CIs were reported and $\alpha = 0.05$ was used to establish statistical

Table 2
Baseline characteristics of the study population, by congestion severity group

Variable	Degree of congestion			p Value
	Low (Score: 0-3) n = 6496	Moderate (Score: 4-6) n = 11,624	High (Score: 7-15) n = 6,604	
Age (years), mean (SD)	79.8 (8.0)	79.7 (7.8)	79.0 (7.7)	<0.001
Men	2,746 (42%)	5,025 (43%)	3,131 (47%)	<0.001
Race				<0.001
White	5,449 (84%)	9,683 (83%)	5,403 (82%)	
Black	618 (10%)	1,183 (10%)	779 (12%)	
Other/unknown	429 (7%)	758 (7%)	422 (6%)	
Prior HF hospitalizations in the past 6 months				<0.001
No	3,555 (54.7%)	6,148 (52.9%)	3,297 (49.9%)	
Yes	1,066 (16.4%)	2,066 (17.8%)	1,428 (21.6%)	
Missing	1,875 (28.9%)	3,410 (29.3%)	1,879 (28.5%)	
EF ≤40%, or moderate/severe dysfunction	2,560 (39%)	4,706 (41%)	2,965 (45%)	<0.001
Acute renal failure	176 (3%)	314 (3%)	224 (3%)	0.02
Anemia	1,088 (17%)	2,210 (19%)	1,368 (21%)	<0.001
Atrial arrhythmia	2,119 (33%)	4,184 (36%)	2,539 (38%)	<0.001
Chronic obstructive pulmonary disease	1,723 (27%)	3,361 (29%)	1,947 (30%)	<0.001
Stroke/Transient Ischemic Attack	1,127 (17%)	2,029 (18%)	1,130 (17%)	0.84
Depression	657 (10%)	1,187 (10%)	724 (11%)	0.20
Diabetes mellitus	2,317 (36%)	4,453 (38%)	2,890 (44%)	<0.001
Dialysis (chronic)	167 (3%)	309 (3%)	121 (2%)	0.001
Hyperlipidemia	1,916 (30%)	3,794 (33%)	2,356 (36%)	<0.001
Hypertension	4,515 (70%)	8,173 (70%)	4,783 (72%)	<0.001
Implantable cardioverter defibrillator	272 (4%)	472 (4%)	337 (5%)	0.003
Pacemaker	1,197 (18%)	1,999 (17%)	1,144 (17%)	0.10
Peripheral vascular disease	852 (13%)	1,703 (15%)	1,135 (17%)	<0.001
Chronic renal insufficiency	1,125 (17%)	2,144 (18%)	1,463 (22%)	<0.001
Smoker in the past year	580 (9%)	1,066 (9%)	613 (9%)	0.77
Admission heart rate (bpm), mean (SD)	83.9 (21.0)	85.2 (21.2)	84.9 (20.9)	<0.001
Admission systolic blood pressure (mmHg), mean (SD)	141.8 (32.1)	142.9 (31.6)	141.2 (31.3)	0.004
Admission serum creatinine (mg/dl), mean (SD)	1.6 (1.3)	1.7 (1.2)	1.7 (1.1)	<0.001
Admission sodium (mEq/L), mean (SD)	137.6 (4.8)	137.8 (4.8)	137.7 (4.9)	0.001
Admission hemoglobin (g/dl), mean (SD)	12.1 (1.9)	12.0 (2.0)	11.9 (2.0)	<0.001
High risk procedure during index hospitalization	77 (1%)	116 (1%)	61 (1%)	0.30
ACE inhibitor and/or ARB at discharge	3,737 (58%)	6,853 (59%)	3,909 (59%)	0.10
Beta-blocker at discharge	3,905 (60%)	6,944 (60%)	4,003 (61%)	0.51
Aldosterone antagonist at discharge	525 (8%)	1,172 (10%)	898 (14%)	<0.001

significance. The Duke University Health System institutional review board approved this study.

Results

There were 29,230 hospitalizations in the OPTIMIZE-HF registry linked to Medicare claims where the patient did not leave against medical advice, 25,844 of which were index hospitalizations (Supplemental Figure 1). There were 24,724 patients with Medicare FFS eligibility during the index hospitalization and through 365 days postdischarge or until death, and these patients were included in the primary study cohort. Analyses of postdischarge outcomes were restricted to the 23,676 patients who were discharged alive from the index hospitalization. Sensitivity analyses related to congestion data collected at discharge from the index hospitalization were restricted to the 13,012 patients with complete data for those variables.

Based on designated cut-points for congestion scoring, of the 24,724 patients in the study population, 6,496 (26%) were in the low congestion group, 11,624 (47%) were in the moderate congestion group, and 6,604 (27%) were in the high congestion group at hospital admission (Supplemental Table A). Total congestion severity scores at admission ranged from 0 to 14 (of 15 possible points), with a median of 5 (Q1, Q3: 3, 7) and mean of 5.07 (SD: 2.37). Dyspnea on exertion was the most common congestion-related symptom for all groups while a majority of the patients in the high congestion group also had dyspnea at rest (Table 2).

Table 3
Observed postdischarge outcomes by congestion severity group, among those discharged alive at index hospitalization

Variable	Degree of congestion: Low (Score: 0-3) n = 6215	Moderate (Score: 4-6) n = 11,150	High (Score: 7-15) n = 6,311	p Value
Mortality (days)				
30	431 (7%)	793 (7%)	500 (8%)	0.08
90	904 (15%)	1729 (16%)	1067 (17%)	0.001
180	1352 (22%)	2604 (23%)	1562 (25%)	<0.001
360	2035 (33%)	3831 (34%)	2257 (36%)	0.001
All-cause rehospitalization (days)				
30	1547 (25%)	2938 (26%)	1667 (26%)	0.08
90	2602 (42%)	4846 (44%)	2727 (43%)	0.10
180	3356 (54%)	6229 (56%)	3544 (56%)	0.02
360	4148 (67%)	7635 (69%)	4346 (69%)	0.01
Heart failure rehospitalization (days)				
30	468 (8%)	972 (9%)	596 (9%)	<0.001
90	899 (15%)	1837 (17%)	1102 (18%)	<0.001
180	1253 (20%)	2553 (23%)	1521 (24%)	<0.001
360	1665 (27%)	3362 (30%)	2022 (32%)	<0.001
Emergency department visits (days)				
30	1533 (25%)	2889 (26%)	1606 (25%)	0.21
90	2707 (44%)	4916 (44%)	2708 (43%)	0.32
180	3573 (58%)	6393 (57%)	3555 (56%)	0.38
360	4367 (70%)	7896 (71%)	4390 (70%)	0.21
Event counts (365 days)				
All cause rehospitalization, mean (SD)	1.7 (1.9)	1.7 (2.0)	1.7 (2.0)	0.04
Heart failure rehospitalization, mean (SD)	0.4 (0.9)	0.5 (1.0)	0.5 (1.0)	<0.001
Emergency department visits, mean (SD)	2.0 (2.5)	2.0 (2.7)	1.9 (2.3)	0.18
Medicare payments including index hospitalization				
2015 US dollars, median (Q1, Q3)	28004.7 (13992.3, 55116.3)	27007.5 (13634.3, 55314.9)	27336.8 (14006.5, 55626.5)	0.65

Patients in the high congestion group had the longest median length of stay (5 days vs 4 days for moderate and low congestion groups); mean length of stay was 0.6 days longer in the high group compared with the low group (Supplemental Table B). The rate of in-hospital mortality, however did not differ significantly between groups. Postdischarge mortality was consistently higher amongst those with more severe congestion scores; these differences were significant at the 90-day, 180-day, and 1-year time points (Table 3; Figure 1). Across all time points, HF rehospitalization was the lowest for the low congestion group and highest for the high congestion group. However, there were no significant group differences for ED visits. Median Medicare payments during the 1 year period, including those related to the index hospitalization, did not differ significantly by congestion group.

In examining the adjusted associations between congestion severity score and postdischarge time-to event outcomes, a 3-point increase in congestion severity score was associated with increased 1-year postdischarge time-to-event outcomes including mortality (hazard ratio [HR] 1.06, 95% confidence interval [CI] 1.03, 1.09), all cause rehospitalization (HR 1.02, 95% CI 1.00, 1.04), and HF rehospitalization (HR 1.09, 95% CI 1.06, 1.12), but not ED visits (HR 0.99, 95% CI 0.97, 1.01) (Table 4). For the count of each outcome, after adjustment, a 3-point increase in congestion severity was associated with increased rate of HF hospitalization (rate ratio 1.06, 95% CI 1.03, 1.10) but decreased rate of ED visits (rate ratio 0.97, 95% CI 0.95, 0.99). To explore these findings, we performed a sensitivity analysis of the count outcomes within the subset of patients who survived the entire year of follow-up. After adjustment, among patients who survived 1 year, an increase in congestion score was associated with an increased rate of HF hospitalization (rate ratio 1.07, 95% CI 1.02, 1.11), and a slightly decreased rate of ED visits (rate ratio 0.98, 95% CI 0.95, 1.00), but was not associated with the rate of all-cause hospitalization (rate ratio 1.01, 95% CI 0.99, 1.04). The findings from the analysis of the associations between congestion severity at the group level and postdischarge outcomes were similar (Supplemental Table C).

There was no evidence of significant interaction in the congestion-outcome associations for any of the subgroups (Supplemental Table D).

Comparing congestion scores at admission and discharge, scores tended to decrease throughout admission. Admission congestion score and discharge congestion score

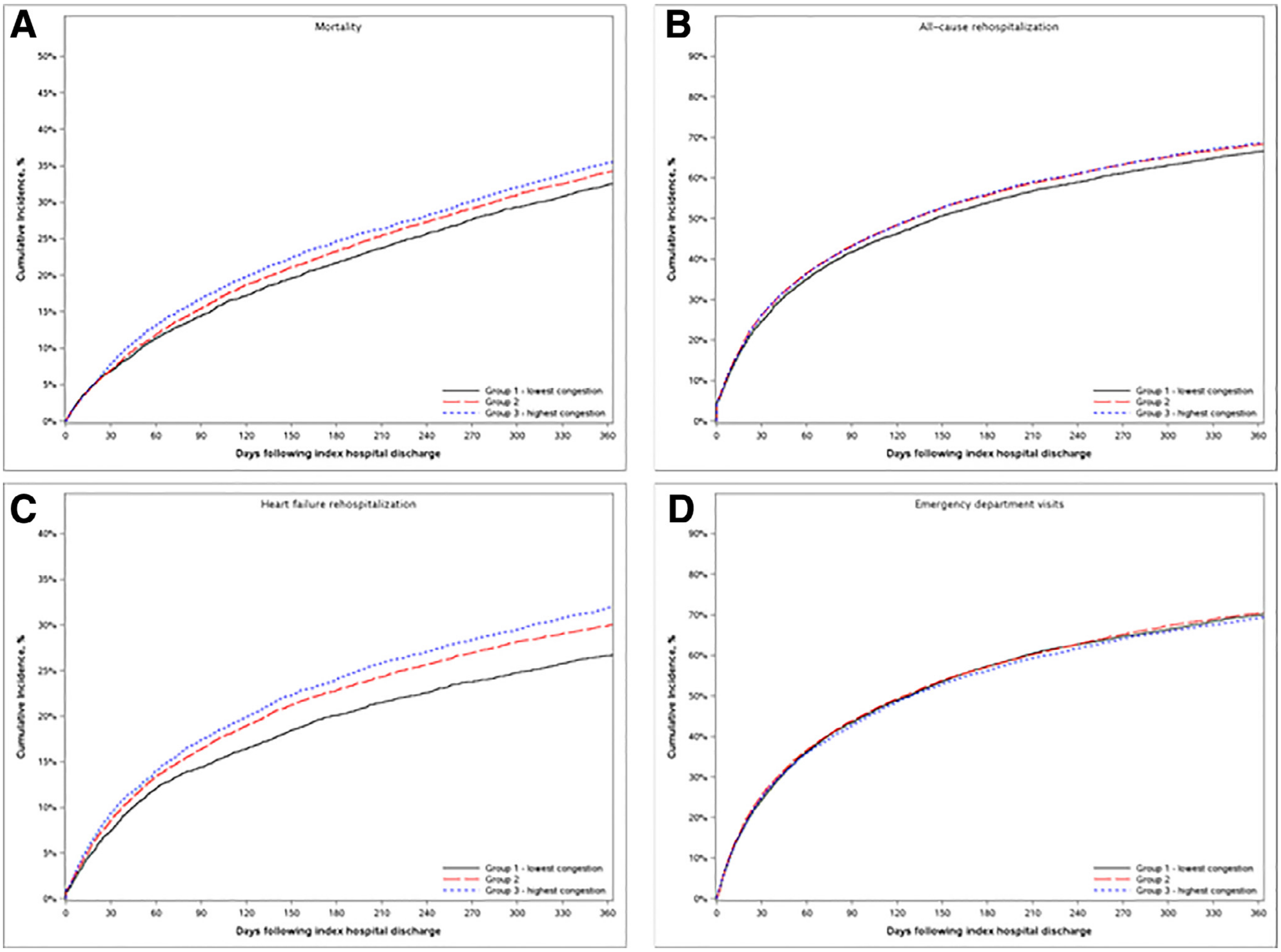

Figure 1. *(A)* Cumulative incidence of mortality by congestion severity group, *(B)* Cumulative incidence of all-cause rehospitalization by congestion severity group, *(C)* Cumulative incidence of cardiovascular rehospitalization by congestion severity group, and *(D)* Cumulative incidence of ED visits by congestion severity group.

were highly correlated (Pearson's $r = 0.79$; $p < 0.0001$; Supplemental Table E). Overall, the mean difference between the admission and discharge based scores was a 1.62 point decrease (SD: 1.49).

Of the 13,012 patients with complete congestion data at the time of hospital discharge, the majority (59%) were in the low congestion group, and 39% were in the moderate congestion group; 7% of patients were still in the high

Table 4
Association between admission congestion severity score as a continuous variable and 1-year postdischarge outcomes

	Unadjusted		Adjusted	
Outcomes	Ratio measure (95% CI)	p Value	Ratio measure (95% CI)	p Value
Time-to-event (hazard ratio)				
Mortality	1.07 (1.04, 1.10)	<0.0001	1.06 (1.03, 1.09)	<0.0001
All cause rehospitalization	1.05 (1.03, 1.07)	<0.0001	1.02 (1.00, 1.04)	0.04
Heart failure rehospitalization	1.14 (1.10, 1.17)	<0.0001	1.09 (1.06, 1.12)	<0.0001
Emergency department visit	1.01 (0.99, 1.03)	0.30	0.99 (0.97, 1.01)	0.28
Count* (rate ratio)				
All cause rehospitalization (count)	1.03 (1.01, 1.05)	<0.001	1.01 (0.99, 1.03)	0.44
Heart failure rehospitalization (count)	1.11 (1.07, 1.15)	<0.0001	1.06 (1.03, 1.10)	<0.001
Emergency department visit (count)	0.99 (0.97, 1.01)	0.30	0.97 (0.95, 0.99)	<0.001

Per 3 point increment on the congestion severity scale.

* Event counts were Winsorized to the 99th percentile for use in modeling (all cause hospitalizations: 9, HF hospitalizations: 4, emergency department visits: 11).

Table 5
Association between discharge congestion severity score as a continuous variable and 1-year postdischarge outcomes

Outcomes	Unadjusted		Adjusted	
	Ratio measure (95% CI)	p Value	Ratio measure (95% CI)	p Value
Time-to-event (hazard ratio)				
Mortality	1.11 (1.05, 1.16)	<0.0001	1.09 (1.03, 1.15)	<0.01
All cause rehospitalization	1.08 (1.04, 1.12)	<0.0001	1.05 (1.01, 1.08)	0.01
Heart failure rehospitalization	1.17 (1.11, 1.24)	<0.0001	1.12 (1.06, 1.18)	<0.0001
Emergency department visit	1.01 (0.97, 1.04)	0.68	0.99 (0.95, 1.02)	0.45
Count* (rate ratio)				
All cause rehospitalization (count)	1.02 (0.98, 1.05)	0.33	0.99 (0.96, 1.02)	0.49
Heart failure rehospitalization (count)	1.10 (1.04, 1.16)	0.001	1.04 (0.99, 1.10)	0.12
Emergency department visit (count)	0.98 (0.94, 1.01)	0.13	0.95 (0.92, 0.98)	0.002

Per 3 point increment on the congestion severity scale.
* Event counts were Winsorized to the 99th percentile.

congestion group at the time of discharge (Supplemental Table F).

A 3-point increment in discharge congestion score was associated with increased adjusted hazards of mortality (HR 1.09, 95% CI 1.03, 1.15), all cause rehospitalization (HR 1.05, 95% CI 1.01, 1.08), and HF rehospitalization (HR 1.12, 95% CI 1.06, 1.18), but not ED visits (HR 0.99, 95% CI 0.95, 1.02) (Table 5). When accounting for multiple potential events, increasing discharge congestion scores were associated with decreased frequency of ED visits (adjusted rate ratio 0.95, 95% CI 0.92, 0.98), but were not associated with increased or decreased frequency of all-cause or HF rehospitalization.

Discussion

In this analysis from the OPTIMIZE-HF registry, we were able to categorize the severity of congestion for patients with HF at the time of hospital admission and discharge in a real-world clinical practice setting. We found the following: (1) most patients have some degree of congestion on hospital admission, (2) congestion improves during hospitalization, but many patients still have signs and symptoms of congestion at discharge, (3) worse congestion at hospital admission is associated with worse outcomes after discharge, and (4) worse congestion at hospital discharge is also associated with worse outcomes.

Among over 24,000 Medicare patients in the OPTIMIZE-HF registry, which included patients with HF regardless of ejection fraction, those with worse congestion at admission had higher rates of reduced ejection fraction and most co-morbid conditions compared with those with less congestion. These results are consistent with prior studies of patients with ADHF showing high rates of congestion on admission and a high burden of co-morbidities.[15,16] Further, our study showed that patients with more severe congestion at admission require significantly longer stays to achieve clinical stability during their index hospitalization. However, despite differences on admission, observed in-hospital mortality was similar between groups.

Within the first month after discharge, those with more severe congestion at admission were more likely to be readmitted for HF. After 6 months, those with more severe congestion were also more likely to have died or have been hospitalized for any reason. At 1 year, worsening congestion was independently associated with increased mortality, all-cause rehospitalization, and HF hospitalizations. The impact of congestion on patients with HF has been well documented in prior studies.[4,6,17−19] While prior studies have shown that congestion itself is a marker for adverse outcomes, we extend the prior results to show that the severity of congestion—the relative number of signs and symptoms of congestion—is associated with the severity of risk.

As expected, congestion symptomatology was ameliorated during the index hospitalization for most patients who survived to discharge, resulting in significant shifts toward the lower congestion groups. However, similar to prior studies from clinical trial populations, many patients in this clinical registry remained congested at the time of discharge from a hospitalization for ADHF.[4−6] Prior studies from clinical trial data found that persistent congestion at the end of a hospitalization results in worse postdischarge outcomes.[4,6,20,21] Examining postdischarge outcomes using real-world clinical data, worse severity of congestion at discharge was associated with increased risk of death or rehospitalization but decreased frequency of ED visits.

The results related to postdischarge ED visits were unexpected. Worsening congestion at admission and discharge was not associated with increased risk of an ED visit, but was associated with decreased frequency of ED visits. Assuming that patients who died had less opportunity to accrue ED visits throughout the follow-up period, we performed a sensitivity analysis within the subset of patients who survived the entire follow-up period. Within this subset, the adjusted rate ratio for ED visits was much closer to the null, although still marginally statistically significant; thus, higher mortality in those with worse congestion may partially explain why there were fewer ED visits in those with worse congestion severity in our main analysis. While HFrEF, HFmrEF, and HFpEF are distinct clinical entities, with different pathophysiology and markedly different medical therapies, ejection fraction did not modify the association between congestion and outcomes.[22,23] This further highlights the burden of congestion in patients with HF regardless of ejection fraction. These results are consistent with prior studies that showed that across all EF categories, patients hospitalized with ADHF had similar measures of congestion, response to decongestion, and outcomes.[24]. All of these groups contribute to the morbidity and mortality of HF in the United States.[22,23]

These results should be interpreted in the context of several limitations. First, our population was limited to Medicare FFS beneficiaries, and while the OPTIMIZE-HF patients were similar to the broader Medicare population with HF,[10] the results may not be generalizable to other populations, including younger patients or those with commercial insurance coverage. Furthermore, the hospitals participating in OPTIMIZE-HF were not randomly selected, and participation in the registry was voluntary. While the registry included academic and community-hospitals of all sizes and all regions of the country, participating hospitals had a larger volume of HF discharges and were more likely to offer advanced cardiovascular services compared with nonparticipating hospitals.[10] Second, we were limited to the variables available in the OPTIMIZE-HF registry. These variables provided information on overall congestion severity but did not allow the level of differentiation between pulmonary congestion and other forms of hemodynamic congestion that direct clinical interaction may afford. Moreover, we only included signs and symptoms of congestion, and did not include other objective findings such as imaging or biomarker data, although these markers are commonly used to assess congestion in clinical practice. Third, the study period occurred from 2003 to 2004. While the data may be dated, the study population and treatment patterns are still highly relevant to current standard of care, and outcomes of patients are similar to contemporary cohorts.[25] We chose to use the OPTIMIZE-HF registry as the dataset includes pertinent patient characteristics and symptoms we sought to explore, and was able to be linked to insurance claims for analysis of clinical and financial outcomes. Fourth, as with all retrospective analyses, unobserved or unmeasured confounders may have influenced the results. In conclusion, for patients hospitalized with ADHF, congestion severity at admission and at discharge was associated with significantly higher likelihood of rehospitalization or mortality in the year following discharge. Further studies are needed to determine if better treatment of congestion can improve outcomes in patients with HF.

Financial Disclosures

Dr. Cooper reported receiving research support from Abbott. Dr. Lippmann reported receiving research support from GlaxoSmithKline during the conduct of the study. Dr. DiBello was an employee and stockholder of GlaxoSmithKline during the conduct of the study. Dr. Gorsh was an employee and stockholder of GlaxoSmithKline during the conduct of the study. Dr. Curtis reports receiving research support from Boston Scientific, Gilead, GlaxoSmithKline, Novartis, and St. Jude Medical. Dr. Sikirica reports being an employee and stockholder of GlaxoSmithKline during the conduct of the study. Dr. Hernandez reported receiving research support from AstraZeneca, GlaxoSmithKline, Luitpold, Merck, and Novartis; and serving as a consultant to Bayer, Boston Scientific, Merck, and Novartis. Dr. Sprecher was an employee and stockholder of GlaxoSmithKline during the conduct of the study. Dr. Saini was an employee and stockholder of GlaxoSmithKline during the conduct of the study, and a former employee and current stockholder of Novartis. Dr. Fonarow reported serving as a consultant to Amgen, Medtronic, Novartis, and St. Jude Medical. Dr. Hammill reported receiving research support from GlaxoSmithKline during the conduct of the study. No other disclosures were reported.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.05.030.

1. Cleland JG, Swedberg K, Follath F, Komajda M, Cohen-Solal A, Aguilar JC, Dietz R, Gavazzi A, Hobbs R, Korewicki J, Madeira HC, Moiseyev VS, Preda I, van Gilst WH, Widimsky J, Freemantle N, Eastaugh J, Mason J. The EuroHeart Failure survey programme—a survey on the quality of care among patients with heart failure in Europe. Part 1: patient characteristics and diagnosis. *Eur Heart J* 2003;24:442–463.
2. Gheorghiade M. Treatment of congestion in acute heart failure syndromes: importance, strategies, and challenges. Introduction. *Am J Med* 2006;119:S1–S2.
3. O'Connor CM, Stough WG, Gallup DS, Hasselblad V, Gheorghiade M. Demographics, clinical characteristics, and outcomes of patients hospitalized for decompensated heart failure: observations from the IMPACT-HF registry. *J Card Fail* 2005;11:200–205.
4. Ambrosy AP, Pang PS, Khan S, Konstam MA, Fonarow GC, Traver B, Maggioni AP, Cook T, Swedberg K, Burnett JC Jr, Grinfeld L, Udelson JE, Zannad F, Gheorghiade M. Clinical course and predictive value of congestion during hospitalization in patients admitted for worsening signs and symptoms of heart failure with reduced ejection fraction: findings from the EVEREST trial. *Eur Heart J* 2013;34:835–843.
5. Lucas C, Johnson W, Hamilton MA, Fonarow GC, Woo MA, Flavell CM, Creaser JA, Stevenson LW. Freedom from congestion predicts good survival despite previous class IV symptoms of heart failure. *Am Heart J* 2000;140:840–847.
6. Lala A, McNulty SE, Mentz RJ, Dunlay SM, Vader JM, AbouEzzeddine OF, DeVore AD, Khazanie P, Redfield MM, Goldsmith SR, Bart BA, Anstrom KJ, Felker GM, Hernandez AF, Stevenson LW. Relief and recurrence of congestion during and after hospitalization for acute heart failure: insights from diuretic optimization strategy evaluation in acute decompensated heart failure (DOSE-AHF) and cardiorenal rescue study in acute decompensated heart failure (CARESS-HF). *Circ Heart Fail* 2015;8:741–748.
7. Fonarow GC, Abraham WT, Albert NM, Gattis WA, Gheorghiade M, Greenberg B, O'Connor CM, Yancy CW, Young J. Organized program to initiate lifesaving treatment in hospitalized patients with heart failure (OPTIMIZE-HF): rationale and design. *Am Heart J* 2004;148:43–51.
8. Gheorghiade M, Abraham WT, Albert NM, Greenberg BH, O'Connor CM, She L, Stough WG, Yancy CW, Young JB, Fonarow GC. Systolic blood pressure at admission, clinical characteristics, and outcomes in patients hospitalized with acute heart failure. *JAMA* 2006;296:2217–2226.
9. Hammill BG, Hernandez AF, Peterson ED, Fonarow GC, Schulman KA, Curtis LH. Linking inpatient clinical registry data to Medicare claims data using indirect identifiers. *Am Heart J* 2009;157:995–1000.
10. Curtis LH, Greiner MA, Hammill BG, DiMartino LD, Shea AM, Hernandez AF, Fonarow GC. Representativeness of a national heart failure quality-of-care registry: comparison of OPTIMIZE-HF and non-OPTIMIZE-HF Medicare patients. *Circ Cardiovasc Qual Outcomes* 2009;2:377–384.
11. Gray R. A class of K-sample tests for comparing the cumulative incidence of a competing risk. *Ann Stat* 1988;16:1141–1154.

12. Kalbfleisch J, Prentice R. *The statistical analysis of failure time data*. New York: Wiley; 1980.
13. Maxwell AE. Comparing the classification of subjects by two independent judges. *Br J Psychiatry* 1970;116:651–655.
14. Sun X, Yang Z. *Generalized McNemar's test for homogeneity of the marginal distributions*. SAS Global Forum [Internet]. 2008 [cited 2017 Feb 9]; Available from: https://works.bepress.com/zyang/17/.
15. De Luca L, Fonarow GC, Adams KF Jr., Mebazaa A, Tavazzi L, Swedberg K, Gheorghiade M. Acute heart failure syndromes: clinical scenarios and pathophysiologic targets for therapy. *Heart Fail Rev* 2007;12:97–104.
16. Adams KF Jr., Fonarow GC, Emerman CL, LeJemtel TH, Costanzo MR, Abraham WT, Berkowitz RL, Galvao M, Horton DP. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). *Am Heart J* 2005;149:209–216.
17. Nohria A, Tsang SW, Fang JC, Lewis EF, Jarcho JA, Mudge GH, Stevenson LW. Clinical assessment identifies hemodynamic profiles that predict outcomes in patients admitted with heart failure. *J Am Coll Cardiol* 2003;41:1797–1804.
18. Stevenson LW, Tillisch JH, Hamilton M, Luu M, Chelimsky-Fallick C, Moriguchi J, Kobashigawa J, Walden J. Importance of hemodynamic response to therapy in predicting survival with ejection fraction less than or equal to 20% secondary to ischemic or nonischemic dilated cardiomyopathy. *Am J Cardiol* 1990;66:1348–1354.
19. Drazner MH, Rame JE, Stevenson LW, Dries DL. Prognostic importance of elevated jugular venous pressure and a third heart sound in patients with heart failure. *N Engl J Med* 2001;345:574–581.
20. Ter Maaten JM, Valente MA, Damman K, Cleland JG, Givertz MM, Metra M, O'Connor CM, Teerlink JR, Ponikowski P, Bloomfield DM, Cotter G, Davison B, Subacius H, van Veldhuisen DJ, van der Meer P, Hillege HL, Gheorghiade M, Voors AA. Combining diuretic response and hemoconcentration to predict rehospitalization after admission for acute heart failure. *Circ Heart Fail* 2016;9:e002845. pii:.
21. Ambrosy AP, Cerbin LP, Armstrong PW, Butler J, Coles A, DeVore AD, Dunlap ME, Ezekowitz JA, Felker GM, Fudim M, Greene SJ, Hernandez AF, O'Connor CM, Schulte P, Starling RC, Teerlink JR, Voors AA, Mentz RJ. Body weight change during and after hospitalization for acute heart failure: patient characteristics, markers of congestion, and outcomes: findings from the ASCEND-HF Trial. *JACC Heart Fail* 2017;5:1–13.
22. Quiroz R, Doros G, Shaw P, Liang CS, Gauthier DF, Sam F. Comparison of characteristics and outcomes of patients with heart failure preserved ejection fraction versus reduced left ventricular ejection fraction in an urban cohort. *Am J Cardiol* 2014;113:691–696.
23. Cheng RK, Cox M, Neely ML, Heidenreich PA, Bhatt DL, Eapen ZJ, Hernandez AF, Butler J, Yancy CW, Fonarow GC. Outcomes in patients with heart failure with preserved, borderline, and reduced ejection fraction in the Medicare population. *Am Heart J* 2014;168:721–730.
24. Ambrosy AP, Bhatt AS, Gallup D, Anstrom KJ, Butler J, DeVore AD, Felker GM, Fudim M, Greene SJ, Hernandez AF, Kelly JP, Samsky MD, Mentz RJ. Trajectory of congestion metrics by ejection fraction in patients with acute heart failure (from the Heart Failure Network). *Am J Cardiol* 2017;120:98–105.
25. Bergethon KE, Ju C, DeVore AD, Hardy NC, Fonarow GC, Yancy CW, Heidenreich PA, Bhatt DL, Peterson ED, Hernandez AF. Trends in 30-day readmission rates for patients hospitalized with heart failure: findings from the Get With The Guidelines-Heart Failure Registry. *Circ Heart Fail* 2016;9:e002594.