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Decongestion and Outcomes in Patients Hospitalized for Acute Heart Failure

Insights From the RELAX-AHF-2 Trial

Matteo Pagnesi, MD, PhD,[a] Laura Staal, PhD,[b] Jozine M. ter Maaten, MD, PhD,[b] Iris E. Beldhuis, MD,[b] Gad Cotter, MD,[c] Beth A. Davison, PhD,[c] Niels Jongs, PhD,[d] G. Michael Felker, MD, MHS,[e] Gerasimos Filippatos, MD,[f] Barry H. Greenberg, MD,[g] Peter S. Pang, MD,[h] Piotr Ponikowski, MD, PhD,[i] Carlo Mario Lombardi, MD,[a] Marianna Adamo, MD, PhD,[a] Thomas Severin, MD,[j] Claudio Gimpelewicz, MD,[j] Adriaan A. Voors, MD, PhD,[b] John R. Teerlink, MD,[k] Marco Metra, MD[a]

ABSTRACT

BACKGROUND The prognostic importance of residual congestion after acute heart failure (AHF) hospitalization is still debated.

OBJECTIVES The authors aimed to assess the impact of residual congestion in a large cohort of patients with AHF enrolled in the RELAX-AHF-2 (Efficacy, Safety and Tolerability of Serelaxin When Added to Standard Therapy in AHF) trial.

METHODS Residual congestion was assessed at day 5 after admission among hospitalized patients using an established composite congestion score (CCS) based on the presence of orthopnea, peripheral edema, and increased jugular venous pressure, ranging from 0 to 8 points. The primary endpoint was a composite of cardiovascular death or rehospitalization for heart failure or renal failure at 180 days.

RESULTS Among the 5,900 AHF patients included in this analysis, 3,380 (57.3%) had at least 1 sign of congestion (ie, CCS ≥1) and 1,066 (18.1%) had a CCS ≥3 at day 5 after admission. Patients with residual congestion at day 5 were more symptomatic, had more comorbidities, received higher doses of loop diuretic agents in-hospital, albeit with lower diuretic response, were less likely to have hemoconcentration, and were more likely to have worsening renal function at day 5. After multivariable adjustment for clinically meaningful variables, any sign of residual congestion and CCS ≥3 at day 5 were both independently associated with a higher risk of the primary endpoint (adjusted HR: 1.32 [95% CI: 1.15-1.51]; $P < 0.001$ and adjusted HR: 1.62 [95% CI: 1.39-1.88]; both $P < 0.001$).

CONCLUSIONS Among patients with AHF who were still hospitalized at day 5, residual congestion was common and independently associated with worse outcome. (Efficacy, Safety and Tolerability of Serelaxin When Added to Standard Therapy in AHF [RELAX-AHF-2]; NCT01870778) (JACC Heart Fail. 2025;13:414–429) © 2025 by the American College of Cardiology Foundation.

From the [a]Institute of Cardiology, ASST Spedali Civili, Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, University of Brescia, Brescia, Italy; [b]Department of Cardiology, University Medical Center Groningen, Groningen, the Netherlands; [c]Momentum Research, Inc, Durham, North Carolina, USA; [d]Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen, Groningen, the Netherlands; [e]Division of Cardiology, Duke University School of Medicine, Durham, North Carolina, USA; [f]Department of Cardiology, Attikon University Hospital, National and Kapodistrian University of Athens, Athens, Greece; [g]Division of Cardiology, University of California, San Diego, California, USA; [h]Department of Emergency Medicine, Indiana University School of Medicine and the Regenstrief Institute, Indianapolis, Indiana, USA; [i]Department of Heart Diseases, Wroclaw Medical University, Wrocław, Poland; [j]Novartis Pharma AG, Basel, Switzerland; and the [k]Section of Cardiology, San Francisco Veterans Affairs Medical Center and School of Medicine, University of California San Francisco, San Francisco, California, USA.

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Heart failure (HF) is a major cause of morbidity and mortality worldwide.[1,2] Signs and symptoms of congestion are the main cause of emergent hospitalization of patients with acute heart failure (AHF) and residual congestion at the time of hospital discharge has been associated with worse outcomes.[3-5] However, the extent of decongestion was dissociated from outcomes in some recent trials of diuretic therapy in AHF. In the DOSE-AHF (Diuretic Optimization Strategies Evaluation in Acute Heart Failure) trial, the high-dose diuretic regimen was associated with a larger net volume loss and a decrease in body weight with no difference in postdischarge outcomes.[6] In the ADVOR (Acetazolamide in Decompensated Heart Failure With Volume Overload) trial, the addition of acetazolamide to loop diuretic agents resulted in greater incidence of successful decongestion among patients with AHF, defined as the absence of more than trace edema, residual pleural effusion, and residual ascites, but this did not result in a significant reduction of mortality or HF rehospitalization at 3 months.[7] Similarly, the addition of hydrochlorothiazide in the CLOROTIC (Safety and Efficacy of the Combination of Loop With Thiazide-Type Diuretics in Patients With Decompensated Heart Failure) trial was associated with a larger reduction in body weight with no difference in outcomes.[8] Thus, further studies are needed to assess the relationship between decongestion and outcomes in patients with AHF.

The interaction between decongestion and other events occurring during AHF hospitalizations, such as worsening renal function (WRF), defined by an increase in serum creatinine plasma concentrations, or diuretic resistance, may also warrant further investigation.[9-12] In a previous analysis of the PROTECT (Placebo-Controlled Randomized Study of the Selective A1 Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized With Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function) (N = 1,698) and RELAX-AHF-2 (Efficacy, Safety and Tolerability of Serelaxin When Added to Standard Therapy in AHF; NCT01870778) (N = 5,586) trials, WRF, defined as a creatinine increase ≥0.3 mg/dL between baseline and day 4, and occurring in 16.8% and 18.5% of the patients, respectively, was associated with an increased rate of cardiovascular (CV) death or CV/renal hospitalization in the patients with a poor diuretic response (≤0.35 kg weight loss/40 mg furosemide equivalent at 4 days) but not in those with a good diuretic response.[13] However, congestion was not evaluated in this analysis, and its interaction with WRF or diuretic response remains poorly studied.

Our aim was to assess the prevalence and prognostic impact of decongestion in a contemporary large cohort of patients with AHF enrolled in the RELAX-AHF-2 randomized trial and evaluate its relationship with other key events in AHF such as diuretic response and WRF.

ABBREVIATIONS AND ACRONYMS

AHF = acute heart failure

BNP = B-type natriuretic peptide

CV = cardiovascular

eGFR = estimated glomerular filtration rate

HF = heart failure

JVP = jugular venous pulse

NT-proBNP = N-terminal pro-B-type natriuretic peptide

RF = renal failure

WRF = worsening renal function

METHODS

STUDY DESIGN. The design of the RELAX-AHF-2 trial has been already described.[14,15] Briefly, RELAX-AHF-2 was a multicenter, international, randomized trial enrolling 6,545 patients hospitalized with AHF between October 2013 and February 2017. The trial was approved at each participating center and written consent was obtained from all participants. Patients ≥18 years of age with the following key inclusion criteria were enrolled: dyspnea, pulmonary congestion on chest radiograph, B-type natriuretic peptide (BNP) ≥500 pg/mL, or N-terminal pro-B-type natriuretic peptide (NT-proBNP) ≥2,000 pg/mL (BNP ≥750 pg/mL or NT-proBNP ≥3,000 pg/mL for patients ≥75 years of age, or with atrial fibrillation), systolic blood pressure ≥125 mm Hg, mild-to-moderate renal impairment (estimated glomerular filtration rate [eGFR] ≥25 and ≤75 mL/min/1.73 m^2), and persistent HF symptoms after initial intravenous loop diuretic treatment (≥40 mg of furosemide equivalents). Enrolled patients were randomized to receive either intravenous serelaxin (30 μg/kg/d) for 48 hours or placebo, in addition to standard care. Because of the neutral effect of serelaxin on the trial coprimary endpoints and on key secondary endpoints, the 2 treatment arms were pooled for the present analysis.[14]

DEFINITIONS. In RELAX-AHF-2, patients were assessed daily during the index AHF hospitalization and physical examination; vital signs and laboratory tests were recorded through day 5 and at day 14.[14,15]

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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Congestion was locally assessed at the different time points using a composite congestion score ranging from 0 to 8 points and based on the sum of scores for orthopnea (0 to 3), peripheral edema (0 to 3), and jugular venous pulse (JVP) (0 to 2), as previously described.[16-18] The present analysis focused on congestion at day 5, that may be considered a proxy of residual congestion for 22.6% of patients that were discharged at day 5 or less. The presence of any sign of residual congestion was defined as a composite congestion score ≥1. Diuretic response was measured as kg weight loss per 40-mg furosemide equivalent from baseline to day 5, similar to previous studies.[13,19,20] Total intravenous dose of loop diuretic agents plus 0.5× total oral dose administered between baseline and day 5 was considered to calculate diuretic response. The following loop diuretic doses were considered equivalent to 40 mg of furosemide: 1 mg bumetanide, 20 mg torsemide, and 50 mg ethacrynic acid.[13] eGFR was calculated using the simplified Modification of Diet in Renal Disease formula. WRF was defined as a creatinine increase ≥0.3 mg/dL between baseline and day 5, according to previous studies.[13,17,20] Change in hemoglobin, hemoconcentration (increase in hemoglobin), weight loss, and change in eGFR and at day 5 were also evaluated.[14,21]

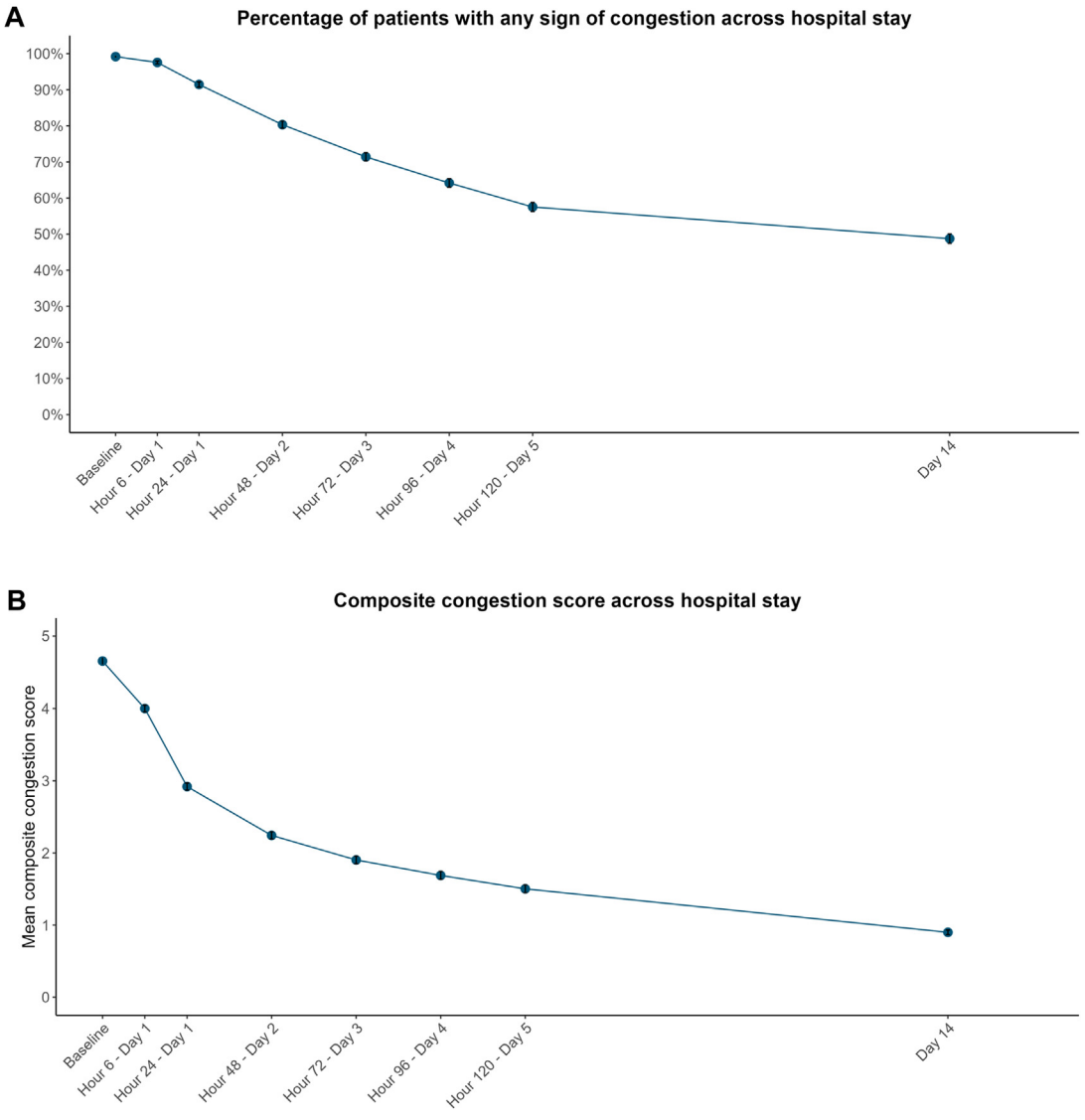
STUDY ENDPOINTS. The primary endpoint was the composite of death from CV causes or rehospitalization for HF or renal failure (RF) at 180 days. Secondary endpoints of interest were death from CV causes at 180 days, death from any cause at 180 days, and rehospitalization for HF or RF at 180 days. All deaths and rehospitalization events through day 180 were reviewed and adjudicated by an independent clinical event committee.

STATISTICAL ANALYSIS. Continuous variables were presented as median (Q1-Q3) or mean ± SD and compared between groups with the independent Student's *t*-test or the Mann-Whitney U test, as appropriate, whereas categorical variables were presented as frequency and percentages, and compared with the chi-square test. Patients' characteristics, in-hospital data, and clinical outcomes were compared between patients with vs without any sign of residual congestion at day 5 and between patients with composite congestion score at day 5 ≥3 vs ≤2, with the ≥3 cutoff selected according to previous studies.[3,16,17]

Cox regression models were used to evaluate the association between congestion parameters and the study endpoints. The impact of any sign of congestion, congestion score as a continuous variable, and congestion score ≥3 vs ≤2 at different time points (baseline, day 3, day 5, day 14) was tested. Univariable and multivariable Cox regression analyses were performed, and unadjusted and adjusted HRs with 95% CI were reported. In multivariable analyses, the impact of congestion was adjusted for age and sex (model 1) and for several covariates of interest (model 2), as previously reported.[21,22] The following variables were included in model 2 for the composite endpoint at day 180 and HF/RF rehospitalization at day 180: age, sex, creatinine, hemoglobin, sodium, blood urea nitrogen, prior cerebrovascular accident, depression, airway disease (asthma, bronchitis, or chronic obstructive pulmonary disease), history of atrial fibrillation or flutter, peripheral artery disease, heart rate, respiratory rate, systolic blood pressure, edema, intravenous loop diuretic agent total dose (in furosemide units) at baseline, history of diabetes mellitus, prior HF hospitalization, study treatment arm (serelaxin vs placebo), geographical region, composite of NT-proBNP or BNP *z*-score, and left ventricular ejection fraction (per 5% increase). In model 2 for CV mortality and all-cause mortality at 180 days, 4 variables (history of atrial fibrillation or flutter, depression, geographical region, and heart rate) were dropped from the reported variable set, and body mass index was added, as previously described.[21,22] The proportional hazards assumption of the Cox models was tested by assessing the Schoenfeld residual's and log-transformed non-normal covariates and was met. The cumulative incidence of the study endpoints according to the composite congestion score at baseline and at day 5, and the presence of any sign of congestion at day 5 was plotted by means of Kaplan-Meier curves. The HR for the impact of increasing values of composite congestion score at day 5 (relative to a congestion score of 0) on the primary endpoint was also plotted. A sensitivity analysis was performed to assess the impact of residual congestion at day 5 on the primary endpoint at 30 days and 90 days. Subgroup analyses were also performed to evaluate the impact of residual congestion at day 5 on the primary composite endpoint in relevant subgroups of interest, and *P* value for interaction between residual congestion and each subgroup variable was calculated.

Correlations between composite congestion score at day 5 or change in composite congestion score at day 5 and continuous variables of interest (eg, diuretic response, change in hemoglobin, and change in eGFR at day 5) were assessed with the Kendall's rank correlation analysis. Predictors of residual composite congestion score ≥3 at day 5 and of the presence of any sign of residual congestion at day 5 were

FIGURE 1 Signs of Congestion Across the AHF Hospitalization



The graphs depict the percentage of patients with any sign of congestion (A) and the trend of the mean composite congestion (B) across hospital stay during the index hospitalization for acute heart failure (AHF), from baseline up to day 14.

evaluated by means of univariable and multivariable logistic regression analysis. The covariates that were significant at the univariable analysis were included in the multivariable logistic regression analysis. Results of these analyses were reported as unadjusted or adjusted OR with 95% CI.

All reported *P* values are 2-sided, and a value of $P < 0.05$ was considered statistically significant. Analyses were performed using R statistical software version 3.4.3 (R Foundation for Statistical Computing).

RESULTS

PATIENT CHARACTERISTICS. Among the 6,545 patients with AHF enrolled in RELAX-AHF-2, the proportion of patients with any sign of congestion (ie, composite congestion score ≥1) decreased

TABLE 1 Baseline Characteristics According to the Presence of Any Sign of Residual Congestion and to Composite Congestion Score at Day 5

	Any Sign of Residual Congestion at Day 5			Composite Congestion Score at Day 5		
	No (n = 2,520)	Yes (n = 3,380)	*P* Value	≤2 (n = 4,834)	≥3 (n = 1,066)	*P* Value
Demographics						
Age, y	73.1 ± 11.1	72.8 ± 11.2	0.338	73.1 ± 11.1	72.3 ± 11.4	0.038
Female	1,077 (42.7)	1,311 (38.8)	0.002	1,992 (41.2)	396 (37.1)	0.016
White	2,363 (93.8)	3,065 (90.7)	<0.001	4,500 (93.1)	928 (87.1)	<0.001
Geographical region			<0.001			<0.001
America/other	596 (23.7)	713 (21.1)		1,028 (21.3)	281 (26.4)	
Eastern Europe	1,148 (45.6)	1,432 (42.4)		2,244 (46.4)	336 (31.5)	
Western Europe	776 (30.8)	1,235 (36.5)		1,562 (32.3)	449 (42.1)	
Medical history						
Hypertension	2,235 (88.7)	3,065 (90.7)	0.014	4,317 (89.3)	983 (92.2)	0.005
Diabetes mellitus	1,063 (42.2)	1,647 (48.7)	<0.001	2,128 (44.0)	582 (54.6)	<0.001
Atrial fibrillation	1,176 (46.7)	1,823 (53.9)	<0.001	2,418 (50.0)	581 (54.5)	0.009
Peripheral artery disease	301 (11.9)	492 (14.6)	0.004	608 (12.6)	185 (17.4)	<0.001
COPD	294 (11.7)	638 (18.9)	<0.001	705 (14.6)	227 (21.3)	<0.001
CKD, baseline eGFR <60 mL/min/1.73 m^2	1,665 (66.1)	2,394 (70.9)	<0.001	3,239 (67.1)	820 (76.9)	<0.001
Smoking history			0.024			<0.001
Current	277 (11.0)	371 (11.0)		542 (11.2)	106 (10.0)	
Former	815 (32.4)	1,203 (35.8)		1,592 (33.0)	426 (40.2)	
Never	1,420 (56.5)	1,791 (53.2)		2,684 (55.7)	527 (49.8)	
Depression	200 (7.9)	366 (10.8)	<0.001	425 (8.8)	141 (13.2)	<0.001
Cerebrovascular accident	348 (13.8)	566 (16.7)	0.002	724 (15.0)	190 (17.8)	0.023
Hyperthyroidism	75 (3.0)	124 (3.7)	0.166	158 (3.3)	41 (3.8)	0.394
Hypothyroidism	255 (10.1)	373 (11.0)	0.277	490 (10.1)	138 (12.9)	0.008
Prior CABG	336 (13.3)	540 (16.0)	0.005	684 (14.1)	192 (18.0)	0.002
Prior PCI	578 (22.9)	825 (24.4)	0.195	1,118 (23.1)	285 (26.7)	0.014
Prior history of HF	1,751 (69.5)	2,635 (78.0)	<0.001	3,521 (72.9)	865 (81.2)	<0.001
Primary ischemic HF etiology	937 (53.6)	1,419 (54.0)	0.818	1,902 (54.1)	454 (52.8)	0.526
Prior HF hospitalization	1,143 (49.2)	1,877 (58.8)	<0.001	2,381 (52.9)	639 (63.0)	<0.001
NYHA functional class, 1 mo before index admission			<0.001			<0.001
I	109 (4.3)	74 (2.2)		160 (3.3)	23 (2.2)	
II	774 (30.7)	910 (26.9)		1,427 (29.5)	257 (24.1)	
III	693 (27.5)	1,288 (38.1)		1,542 (31.9)	439 (41.2)	
IV	143 (5.7)	305 (9.0)		323 (6.7)	125 (11.7)	
Missing	801 (31.8)	803 (23.8)		1,382 (28.6)	222 (20.8)	
Cardiac resynchronization therapy	77 (3.1)	147 (4.3)	0.012	174 (3.6)	50 (4.7)	0.110
Implantable cardioverter defibrillator	181 (7.2)	333 (9.9)	<0.001	386 (8.0)	128 (12.0)	<0.001
Physical examination and vital signs						
Body mass index, kg/m^2	28.6 ± 5.6	30.7 ± 6.7	<0.001	29.3 ± 6.0	32.0 ± 7.1	<0.001
Weight, kg	80 ± 18	87 ± 21	<0.001	82 ± 19	91 ± 23	<0.001
Systolic blood pressure, mm Hg	142.2 ± 14.8	141.6 ± 15.6	0.024	141.9 ± 15.0	141.7 ± 16.3	0.185
Diastolic blood pressure, mm Hg	80.1 ± 13.9	79.2 ± 13.9	0.032	79.8 ± 13.8	78.7 ± 14.2	0.011
Heart rate, beats/min	81.5 ± 16.2	81.1 ± 15.8	0.456	81.3 ± 16.0	80.9 ± 16.0	0.387
Respiratory rate, breaths/min	21.6 ± 4.4	21.7 ± 4.5	0.394	21.6 ± 4.4	22.1 ± 4.6	<0.001
Composite congestion score	4.1 ± 1.8	5.0 ± 1.7	<0.001	4.4 ± 1.7	5.6 ± 1.7	<0.001
Any sign of congestion	2,436 (98.4)	3,262 (99.7)	<0.001	4,697 (99.0)	1,001 (99.5)	<0.001
Dyspnea on exertion			<0.001			<0.001
None	9 (0.4)	14 (0.4)		17 (0.4)	6 (0.6)	
Mild	110 (4.4)	99 (3.0)		180 (3.8)	29 (2.7)	
Moderate	1,118 (44.8)	1,238 (36.9)		2,021 (42.1)	335 (31.8)	
Severe, including dyspnea at rest	1,260 (50.5)	2,003 (59.7)		2,578 (53.8)	685 (64.9)	

Continued on the next page

TABLE 1 Continued

	Any Sign of Residual Congestion at Day 5			Composite Congestion Score at Day 5		
	No (n = 2,520)	Yes (n = 3,380)	*P* Value	≤2 (n = 4,834)	≥3 (n = 1,066)	*P* Value
Edema			<0.001			<0.001
None	520 (20.7)	368 (10.9)		819 (17.0)	69 (6.5)	
1+	912 (36.3)	846 (25.1)		1,546 (32.1)	212 (20.0)	
2+	797 (31.7)	1,262 (37.5)		1,703 (35.3)	356 (33.6)	
3+	284 (11.3)	892 (26.5)		753 (15.6)	423 (39.9)	
Jugular venous pulse, cm H_2O			<0.001			<0.001
<6	800 (32.3)	778 (23.8)		1,406 (29.6)	172 (17.1)	
6-10	1,216 (49.1)	1,514 (46.2)		2,291 (48.3)	439 (43.6)	
>10	460 (18.6)	983 (30.0)		1,047 (22.1)	396 (39.3)	
Orthopnea			<0.001			<0.001
None	122 (4.9)	94 (2.8)		184 (3.8)	32 (3.0)	
1 pillow, 10 cm	553 (22.0)	412 (12.2)		869 (18.0)	96 (9.1)	
2 pillows, 20 cm	1,229 (48.9)	1,628 (48.4)		2,406 (49.9)	451 (42.6)	
>30°	609 (24.2)	1,232 (36.6)		1,361 (28.2)	480 (45.3)	
Rales			<0.001			<0.001
None	113 (4.5)	211 (6.3)		220 (4.6)	104 (9.8)	
<1/3	1,039 (41.4)	1,299 (38.6)		1,981 (41.1)	357 (33.7)	
1/3-2/3	1,194 (47.5)	1,561 (46.4)		2,262 (46.9)	493 (46.6)	
>2/3	166 (6.6)	296 (8.8)		357 (7.4)	105 (9.9)	
Laboratory values						
NT-proBNP, pg/mL	5,732 (3,363-9,006)	6,327 (3,712-10,717)	<0.001	6,018 (3,519-9,384)	6,301 (3,686-11,708)	0.003
BNP, pg/mL	1,052 (735-1,666)	1,198 (792-1,992)	0.011	1,084 (750-1,804)	1,275 (827-2,128)	0.013
Blood urea nitrogen, mg/dL	8.2 (6.4-10.9)	9.1 (7.0-12.4)	<0.001	8.6 (6.6-11.2)	10.0 (7.5-13.6)	<0.001
Creatinine, μmol/L	108 (93-133)	115 (97-143)	<0.001	111 (95-135)	124 (103-155)	<0.001
eGFR, mL/min/1.73 m^2	54 (43-65)	50 (39-62)	<0.001	53 (42-64)	47 (36-59)	<0.001
Urea/creatinine ratio	40.2 (33.0-49.3)	41.6 (33.4-51.4)	0.003	40.6 (33.1-49.9)	43.3 (34.4-54.8)	<0.001
Sodium, mmol/L	140 (138-142)	140 (138-142)	0.126	140 (138-142)	140 (137-142)	0.046
Potassium, mmol/L	4.3 (3.9-4.7)	4.3 (3.9-4.7)	0.341	4.3 (3.9-4.7)	4.3 (3.9-4.7)	0.121
Hemoglobin, g/L	128 (115-141)	125 (111-139)	<0.001	127 (114-141)	121 (108-136)	<0.001
Echocardiographic data						
LVEF, %, at index hospitalization	39 (30-50)	38 (28-50)	0.407	38 (30-50)	38 (28-50)	0.867
LVEF categories			0.016			0.003
HFrEF, LVEF ≤40%	1,227 (41.2)	1,661 (52.4)		2,384 (52.0)	504 (51.2)	
HFmrEF, LVEF 41%-49%	569 (23.7)	655 (20.7)		1,037 (22.6)	187 (19.0)	
HFpEF, LVEF ≥50%	600 (25.0)	855 (27.0)		1,161 (25.3)	294 (29.8)	
Moderate-severe MR	1,229 (48.8)	1,837 (54.3)	<0.001	2,505 (51.8)	561 (52.6)	0.658
Baseline medical therapy						
ACEI or ARBs	1,663 (66.0)	2,209 (65.4)	0.630	3,189 (66.0)	683 (64.1)	0.252
Beta-blockers	1,764 (70.0)	2,435 (72.0)	0.092	3,425 (70.9)	774 (72.6)	0.268
MRA	694 (27.5)	1,000 (29.6)	0.091	1,400 (29.0)	294 (27.6)	0.387
Calcium channel blockers	514 (20.4)	783 (23.2)	0.012	1,036 (21.4)	261 (24.5)	0.033
Oral loop diuretic agents	1,411 (56.0)	2,230 (66.0)	<0.001	2,893 (59.8)	748 (70.2)	<0.001
Oral loop diuretic agents total daily dose, mg[a]	46 ± 37	58 ± 68	<0.001	50 ± 47	66 ± 88	<0.001

Values are n (%), mean ± SD, or median (Q1-Q3), unless otherwise indicated. [a]Furosemide equivalent: ×40 for bumetanide, ×2 for torsemide, and ×0.8 for ethacrynic acid.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BNP = brain natriuretic peptide; CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; HF = heart failure; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction; MR = mitral regurgitation; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PCI = percutaneous coronary intervention.

TABLE 2 In-Hospital Data According to the Presence of Any Sign of Residual Congestion and to Composite Congestion Score at Day 5

	Any Sign of Residual Congestion at Day 5			Composite Congestion Score at Day 5		
	No (n = 2,520)	Yes (n = 3,380)	*P* Value	≤2 (n = 4,834)	≥3 (n = 1,066)	*P* Value
Diuretic doses and length of stay						
Total IV loop diuretic agents dose through day 5, mg[a]	238 ± 247	384 ± 469	<0.001	273 ± 281	542 ± 674	<0.001
Total oral loop diuretic agents dose through day 5, mg[a]	249 ± 215	317 ± 377	0.025	274 ± 285	338 ± 421	0.810
Length of ICU and/or CCU stay, d	3.0 ± 4.3	4.2 ± 9.0	0.024	3.1 ± 5.1	6.2 ± 13.2	0.605
Length of hospital stay, d	7.5 ± 5.7	10.5 ± 10.1	<0.001	8.2 ± 6.5	14.0 ± 13.8	<0.001
Diuretic response and congestion status at day 5						
Weight loss at day 5, % change	−3.5 (−6.0 to −1.6)	−3.5 (−6.2 to −1.4)	0.444	−3.5 (−6.1 to −1.6)	−3.0 (−6.4 to −0.7)	0.001
Diuretic response through day 5, kg of weight change per 40 mg of furosemide	−0.4 (−0.8 to −0.2)	−0.3 (−0.7 to −0.1)	<0.001	−0.4 (−0.8 to −0.2)	−0.2 (−0.5 to 0.0)	<0.001
Hemoconcentration, increase in hemoglobin at day 5	1,187 (54.5)	1,230 (42.8)	<0.001	2,118 (51.2)	299 (32.7)	<0.001
Change in hemoglobin at day 5, % change from baseline	1.4 (−4.1 to 7.0)	−1.1 (−6.4 to 4.8)	<0.001	0.8 (−4.7 to 6.6)	−3.1 (−8.7 to 2.3)	<0.001
Any sign of congestion at day 5	0 (0)	3,380 (100)	<0.001	2,314 (47.9)	1,066 (100)	<0.001
Dyspnea on exertion at day 5			<0.001			<0.001
None	1,339 (53.2)	508 (15.0)		1,783 (36.9)	64 (6.0)	
Mild	1,033 (41.1)	1,568 (46.4)		2,344 (48.6)	257 (24.1)	
Moderate	136 (5.4)	847 (25.1)		663 (13.7)	320 (30.0)	
Severe, including dyspnea at rest	7 (0.3)	454 (13.4)		37 (0.8)	424 (39.8)	
Orthopnea at day 5			<0.001			<0.001
None	2,520 (100)	824 (24.4)		3,306 (68.4)	38 (3.6)	
1 pillow, 10 cm	0 (0)	1,694 (50.1)		1,403 (29.0)	291 (27.3)	
2 pillows, 20 cm	0 (0)	436 (12.9)		125 (2.6)	311 (29.2)	
>30°	0 (0)	426 (12.6)		0 (0.0)	426 (40.0)	
Edema, any degree, at day 5	0 (0)	1,958 (57.9)	<0.001	972 (20.1)	986 (92.5)	<0.001
Jugular venous pulse at day 5, cm			<0.001			<0.001
<6	2,520 (100)	2,129 (63.0)		4,394 (90.9)	255 (23.9)	
6-10	0 (0)	828 (24.5)		435 (9.0)	393 (36.9)	
>10	0 (0)	423 (12.5)		5 (0.1)	418 (39.2)	
Rales, any degree, at day 5	202 (8.0)	1,200 (35.5)	<0.001	724 (15.0)	678 (63.6)	<0.001
Change in vital signs at day 5, % change from baseline						
Systolic blood pressure	−11.5 (−19.0 to −4.1)	−10.1 (−17.4 to −2.9)	<0.001	−10.9 (−18.3 to −3.7)	−9.7 (−17.4 to −2.4)	0.008
Diastolic blood pressure	−9.1 (−20.0 to 1.6)	−8.7 (−19.1 to 2.3)	0.239	−8.7 (−19.5 to 1.7)	−9.1 (−20.0 to 2.6)	0.683
Respiratory rate	−19.0 (−31.6 to −6.2)	−16.7 (−27.8 to −5.6)	<0.001	−18.2 (−30.0 to −6.2)	−13.6 (−25.0 to −4.0)	<0.001
Change in renal function at day 5, % change from baseline, and WRF						
Creatinine	4.0 (−8.3 to 19.0)	2.8 (−11.3 to 18.8)	0.005	3.4 (−9.8 to 18.7)	3.4 (−12.1 to 19.6)	0.607
eGFR	−4.5 (−18.5 to 10.9)	−3.1 (−17.7 to 14.9)	0.004	−3.7 (−18.0 to 12.6)	−3.9 (−18.5 to 16.1)	0.584
Blood urea nitrogen	20.6 (−5.4 to 54.5)	15.1 (−11.0 to 48.9)	<0.001	18.3 (−8.1 to 51.9)	13.1 (−10.6 to 47.2)	0.014
Urea/creatinine ratio	14.3 (−6.1 to 38.4)	10.5 (−8.5 to 34.9)	0.003	13.2 (−7.0 to 37.3)	8.0 (−10.2 to 31.2)	0.001
WRF through day 5	406 (18.1)	605 (20.5)	0.030	793 (18.6)	218 (23.2)	0.002

Values are n (%), mean ± SD, or median (Q1-Q3), unless otherwise indicated. [a]Furosemide equivalent: ×40 for bumetanide, ×2 for torsemide, and ×0.8 for ethacrynic acid.
CCU = coronary care unit; ICU = intensive care unit; IV = intravenous; WRF = worsening renal function; other abbreviations as in Table 1.

throughout hospitalization, from 99.2% at baseline to 91.5% at day 1, 71.4% at day 3, and 57.5% at day 5 (Figure 1). Similarly, the mean composite congestion score decreased across hospital stay, from 4.66 at baseline to 2.92 at day 1, 1.90 at day 3, and 1.50 at day 5 (Figure 1).

Among the 5,900 patients with available data regarding congestion status at day 5, 3,380 (57.3%) had at least 1 sign of congestion at day 5, and 1,066 (18.1%) had a composite congestion score ≥3 at day 5. Both patients with any sign of residual congestion and those with congestion score ≥3 at day 5 were less frequently female and more likely to have hypertension, diabetes mellitus, atrial fibrillation, peripheral artery disease, chronic obstructive pulmonary disease, chronic kidney disease, prior cerebrovascular accident, prior coronary artery bypass graft, prior HF hospitalization, and higher NYHA functional class, as

TABLE 3 Impact of Congestion on 180-Day Clinical Outcomes (Cox Regression Analyses)

	Univariable Analysis		Multivariable Model 1 (Adjusted for Age and Sex)		Multivariable Model 2 (Full Model)[a]	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Primary endpoint, CV death or HF/RF rehospitalization at 180 d						
Baseline composite congestion score						
Continuous variable, 1-U increase	1.07 (1.04-1.10)	<0.001	1.07 (1.04-1.10)	<0.001	1.01 (0.97-1.06)	0.559
≥3 vs ≤2	1.08 (0.92-1.26)	0.369	1.08 (0.92-1.27)	0.356	0.89 (0.71-1.12)	0.310
Composite congestion score at day 3						
Continuous variable, 1-U increase	1.12 (1.10-1.14)	<0.001	1.12 (1.10-1.14)	<0.001	1.08 (1.05-1.11)	<0.001
≥3 vs ≤2	1.53 (1.37-1.71)	<0.001	1.54 (1.38-1.72)	<0.001	1.031 (1.14-1.51)	<0.001
Any sign of congestion at day 3, yes vs no	1.25 (1.11-1.41)	<0.001	1.25 (1.11-1.41)	<0.001	1.04 (0.89-1.21)	0.570
Composite congestion score at day 5						
Continuous variable, 1-U increase	1.14 (1.11-1.16)	<0.001	1.14 (1.11-1.16)	<0.001	1.10 (1.07-1.13)	<0.001
≥3 vs ≤2	1.91 (1.70-2.15)	<0.001	1.92 (1.71-2.17)	<0.001	1.62 (1.39-1.88)	<0.001
Any sign of congestion at day 5, yes vs no	1.53 (1.37-1.71)	<0.001	1.53 (1.37-1.71)	<0.001	1.32 (1.15-1.51)	<0.001
Composite congestion score at day 14						
Continuous variable, 1-U increase	1.29 (1.24-1.34)	<0.001	1.29 (1.24-1.34)	<0.001	1.17 (1.11-1.23)	<0.001
≥3 vs ≤2	2.24 (1.93-2.61)	<0.001	2.24 (1.93-2.61)	<0.001	1.60 (1.30-1.98)	<0.001
Any sign of congestion at day 14, yes vs no	1.70 (1.51-1.92)	<0.001	1.69 (1.50-1.91)	<0.001	1.31 (1.13-1.53)	<0.001
CV death at 180 d						
Baseline composite congestion score						
Continuous variable, 1-U increase	1.17 (1.11-1.23)	<0.001	1.19 (1.13-1.25)	<0.001	1.13 (1.05-1.22)	<0.001
≥3 vs ≤2	1.29 (0.97-1.72)	0.074	1.30 (0.98-1.74)	0.063	1.07 (0.70-1.62)	0.759
Composite congestion score at day 3						
Continuous variable, 1-U increase	1.21 (1.17-1.25)	<0.001	1.21 (1.17-1.25)	<0.001	1.17 (1.12-1.22)	<0.001
≥3 vs ≤2	2.12 (1.78-2.53)	<0.001	2.15 (1.80-2.57)	<0.001	1.73 (1.38-2.17)	<0.001
Any sign of congestion at day 3, yes vs no	1.67 (1.34-2.07)	<0.001	1.67 (1.34-2.08)	<0.001	1.43 (1.09-1.89)	0.010
Composite congestion score at day 5						
Continuous variable, 1-U increase	1.20 (1.16-1.24)	<0.001	1.20 (1.16-1.23)	<0.001	1.16 (1.12-1.21)	<0.001
≥3 vs ≤2	2.40 (1.99-2.90)	<0.001	2.44 (2.02-2.94)	<0.001	2.08 (1.64-2.63)	<0.001
Any sign of congestion at day 5, yes vs no	1.88 (1.55-2.29)	<0.001	1.89 (1.55-2.29)	<0.001	1.77 (1.40-2.25)	<0.001
Composite congestion score at day 14						
Continuous variable, 1-U increase	1.25 (1.17-1.34)	<0.001	1.26 (1.17-1.35)	<0.001	1.19 (1.09-1.30)	<0.001
≥3 vs ≤2	2.19 (1.67-2.87)	<0.001	2.20 (1.68-2.88)	<0.001	1.95 (1.41-2.71)	<0.001
Any sign of congestion at day 14, yes vs no	1.44 (1.16-1.78)	<0.001	1.42 (1.15-1.76)	0.001	1.19 (0.92-1.53)	0.183

Continued on the next page

compared with those without any sign of residual congestion and with congestion score ≤2, respectively (Table 1). Both patients with any residual sign of congestion and those with congestion score ≥3 at day 5 had higher NT-proBNP, blood urea nitrogen, and creatinine serum concentrations, and lower eGFR and hemoglobin levels at baseline, as compared with the others (Table 1).

IN-HOSPITAL DATA. In-hospital data are reported in Table 2. Total intravenous loop diuretic agent dose through day 5 and length of hospital stay were higher in patients with vs those without any sign of residual congestion at day 5 and in patients with composite congestion score ≥3 vs those with ≤2 at day 5. These patients with residual congestion also had lower diuretic response and lesser increase in hemoglobin and urea/creatinine ratio through day 5, were less likely to have hemoconcentration at day 5, and were more likely to have WRF at day 5. Moreover, eGFR reduction and blood urea nitrogen increase at day 5 were less pronounced in patients with vs without any sign of residual congestion at day 5.

Significant correlations were observed between composite congestion score at day 5 and diuretic response at day 5 (tau = 0.118; $P < 0.001$), change in hemoglobin at day 5 (tau = −0.133; $P < 0.001$), and change in eGFR at day 5 (tau = 0.032; $P = 0.002$), respectively (Supplemental Figure 1). Similarly, change in composite congestion score from baseline to day 5 was significantly correlated with diuretic

TABLE 3 Continued

	Univariable Analysis		Multivariable Model 1 (Adjusted for Age and Sex)		Multivariable Model 2 (Full Model)[a]	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
All-cause death at 180 d						
Baseline composite congestion score						
Continuous variable, 1-U increase	1.16 (1.11-1.21)	<0.001	1.18 (1.12-1.22)	<0.001	1.11 (1.04-1.19)	0.001
≥3 vs ≤2	1.31 (1.02-1.69)	0.029	1.33 (1.031.71)	0.022	1.04 (0.72-1.51)	0.817
Composite congestion score at day 3						
Continuous variable, 1-U increase	1.20 (1.17-1.24)	<0.001	1.21 (1.17-1.24)	<0.001	1.17 (1.12-1.21)	<0.001
≥3 vs ≤2	2.12 (1.81-2.47)	<0.001	2.16 (1.85-2.52)	<0.001	1.79 (1.47-2.18)	<0.001
Any sign of congestion at day 3, yes vs no	1.73 (1.43-2.10)	<0.001	1.74 (1.44-2.11)	<0.001	1.48 (1.16-1.90)	0.001
Composite congestion score at day 5						
Continuous variable, 1-U increase	1.27 (1.20-1.35)	<0.001	1.28 (1.21-1.36)	<0.001	1.24 (1.16-1.34)	<0.001
≥3 vs ≤2	2.28 (1.81-2.87)	<0.001	2.30 (1.82-2.89)	<0.001	2.22 (1.68-2.95)	<0.001
Any sign of congestion at day 5, yes vs no	1.86 (1.57-2.20)	<0.001	1.87 (1.58-2.21)	<0.001	1.72 (1.40-2.12)	<0.001
Composite congestion score at day 14						
Continuous variable, 1-U increase	1.29 (1.22-1.37)	<0.001	1.30 (1.23-1.37)	<0.001	1.24 (1.15-1.33)	<0.001
≥3 vs ≤2	2.42 (1.94-3.01)	<0.001	2.41 (1.94-3.00)	<0.001	2.22 (1.69-2.92)	<0.001
Any sign of congestion at day 14, yes vs no	1.57 (1.30-1.90)	<0.001	1.55 (1.29-1.87)	<0.001	1.33 (1.06-1.67)	0.013
HF/RF rehospitalization at 180 d						
Baseline composite congestion score						
Continuous variable, 1-U increase	1.04 (1.00-1.07)	0.033	1.04 (1.00-1.07)	0.031	0.99 (0.94-1.04)	0.624
≥3 vs ≤2	1.03 (0.86-1.24)	0.734	1.03 (0.86-1.24)	0.738	0.88 (0.68-1.14)	0.339
Composite congestion score at day 3						
Continuous variable, 1-U increase	1.08 (1.05-1.11)	<0.001	1.08 (1.05-1.11)	<0.001	1.04 (1.00-1.07)	0.046
≥3 vs ≤2	1.35 (1.19-1.53)	<0.001	1.35 (1.19-1.53)	<0.001	1.12 (0.95-1.32)	0.189
Any sign of congestion at day 3, yes vs no	1.16 (1.02-1.33)	0.026	1.16 (1.02-1.33)	0.027	0.96 (0.80-1.13)	0.600
Composite congestion score at day 5						
Continuous variable, 1-U increase	1.11 (1.09-1.14)	<0.001	1.11 (1.09-1.14)	<0.001	1.07 (1.03-1.10)	<0.001
≥3 vs ≤2	1.77 (1.55-2.03)	<0.001	1.78 (1.55-2.03)	<0.001	1.40 (1.18-1.67)	<0.001
Any sign of congestion at day 5, yes vs no	1.46 (1.29-1.65)	<0.001	1.45 (1.29-1.65)	<0.001	1.16 (0.99-1.35)	0.067
Composite congestion score at day 14						
Continuous variable, 1-U increase	1.31 (1.25-1.36)	<0.001	1.31 (1.25-1.36)	<0.001	1.14 (1.08-1.21)	<0.001
≥3 vs ≤2	2.28 (1.93-2.69)	<0.001	2.28 (1.93-2.69)	<0.001	1.47 (1.16-1.85)	0.002
Any sign of congestion at day 14, yes vs no	1.82 (1.59-2.08)	<0.001	1.82 (1.59-2.07)	<0.001	1.30 (1.10-1.53)	0.002

Cardiovascular (CV) death at day 180 and all-cause death at day 180 were adjusted for: age (y), sex, creatinine (μmol/L), hemoglobin (g/L), sodium (mmol/L), blood urea nitrogen (mg/dL), asthma/bronchitis/COPD, peripheral artery disease, respiratory rate (breaths/min), systolic blood pressure (mm Hg), body mass index (kg/m^2), edema, IV loop diuretic agent total dose (in furosemide units) at baseline, history of diabetes mellitus, prior HF hospitalization, actual study treatment (serelaxin vs placebo), composite of NT-proBNP or BNP *z*-score, and LVEF per 5% increase. [a]Composite endpoint at day 180 and HF/renal failure (RF) rehospitalization at day 180 were adjusted for: age (y), sex, creatinine (μmol/L), hemoglobin (g/L), sodium (mmol/L), blood urea nitrogen (mg/dL), cerebrovascular accident, depression, asthma/bronchitis/COPD, atrial fibrillation/flutter, peripheral artery disease, heart rate (beats/min), respiratory rate (breaths/min), systolic blood pressure (mm Hg), edema, IV loop diuretic agents total dose (in furosemide units) at baseline, history of diabetes mellitus, prior HF hospitalization, actual study treatment (serelaxin vs placebo), grouped geographical region, composite of NT-proBNP or BNP *z*-score, and LVEF per 5% increase.

Abbreviations as in Tables 1 and 2.

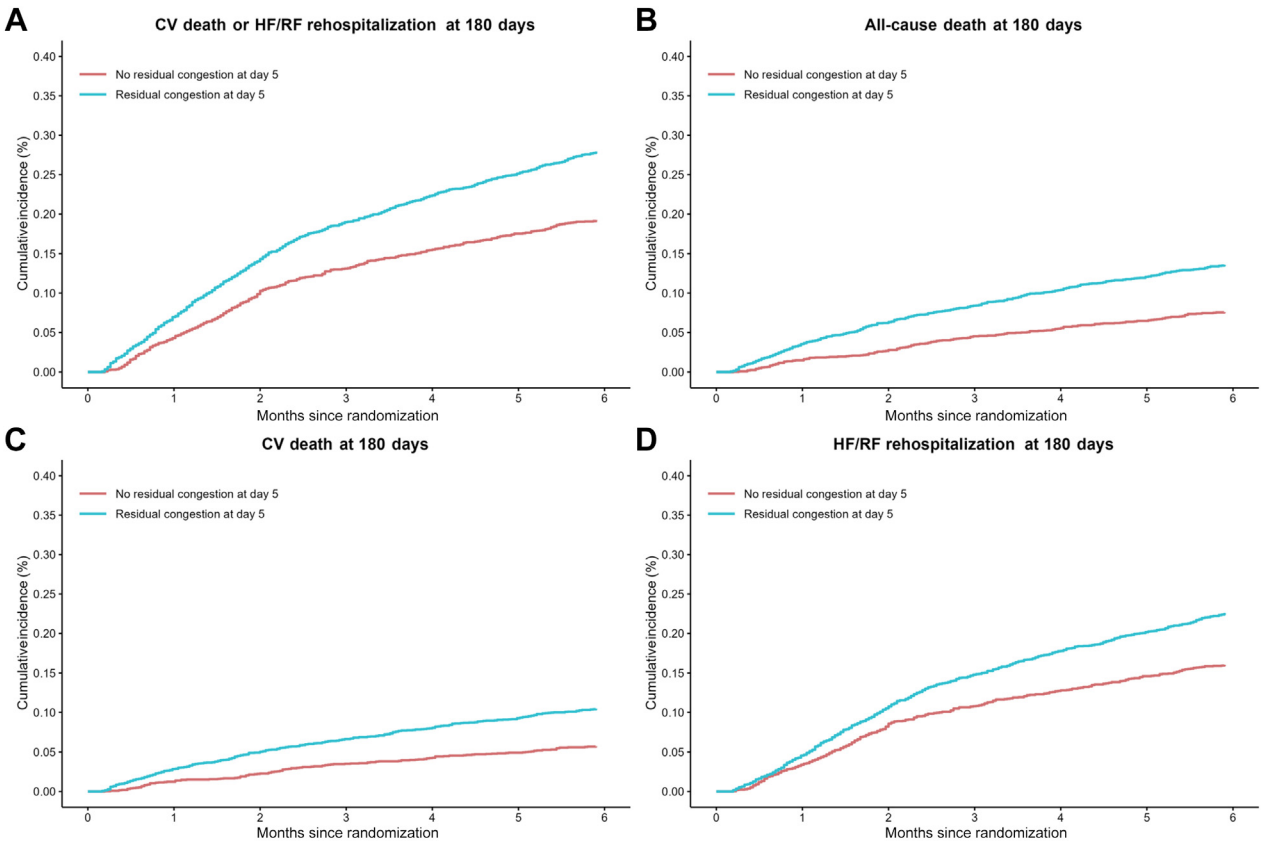
response at day 5 (tau = 0.168; $P < 0.001$), change in hemoglobin and change in eGFR at day 5 (tau = −0.101; $P < 0.001$ and tau = −0.023; $P = 0.025$, respectively) (Supplemental Figure 2).

PREDICTORS OF RESIDUAL CONGESTION AT DAY 5. By multivariable logistic regression analysis (Supplemental Table 1), the independent predictors of composite congestion score ≥3 at day 5 were eGFR, peripheral edema 3+, JVP >10 cm H_2O, orthopnea >30°, pulmonary rales >2/3 lung fields, all assessed at baseline, and diuretic response and change in hemoglobin at day 5.

The independent predictors of persistence of any sign of residual congestion at day 5 were NT-proBNP, eGFR, peripheral edema 3+, JVP >10 cm H_2O, orthopnea >30°, pulmonary rales >2/3 lung fields, all assessed at baseline, as well as diuretic response, change in hemoglobin, and change in eGFR at day 5.

IMPACT OF RESIDUAL CONGESTION ON CLINICAL OUTCOMES. Baseline congestion score as a continuous variable was associated with an increased risk of the primary composite endpoint at univariable analysis and after adjustment for age and sex, but this was

FIGURE 2 Kaplan-Meier Curves for 180-Day Clinical Outcomes in Patients With vs Without Any Sign of Congestion at Day 5

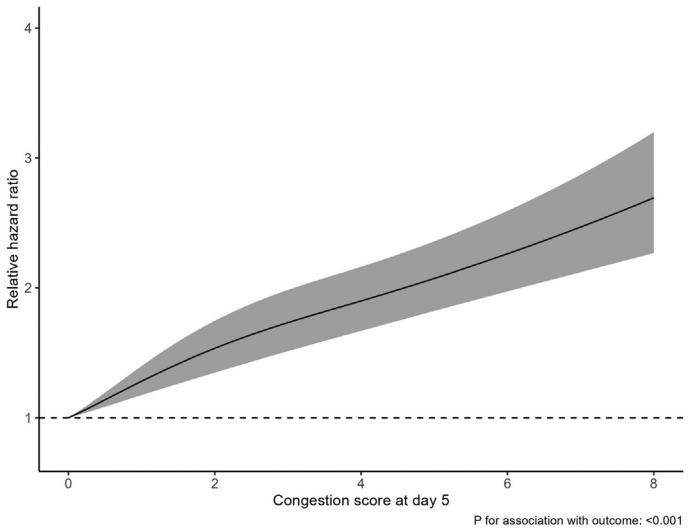


The figure shows Kaplan-Meier curves for the primary composite endpoint of cardiovascular (CV) death or rehospitalization for heart failure (HF) or renal failure (RF) (A), all-cause death (B), CV death (C) and HF/RF rehospitalization (D) through day 180 in patients with vs without any sign congestion at day 5.

not confirmed after full multivariable adjustment (adjusted HR for 1-U increase: 1.01 [95% CI: 0.97-1.06]; $P = 0.559$). Baseline congestion score ≥3 was not associated with the primary endpoint at univariable or multivariable analyses (**Table 3**, Supplemental Figure 3). By contrast, congestion score at day 3 was independently associated with an increased risk of the primary endpoint either as a continuous variable or as ≥3 vs ≤2, and this relationship remained significant after full multivariable adjustment. With regard to congestion at day 5, the risk of the primary endpoint was significantly higher in the patients with any sign of residual congestion (**Table 3**, **Figure 2**), and this was confirmed after adjustment for all covariates at multivariable analysis (adjusted HR: 1.32 [95% CI: 1.15-1.51]; $P < 0.001$). Higher congestion score at day 5 was independently associated with an increased risk of the primary endpoint also when evaluated as a continuous variable (fully adjusted HR for 1-U increase: 1.10 [95% CI: 1.07-1.13]; $P < 0.001$) (**Figure 3**). Similarly, the patients with congestion score ≥3 at day 5 had a higher risk of the primary endpoint than the others (**Figure 4**), even after full multivariable adjustment (adjusted HR: 1.62 [95% CI: 1.39-1.88]; $P < 0.001$). A sensitivity analysis confirmed the independent association between residual congestion at day 5 and the primary endpoint assessed at day 30 and at day 90 (Supplemental Table 2). Higher congestion score at day 14 and the presence of any sign of residual congestion at day 14 were also independently associated with an increased risk of the primary endpoint (**Table 3**).

Similar findings were observed for the secondary endpoints. In detail, higher congestion score at day 5 and the presence of any sign of residual congestion at day 5 were both independently associated with an increased risk of CV death and all-cause death at day

FIGURE 3 Impact of Increasing Values of Composite Congestion Score at Day 5 on the Primary Endpoint



The figure shows the HR for the impact of increasing values of composite congestion score at day 5 (relative to a congestion score of 0, ie, lack of any sign of congestion) on the primary composite endpoint of CV death or rehospitalization for HF or RF through day 180. Abbreviations as in Figure 2.

180 (Figures 2 and 4, Table 3). Congestion score at day 5 was also independently associated with HF/RF rehospitalization at day 180, whereas the impact of any sign of congestion at day 5 on this endpoint was present at univariable analysis and after adjustment for age and sex, but not after full multivariable adjustment (Table 3).

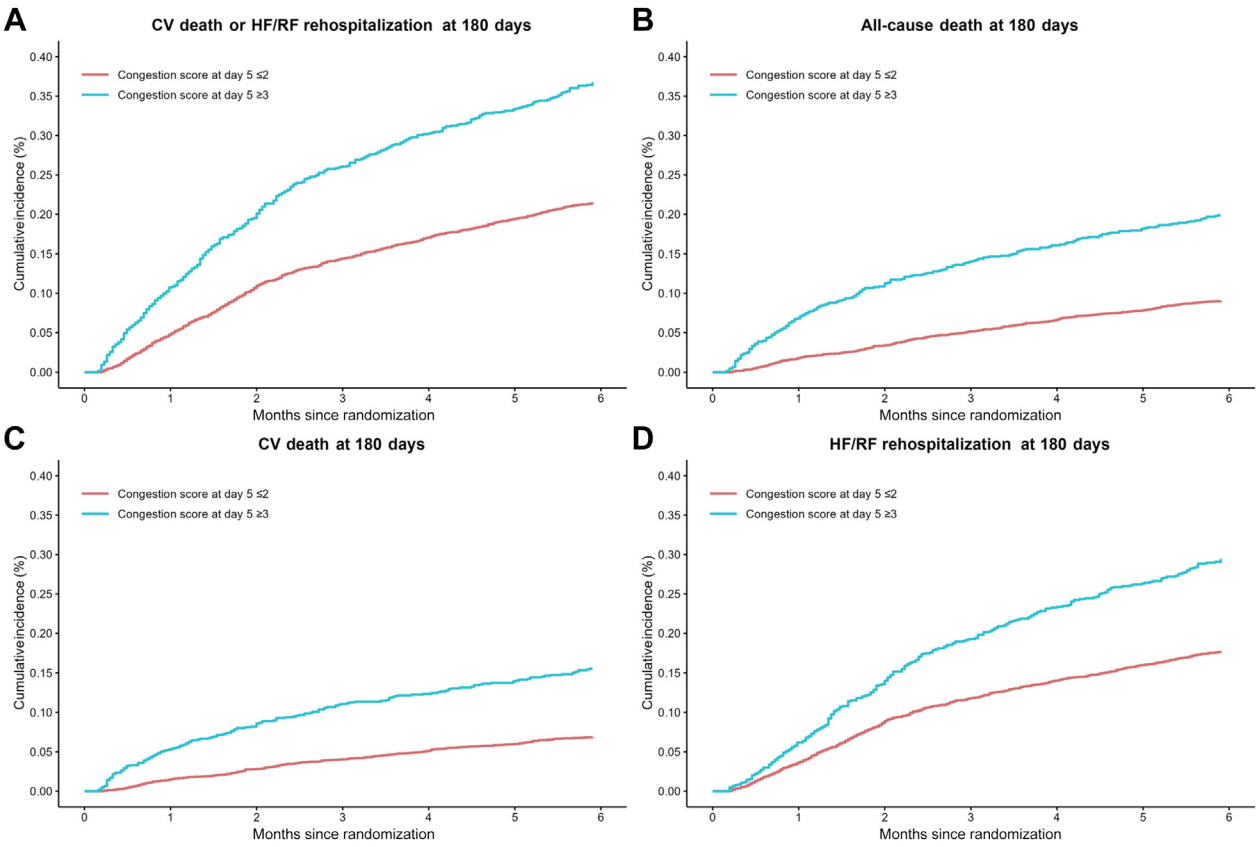
At subgroup analysis, no significant interaction was observed between any sign of congestion at day 5 and relevant subgroups of interest with respect to the primary endpoint (Table 4), including those subgroups based on diuretic response, eGFR change, or WRF at day 5. Significant interaction was observed between congestion score ≥3 vs ≤2 at day 5 and baseline NT-proBNP, with a more pronounced impact of 5-day congestion score ≥3 on the primary endpoint among the patients with NT-proBNP > median value (HR: 2.10 [95% CI: 1.77-2.50]) as compared with those with NT-proBNP ≤ median value (HR: 1.54 [95% CI: 1.22-1.93]; *P* for interaction = 0.029).

DISCUSSION

Our post hoc analysis of the RELAX-AHF-2 trial demonstrated that residual congestion was common among 5,900 patients with AHF still hospitalized at 5 days after admission and was independently associated with worse prognosis after discharge (Central Illustration). In detail, any sign of residual congestion at day 5, defined as a composite congestion score ≥1, and composite congestion score ≥3 at day 5 were present in 57.3% and 18.1% of patients, respectively, were associated with a worse clinical profile at presentation and during hospital stay, and had an independent impact on 180-day clinical outcomes. Of note, the impact of residual congestion at day 5 on the primary composite endpoint of CV death or HF/RF rehospitalization at 180 days remained significant with no heterogeneity in relevant subgroups of interest based on age, sex, left ventricular ejection fraction, eGFR, hemoconcentration, diuretic response, eGFR change, and WRF, except for a significant interaction observed between congestion score ≥3 at day 5 and baseline NT-proBNP. The impact of residual congestion at day 5 was also confirmed when evaluating the primary composite endpoint at day 30 and at day 90.

Although residual congestion before discharge was already identified as common and associated with worse outcomes in AHF,[4,16] recent trials of diuretic therapy in AHF did not demonstrate a link between decongestion and postdischarge hard clinical outcomes, including mortality and rehospitalizations.[6-8] Moreover, a previous analysis of the EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan) trial evaluated the impact of residual congestion before discharge in 2,061 patients with AHF, but included only patients with reduced ejection fraction who were enrolled between 2003 and 2006.[3] This prompted us to further assess the relationship between decongestion and outcomes in a larger, contemporary data set of well-phenotyped patients with AHF enrolled in RELAX-AHF-2 trial. Although the composite congestion score and the proportion of patients with any sign of congestion progressively decreased during hospitalization (Figures 1 and 2), the majority of enrolled patients (57.8%) still had at least 1 sign of residual congestion at day 5, and the proportion of patients with significant residual congestion at day 5 was meaningful (ie, 18.1% of patients with composite score ≥3). These findings are in line with previous studies.[3,16,23] The patients with residual congestion at day 5 had a worse clinical profile with more comorbidities, higher baseline NYHA functional classes, more pronounced signs and symptoms of congestion at hospital admission, higher natriuretic peptides,

FIGURE 4 Kaplan-Meier Curves for 180-Day Clinical Outcomes in Patients With Composite Congestion Score ≥3 vs ≤2 at Day 5



The figure shows Kaplan-Meier curves for the primary composite endpoint of CV death or rehospitalization for HF or RF (A), all-cause death (B), CV death (C) and HF/RF rehospitalization (D) through day 180 in patients with composite congestion score ≥3 vs ≤2 at day 5. Abbreviations as in Figure 2.

and lower eGFR. They also needed a longer hospitalization, received a higher intravenous loop diuretic dose, had lower in-hospital diuretic response, were less likely to have hemoconcentration at day 5, and more likely to have WRF at day 5. Baseline signs and symptoms of congestion, diuretic response, and hemoconcentration at day 5 independently predicted residual congestion at day 5. These findings confirm previous studies reporting an inverse relationship between diuretic response and residual congestion,[16] and demonstrate that WRF has a prognostic impact only among patients with persistent congestion or those with poor diuretic response.[10,13]

In our study, residual congestion at day 5 was independently associated with a higher risk of 180-day CV death or HF/RF rehospitalization. This was confirmed after extensive adjustment in a previously validated multivariable model including several covariates of interest.[21,22] Of note, a higher congestion score at day 5 was independently associated with an increased risk of the primary endpoint, with each 1-U increase in the congestion score determining a 10% increase in the risk of this composite outcome. The presence of a composite congestion score at day 5 ≥3 was also independently associated with a higher risk of the primary endpoint, confirming the prognostic impact of such 3-point congestion score cutoff that was already identified by previous studies.[3,16,17] These findings confirm other studies demonstrating the prognostic impact of residual congestion before discharge in patients hospitalized for AHF.[3,16,23]

Although residual congestion is a sign of severe HF and may represent a useful marker to identify AHF patients at high risk of postdischarge clinical outcomes, questions remain regarding the effectiveness on clinical outcomes of a strategy based on intensive and rapid decongestion in AHF.[24-26] Indeed, evidence

TABLE 4 Impact of Residual Congestion at Day 5 on the Primary Endpoint (Composite of CV Death or HF/RF Rehospitalization at 180 Days) in Relevant Subgroups of Interest (Subgroup Analysis)

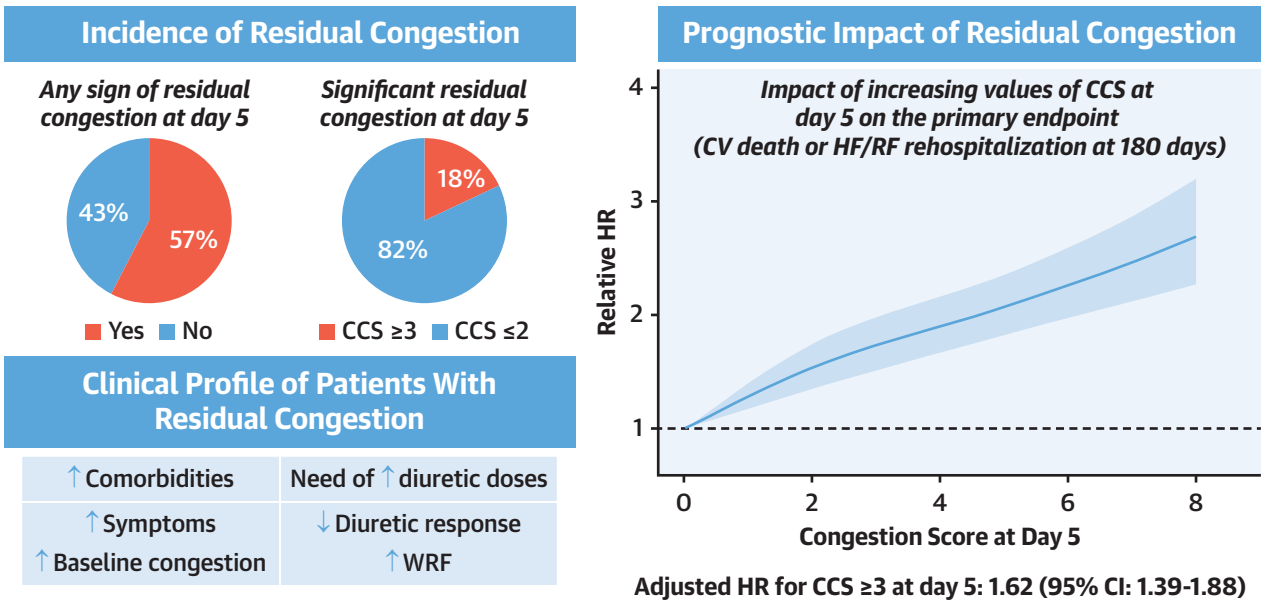
	Composite Congestion Score at Day 5 (≥3 vs ≤2) Within Each Subgroup	*P* Value for Interaction[a]	Any Residual Sign of Congestion at Day 5 (Yes vs No) Within Each Subgroup	*P* Value for Interaction[b]
Age, y		0.815		0.081
≥75	1.90 (1.61-2.24)		1.40 (1.21-1.62)	
<75	1.95 (1.65-2.31)		1.70 (1.45-2.01)	
Sex		0.503		0.617
Men	1.86 (1.60-2.16)		1.57 (1.36-1.81)	
Women	2.01 (1.66-2.43)		1.48 (1.24-1.75)	
LVEF at index hospitalization		0.552		0.415
HFrEF, LVEF ≤40%	2.08 (1.78-2.43)		1.48 (1.28-1.70)	
HFmrEF, LVEF 41%-49%	1.83 (1.36-2.47)		1.61 (1.22-2.11)	
HFpEF, LVEF ≥50%	1.78 (1.36-2.34)		1.80 (1.38-2.37)	
Baseline eGFR		0.217		0.793
eGFR ≤median value, 52 mL/min/1.73 m^2	1.71 (1.48-1.98)		1.46 (1.26-1.68)	
eGFR >median value, 52 mL/min/1.73 m^2	2.01 (1.64-2.46)		1.50 (1.26-1.79)	
Baseline NT-proBNP		0.029		0.439
NT-proBNP ≤median value, 6,074 pg/mL	1.54 (1.22-1.93)		1.37 (1.13-1.66)	
NT-proBNP >median value, 6,074 pg/mL	2.10 (1.77-2.50)		1.51 (1.28-1.78)	
Hemoconcentration at day 5, increase in hemoglobin		0.875		0.221
No	1.86 (1.59-2.17)		1.55 (1.32-1.83)	
Yes	1.91 (1.52-2.40)		1.34 (1.12-1.61)	
Change in hemoglobin at day 5, % change from baseline		0.875		0.221
Change ≤median value, 0%	1.86 (1.59, 2.17)		1.55 (1.32-1.83)	
Change >median value, 0%	1.91 (1.52, 2.40)		1.34 (1.12-1.61)	
Weight loss at day 5, % change from baseline		0.568		0.061
Weight loss ≤median value, −3.51%	1.84 (1.52-2.23)		1.37 (1.15-1.62)	
Weight loss >median value, −3.51%	1.97 (1.68-2.31)		1.70 (1.45-1.98)	
Diuretic response at day 5, kg of weight change per 40 mg of furosemide		0.315		0.542
Diuretic response ≤median value, −0.375 kg/40 mg furosemide	1.70 (1.30-2.22)		1.69 (1.34-2.14)	
Diuretic response >median value, −0.375 kg/40 mg furosemide	2.01 (1.67-2.40)		1.54 (1.26-1.87)	
Change in eGFR at day 5, % change from baseline		0.557		0.087
Change ≤median value, −3.81%	1.88 (1.57-2.25)		1.34 (1.14-1.58)	
Change >median value, −3.81%	2.03 (1.70-2.42)		1.65 (1.39-1.95)	
Worsening renal function at day 5		0.475		0.285
Yes	2.09 (1.61-2.70)		1.31 (1.02-1.68)	
No	1.90 (1.65-2.20)		1.54 (1.35-1.75)	

Values are HR (95% CI), unless otherwise indicated. [a]*P* value for interaction between composite congestion score at day 5 ≥3 vs ≤2 and the subgroup of interest. [b]*P* value for interaction between any sign of congestion at day 5 (yes vs no) and the subgroup of interest.

Abbreviations as in Table 1.

from recent randomized trials, including DOSE-AHF, ADVOR, and CLOROTIC, suggests that high-dose diuretic therapy or upfront combination diuretic therapy are effective strategies to achieve successful decongestion, but did not result in a significant reduction of postdischarge outcomes.[6-8] Of note, these trials were not powered for hard postdischarge clinical outcomes, and their primary endpoints were in-hospital outcomes based on symptoms or signs related to congestion or change in renal function.[6-8] The differences between trials in terms of assessment of congestion and study endpoints may also explain some differences in the occurrence of residual congestion and its relationship with postdischarge outcomes.[6-8] Furthermore, the primary endpoints of these trials were evaluated at 3 days after randomization, thus questions remain regarding the potential prognostic impact of decongestive strategies aiming at true euvolemia before discharge (ie, obtaining full decongestion even after 3 days).[6-8] Interestingly, analyses from the ESC Heart Failure Registry have also shown that intravenous treatment with vasodilators or inotropes has a negative impact only on in-hospital, but not on postdischarge, outcomes.[27] Only administration of evidence-based oral treatment for HF before and early after discharge and

CENTRAL ILLUSTRATION **Decongestion and Outcomes in Acute Heart Failure: An Analysis of 5,900 Patients From RELAX-AHF-2**



Pagnesi M, et al. JACC Heart Fail. 2025;13(3):414–429.

Among the 5,900 patients with acute heart failure (HF) included in this analysis of the RELAX-AHF-2 (Relaxin in Acute Heart Failure 2) trial, at least 1 sign of residual congestion (ie, composite congestion score [CCS] ≥1) was observed in 3,380 patients (57.3%) and CCS ≥3 was observed in 1,066 patients (18.1%) at day 5 after admission (upper left). Patients with residual congestion at day 5 had more comorbidities, were more symptomatic and with more signs of congestion at baseline, needed higher doses of loop diuretic agents, albeit with lower diuretic response, and were more likely to have worsening renal function (WRF) at day 5 (lower left). Residual congestion at day 5 had a strong, independent prognostic impact. The risk of the primary endpoint (composite of cardiovascular [CV] death or rehospitalization for HF or renal failure [RF] through 180 days) was progressively higher at increasing values of 5 day. The adjusted HR for CCS ≥3 at day 5 with respect to the primary endpoint was of 1.62 (95% CI: 1.39-1.88; $P < 0.001$).

high-intensity treatment and follow-up in the first weeks after discharge had a favorable impact on postdischarge outcomes.[28-30]

Of note, we observed that the association between residual congestion at day 5 and 180-day CV death or HF/RF rehospitalization persisted irrespective from age, sex, baseline left ventricular ejection fraction, in-hospital diuretic response, or WRF. This suggests that the prognostic impact of congestion at day 5 is maintained across different AHF profiles, differently from WRF that was associated with worse clinical outcomes especially in patients with suboptimal decongestion or with poor diuretic response.[10,13]

STUDY LIMITATIONS. The present study is a post hoc analysis of the RELAX-AHF-2 trial, therefore data collection in the trial was not designed specifically to evaluate the association between decongestion and outcomes. Confounding variables that were not identified or considered may have influenced the study findings. Congestion status was locally assessed by the study investigators at each enrolling site and not centrally adjudicated, thus potentially introducing inconsistencies between centers, but also across patients enrolled in the same center (if the assessor was not the same every day). As previously noted, RELAX-AHF-2 inclusion criteria resulted in the enrolment of a lower-risk population as compared with other AHF registry-based studies,[31] whereas inclusion of sicker patients may have increased the number of patients with residual congestion at day 5 or with clinical events through follow-up.

CONCLUSIONS

In patients with AHF enrolled in RELAX-AHF-2, residual congestion at day 5 after hospital admission was common, was associated with a worse clinical

profile at presentation and during hospital stay and had an independent prognostic impact on clinical outcomes at day 180. Future studies are needed to evaluate whether tailored in-hospital decongestive strategies and/or outpatient interventions in patients with residual congestion may improve postdischarge outcomes after HF hospitalization.

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ADDRESS FOR CORRESPONDENCE: Prof Marco Metra, Institute of Cardiology, Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, University of Brescia, Piazzale Spedali Civili 1, BS 25123 Brescia, Italy. E-mail: metramarco@libero.it.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In a large, well-phenotyped cohort of patients hospitalized for AHF, residual congestion at day 5 was common and independently associated with a higher risk of CV mortality or rehospitalization for HF or RF at day 180.

TRANSLATIONAL OUTLOOK: Although residual congestion is a marker of worse outcome in patients with AHF, it is unclear whether tailored decongestive strategies may improve long-term outcomes after HF hospitalization. Further dedicated studies are needed to evaluate the optimal in-hospital or outpatient management strategies in patients with AHF and residual congestion.

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KEY WORDS acute heart failure, congestion, decongestion, heart failure, hospitalization, mortality

APPENDIX For supplemental figures and tables, please see the online version of this paper.