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RESEARCH ARTICLE

Clinical profiles and prognostic impact of residual intravascular and tissue congestion in acute heart failure

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Aims Residual congestion (RC) is common at discharge after acute decompensated heart failure (ADHF) and is associated with early mortality and rehospitalization. The prognostic value of distinct RC phenotypes (i.e. intravascular and tissue congestion) remains unclear. This analysis investigated RC phenotypes and their outcomes.

Methods and results Patients with congestion at admission from two large ADHF trials, PROTECT (rolofylline; index) and RELAX-AHF-2 (serelaxin; replication), were classified based on clinical signs at day 7/discharge as intravascular (jugular venous pressure) or tissue (pulmonary rales/peripheral oedema) congestion, each alone, combined or neither. Cox regression assessed 180-day mortality after adjusting for risk factors. Overall, 1557 patients with predominantly combined (i.e. tissue and intravascular) congestion at admission were included, with a median age of 72 years. By day 7 or discharge, 580 (37%) patients had RC. In these patients, intravascular congestion ($n = 260$; 45%) was most common, followed by combined ($n = 185$; 32%) and tissue ($n = 135$; 23%) congestion. During hospitalization, patients with solely intravascular RC had greater diuretic responses, shorter hospital stays and received lower doses of intravenous loop diuretics than those with tissue or combined congestion (all $p < 0.05$). Residual intravascular and tissue congestion were independently associated with increased 180-day mortality (hazard ratio [HR] 1.69, 95% confidence interval [CI] 1.15–2.49, and HR 2.07, 95% CI 1.25–3.41, respectively) compared to decongested patients. In the RELAX-AHF-2 substudy ($n = 476$), similar findings were observed.

Conclusions Patients with intravascular RC had better diuretic responses and shorter hospital stays than those with tissue/combined RC, but worse outcomes than decongested patients. This study highlights the importance of RC assessment to identify at-risk patients. Future studies should evaluate phenotype-guided treatments.

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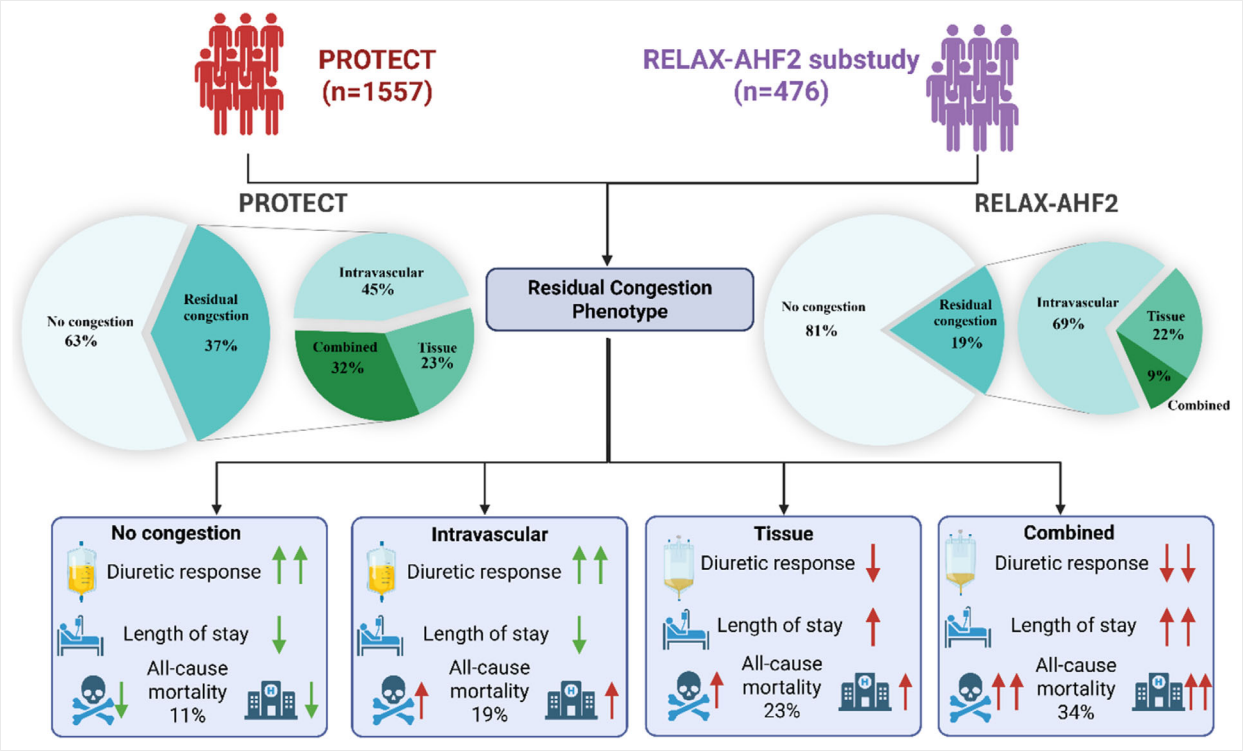
Graphical Abstract



This study investigated the prognostic value of residual congestion phenotypes at discharge in acute heart failure. Patients with intravascular residual congestion had better diuretic responses and shorter hospital stays than those with tissue/combined residual congestion, but worse outcomes than decongested patients.

Keywords Acute heart failure • Congestion • Phenotypes • Diuretics • Prognosis

Introduction

Heart failure (HF) is a common cause of hospitalization worldwide, with the main driver of hospitalization being congestion.[1] For acute decompensated HF (ADHF), the primary goal is to achieve euvolaemia, primarily by use of loop diuretics.[2] However, fully resolving congestion remains challenging, as residual congestion (RC) at discharge is both common and a critical determinant of adverse outcomes, including rehospitalization and mortality.[2–5] Still, the treatment of congestion has changed little over the decades.[2] The standard, one-size-fits-all approach to decongestion with a predominant focus on the administration of loop diuretics has proven insufficient. Moreover, some studies even suggest that aggressive diuretic strategies may worsen patient outcomes despite reductions in congestion, suggesting the need for more individualized management strategies.[6]

A major challenge in the treatment of (residual) congestion is the heterogeneity of congestion phenotypes. To combat this, two distinct congestion phenotypes have been proposed: intravascular congestion and tissue congestion.[2] Intravascular congestion may be due to plasma volume expansion following water retention, or redistribution of blood from peripheral venous reservoirs resulting from heightened venous tone triggered by neurohormonal activation.[2,7,8] The development of tissue congestion is usually more gradual as a result of renal salt and water retention, increased capillary hydrostatic pressure and capillary permeability.[2,7] This eventually overwhelms lymphatic drainage, causing fluid to accumulate in the interstitial space.[2,7] While these phenotypes provide a framework to categorize patients early during hospitalization to guide treatment,[7] congestion phenotypes may change due to diuretic treatment.[2]

Little is known about how RC phenotypes evolve during hospitalization, how they relate to clinical characteristics or respond to therapy. Understanding these relationships is crucial, as different phenotypes may require tailored approaches to treat RC and carry important prognostic implications. This analysis explores the

clinical characteristics of RC phenotypes and their association with patient outcomes which may inform targeted decongestion strategies in ADHF.

Methods

Study population

This study utilized two randomized trials of ADHF as index and replication cohorts. The PROTECT (Placebo-controlled Randomized Study of 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) trial was a multicentre, randomized, double-blind, placebo-controlled phase III study of rolofylline in patients with ADHF requiring intravenous (IV) diuretic therapy.[9,10] A total of 2033 patients with mild-to-moderate renal impairment (estimated creatinine clearance 20–80 ml/min) were randomized to receive either rolofylline or placebo. The primary findings of the study were neutral. Inclusion criteria included dyspnoea at rest or minimal exertion, anticipated need for IV furosemide and evidence of fluid overload. Key exclusion criteria included systolic blood pressure <90 mmHg or ≥160 mmHg, B-type natriuretic peptide (BNP) <500 pg/ml or N-terminal pro-B-type natriuretic peptide (NT-proBNP) <2000 pg/ml, as well as ongoing or planned ultrafiltration or dialysis. Further details on the trial protocol and outcome have been published elsewhere.[9,10]

We replicated our findings in 1020 patients from the RELAX-AHF-2 (Relaxin for the Treatment of Acute Heart Failure-2) trial, who participated in a biomarker substudy that included additional clinical congestion assessments at discharge. The RELAX-AHF-2 trial was a multinational, randomized, placebo-controlled, double-blind phase III trial of serelaxin infusion in patients with ADHF. The findings of the primary study were neutral. However, in the biomarker substudy, serelaxin did reduce worsening HF through day 5 and biomarkers of end-organ damage.[11] Briefly, the primary trial enrolled 6545 patients aged ≥18 years with acute HF and congestion visible on chest radiographs, mild-to-moderate renal impairment (estimated glomerular filtration rate 25–75 ml/min/1.73 m^2), elevated levels of BNP or NT-proBNP, symptoms of dyspnoea, and systolic blood pressure >125 mmHg. The protocol and results have been described in detail in previous reports.[12,13]

Both trials complied with the Declaration of Helsinki, all patients provided written informed consent, and the ethics committees at each trial centre approved the trials.

Assessment of diuretic response

We quantified diuretic response as change in weight between day 1 and day 4 per 40 mg of furosemide equivalent dose administered over days 1–3 (equivalents: 1 mg bumetanide, 20 mg torsemide, 50 mg ethacrynic acid). Total diuretic dose was calculated as the sum of the total IV furosemide-equivalent doses of loop diuretics administered from days 1 to 3, plus 0.5 × the oral dose during the same period to account for reduced oral bioavailability. In the index (PROTECT) cohort, patients with weight loss >20 kg ($n = 3$) had their weight loss set to NA, and 278 patients without loop diuretic dosing or weight data at day 4 were excluded from diuretic response calculations.[14] For the replication (RELAX-AHF-2) cohort, the diuretic response was similarly calculated, as published previously.[15]

Assessment of congestion phenotypes and biomarkers

Jugular venous pressure (JVP), peripheral oedema, and pulmonary rales/crackles were assessed at baseline and on day 7 or discharge, whichever came first, in the index (PROTECT) cohort to classify patients into four distinct congestion phenotypes:

1) Intravascular congestion, defined as a JVP >6 cm H_2O without signs of tissue congestion.
2) Tissue congestion, defined as having no signs of intravascular congestion, and:
   a. Peripheral oedema graded as ≥2+ (moderate); or
   b. Pulmonary rales heard over ≥1/3 of the lung fields; or
   c. Both mild peripheral oedema (1+) and pulmonary rales present over <1/3 of the lung fields.
3) Combined congestion: characterized by the presence of both intravascular and tissue congestion.
4) No congestion: neither intravascular nor tissue congestion, and no missing evaluations of JVP, peripheral oedema or pulmonary rales.

Patients without congestion at baseline, or missing congestion phenotypes at baseline or day 7/discharge were excluded, resulting in a final number of 1557 patients for the index (PROTECT) cohort. We used a similar approach in the replication (RELAX-AHF-2) cohort leading to a final number of 476 patients. For a detailed breakdown of these exclusions, please refer to online supplementary *Figure Appendix S1*.

Biomarker measurements

Brain natriuretic peptide and bioactive adrenomedullin (bio-ADM) were measured from EDTA plasma samples at baseline and day 7 or discharge, cancer antigen-125 (CA125) at baseline only and interleukin 6 (IL-6) on day 7/discharge. In the index cohort (PROTECT), plasma bio-ADM was quantified using an immunoassay (Sphingotec GmbH, Henningsdorf, Germany).[16] BNP was measured using a highly sensitive single molecule counting (SMC™) technology (Erenna® Immunoassay System; Singulex Inc., Alameda, CA, USA).[16] CA125 was measured using a chemiluminescent microparticle immunoassay performed on the ARCHITECT i System (Abbott Laboratories, Abbott Park, IL, USA). IL-6 was measured in 1591 patients using high-sensitivity single-molecule counting technology (Singulex Inc.).

Long-term outcomes

The primary endpoint was all-cause mortality at 180 days. The secondary endpoint was a combined outcome of all-cause mortality or HF rehospitalization at 60 days in the index (PROTECT) cohort. Due to the limited sample size of the RELAX-AHF-2 substudy, long-term outcomes were not assessed in the replication cohort.

Statistical analysis

Descriptive statistics were used to examine differences in clinical characteristics between congestion phenotypes. Variables that were normally distributed were reported as means with standard deviations, while those that were non-normally distributed were presented as medians with interquartile ranges. Categorical variables were

expressed as numbers with percentages. The clinical characteristics across congestion phenotypes at discharge or day 7 were compared using one-way analysis of variance (ANOVA) for continuous variables that followed a normal distribution, the Kruskal–Wallis test for continuous variables that did not follow a normal distribution, and either the χ^2 test or Fisher's exact test for categorical variables. To compare clinical characteristics and biomarker concentrations between congestion phenotypes, we used the Kruskal–Wallis test. Pairwise comparisons were adjusted for multiple testing using the Benjamini–Hochberg procedure.

We used Kaplan–Meier analyses to compare events of 180-day all-cause mortality or a combined outcome of 60-day HF rehospitalization or mortality in the index (PROTECT) cohort. Lastly, we used Cox regression analyses to estimate hazard ratios (HR) for each congestion phenotype, adjusting for age, previous HF hospitalization, systolic blood pressure, plasma sodium, log-blood urea nitrogen, log-creatinine, albumin, rolofylline treatment, log-BNP, and log-body mass index (BMI). Schoenfeld residuals were checked to assess proportionality. Data are available upon reasonable request.

Results

Clinical characteristics of residual congestion phenotypes

For patients in the index cohort (PROTECT), the median age was 72 years, 72% had HF with reduced ejection fraction with a median ejection fraction of 30% and a median BNP concentration of 455 pg/ml at baseline. At baseline, 6% ($n = 88$) of patients presented with intravascular congestion, 11% with tissue congestion ($n = 176$), and 83% of patients had the combined congestion phenotype ($n = 1293$) (*Figure 1A*). By day 7/discharge, 37% of all patients had RC (*Figure 1B*). Among these patients, intravascular RC ($n = 260$; 45%) was the most common phenotype, whereas 23% had tissue RC ($n = 135$) and 32% had combined RC ($n = 185$). Of the patients with intravascular RC at day 7 or discharge, 11% ($n = 29$) had intravascular congestion, 2% ($n = 5$) had tissue congestion, and 87% ($n = 226$) had combined congestion at baseline. Similarly, of those with tissue RC at day 7/discharge, only one presented with intravascular congestion, 13% ($n = 17$) with tissue congestion, and 87% ($n = 117$) presented with a combined congestion phenotype (*Figure 1A*). *Table 1* shows the clinical characteristics per RC phenotype at day 7/discharge. Patients with intravascular RC had a lower BMI ($p < 0.002$), higher albumin ($p < 0.001$) and lower serum sodium concentrations ($p = 0.03$) compared to those with tissue RC. Patients with a combined RC phenotype had the highest BMI and creatinine levels, the lowest haemoglobin, and were most likely to have a prior HF hospitalization (all $p < 0.001$).

Similar trends were observed in the RELAX-AHF-2 cohort (*Figure 1C,D*). In RELAX-AHF-2, intravascular congestion was even more overrepresented at discharge, despite a lower total fraction of patients having RC phenotypes. However, smaller sample sizes limited statistical testing of differences in clinical characteristics between congestion phenotypes (online supplementary *Table Appendix S1*). As the combined RC group comprised only eight patients, this group was excluded from further analyses.

Biomarkers and residual congestion phenotypes

Patients with intravascular RC had significantly higher BNP and bio-ADM concentrations at day 7 or discharge compared to patients without RC (both $p < 0.001$). Patients with a combined RC phenotype had the highest concentrations of BNP, bio-ADM and CA125 and IL-6 across all time points (all $p < 0.005$) (*Table 1*). Compared with patients with tissue RC, patients with intravascular RC had lower bio-ADM concentrations ($p = 0.005$) and trended towards lower IL-6 concentrations ($p = 0.063$) at day 7/discharge.

Diuretic response and in-hospital outcomes according to residual congestion phenotypes

In the index cohort, patients with intravascular RC on day 7 or discharge had an almost twofold diuretic response by day 4 (−0.40 kg/40 mg furosemide, 95% confidence interval [CI] −0.82 to −0.13) compared to those with tissue RC (−0.22 kg/40 mg, 95% CI −0.62 to −0.02) or combined RC (−0.16 kg/40 mg, 95% CI −0.43 to 0.00) (*Figure 2A*). Patients with intravascular RC on day 7/discharge lost more weight through the first 4 days of hospitalization (−2.80 kg, 95% CI −4.50 to −1.22) compared to patients with tissue RC (−2.00 kg, 95% CI −4.00 to −0.20) (*Figure 2B*), however, weight loss did not differ significantly between patients with intravascular RC and those that were completely decongested ($p = 0.266$). Patients with intravascular RC received only slightly higher doses of furosemide (280 mg, 95% CI 158–520) than successfully decongested patients (240 mg, 95% CI 120–440) (*Figure 2C*). In contrast, patients with tissue or combined RC received respectively twofold and >2.5-fold higher IV diuretic doses by day 7/discharge (*Figure 2C*).

Almost 80% of patients with intravascular RC had been switched from IV to oral diuretics by day 7 or discharge. In contrast, more than half of patients with tissue or combined RC were still receiving IV loop diuretics at day 7/discharge ($p < 0.001$) (*Figure 2E*). Moreover, the median length of stay was similar for patients with intravascular RC and those who had been successfully decongested, whereas those with residual tissue and combined congestion had longer lengths of stay (both $p < 0.001$) (*Figure 2D*). Similar trends were seen in the RELAX-AHF-2 cohort for diuretic response at 4 days and total IV loop diuretic doses over the first 5 days (*Table 2*).

Post-hospitalization outcomes and residual congestion phenotypes

All RC phenotypes were associated with an increased risk of all-cause mortality at 180 days (*Figure 3A*), as well as the combined endpoint of all-cause mortality or rehospitalization through day 60 (*Figure 3B*) compared to patients without RC. Even after correcting for previously established predictors of adverse outcomes in ADHF, intravascular RC at day 7/discharge was associated with a higher risk of 180-day mortality (HR 1.69, 95% CI 1.15–2.49) compared to successfully decongested patients. Moreover, the

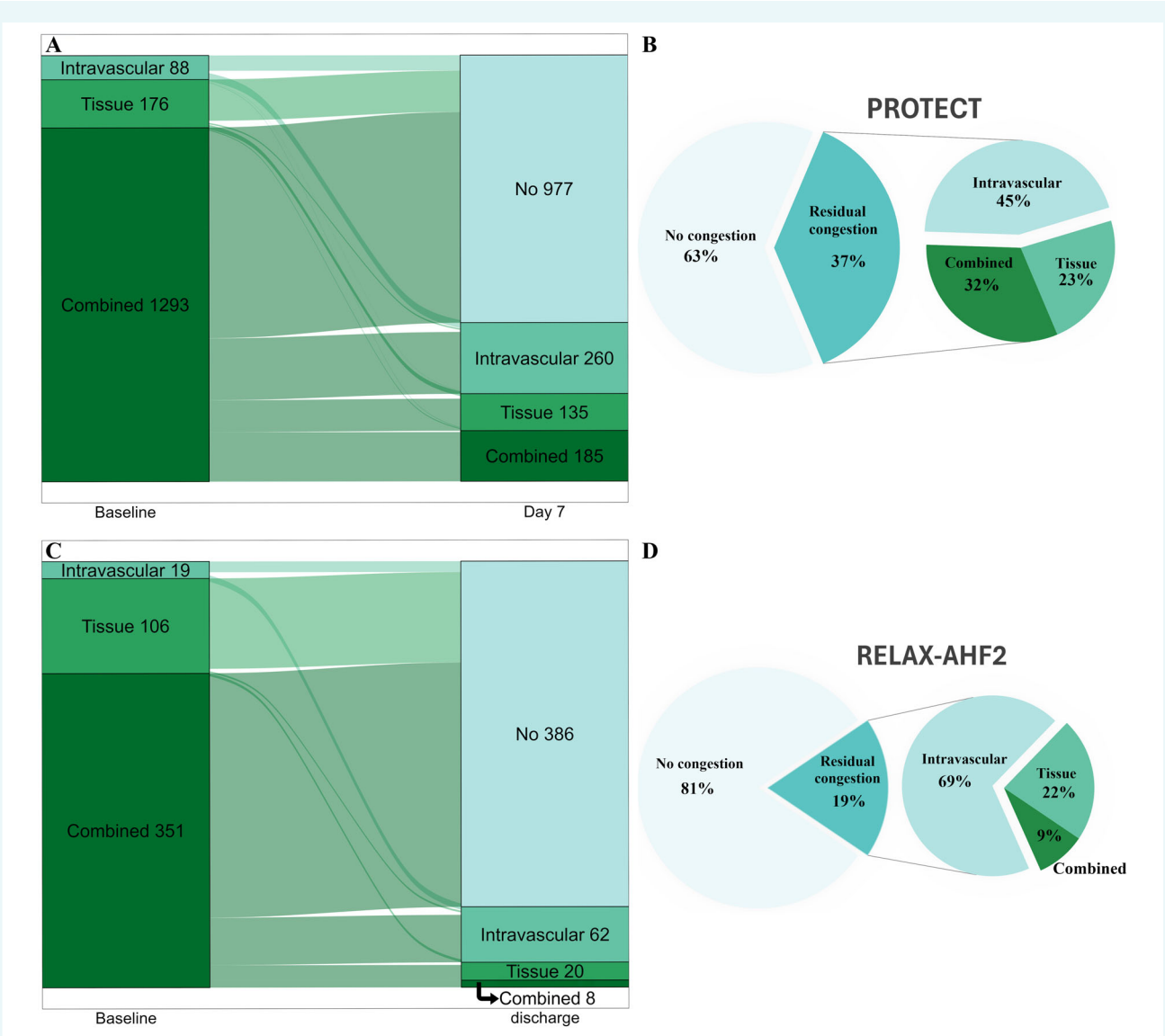


Figure 1 Congestion phenotypes at baseline and discharge. (*A*) Temporal changes of congestion phenotypes between baseline and day 7 or discharge in the index cohort (PROTECT). (*B*) Prevalence of congestion phenotypes at day 7 or discharge in the index cohort. (*C*) Temporal changes of congestion phenotypes between baseline and discharge in the replication cohort (RELAX-AHF-2). (*D*) Prevalence of congestion phenotypes at discharge in the replication cohort cohort.

combined (HR 2.18, 95% CI 1.44–3.30) and tissue (HR 2.07, 95% CI 1.25–3.41) RC phenotypes showed even higher HRs, suggesting they may be associated with additional risk (*Table 3*). Pairwise comparisons between RC phenotypes can be found in online supplementary *Table S2*. Further, the relationship between baseline congestion phenotypes and all-cause mortality or rehospitalization can be found in online supplementary *Table S3*.

Discussion

This analysis highlights the heterogeneity of congestion phenotypes in ADHF at discharge and their implications for clinical management and outcomes. Our key findings are: (i) by day 7/discharge, 37% of patients still had RC, with intravascular RC being the most common individual phenotype. Nearly all patients (87%) with RC, whether intravascular or tissue, initially presented with combined congestion; (ii) most patients with intravascular RC at day 7/discharge had initially responded well to diuretics and had shorter hospital stays, lower cumulative diuretic doses, and greater weight loss during their hospitalization; (iii) in contrast, patients with residual tissue or combined RC had poor diuretic responses, received higher diuretic doses, and were less frequently switched from IV to oral loop diuretics by day 7/discharge; (iv) despite these differences, both intravascular and tissue/combined RC were associated with increased 180-day mortality risk, with the highest risk observed in those with tissue or combined RC (*Graphical Abstract*).

Table 1 Clinical characteristics per residual congestion phenotype in the index (PROTECT) cohort

	No RC ($n = 977$)	Intravascular RC ($n = 260$)	Tissue RC ($n = 135$)	Combined RC ($n = 185$)	p-value overall
Age (years)	72 [64–79]	71 [60–78]	72 [63–78]	72 [62–78]	0.127
Male sex, *n* (%)	338 (34.6)	82 (31.5)	46 (34.1)	54 (29.2%)	0.469
BMI (kg/m^2) at screening	27.3 [24.2–31.0]	27.1 [24.1–31.0]	29.1 [25.8–35.3]	30.8 [27.1–34.6]	<0.001
Systolic blood pressure (mmHg) at screening	125 [110–140]	120 [110–139]	125 [110–137]	120 [106–135]	0.007
Diastolic blood pressure (mmHg) at screening	75 [68–80]	72 [66–80]	72 [68–80]	70 [62–80]	0.036
Heart rate (bpm) at screening	79 [70–90]	76 [68–88]	80 [70–94]	78 [70–90]	0.189
Past hospitalization, *n* (%)	452 (46.3)	126 (48.5)	57 (42.2)	122 (65.9)	<0.001
Rolofylline 30 mg allocation, *n* (%)	667 (68.3)	176 (67.7)	92 (68.1)	112 (60.5)	0.229
History of hypertension, *n* (%)	784 (80.2)	197 (75.8)	108 (80.0)	155 (83.8)	0.206
History of diabetes mellitus, *n* (%)	413 (42.3)	120 (46.2)	70 (52.2)	109 (58.9)	<0.001
History of ischaemic heart disease, *n* (%)	690 (70.7)	169 (65.0)	92 (68.7)	127 (69.0)	0.364
History of atrial fibrillation, *n* (%)	503 (51.8)	135 (52.5)	73 (54.5)	127 (69.4)	<0.001
Left ventricular ejection fraction (%)	30 [23–40]	29 [20–36]	25 [22–37]	30 [20–40]	0.139
Heart failure category, *n* (%)					0.356
HFmrEF	72 (16.4)	20 (14.4)	4 (7.02)	16 (15.4)	
HFpEF	57 (13.0)	12 (8.63)	8 (14.0)	16 (15.4)	
HFrEF	309 (70.5)	107 (77.0)	45 (78.9)	72 (69.2)	
Laboratory measurements					
Urea (mg/dl) on day 7/discharge	32.0 [24.0–43.0]	34.0 [24.0–47.5]	34.0 [23.2–47.0]	43.0 [30.0–61.0]	<0.001
Creatinine (mg/dl) on day 7/discharge	1.40 [1.10–1.80]	1.40 [1.10–1.90]	1.40 [1.20–1.87]	1.70 [1.30–2.20]	<0.001
Hb (g/dl) on day 7/discharge	13.1 [11.6–14.7]	12.8 [11.3–14.5]	12.5 [11.1–14.0]	11.6 [10.2–13.1]	<0.001
Albumin (g/dl) on day 7/discharge	4.00 [3.70–4.20]	3.90 [3.60–4.20]	3.80 [3.40–4.00]	3.65 [3.30–3.90]	<0.001
Sodium (mEq/L) on day 7/discharge	139 [136–141]	138 [135–140]	139 [137–142]	138 [135–140]	0.008
Potassium (mEq/L) on day 7/discharge	4.5 [4.2–5.0]	4.40 [4.1–4.8]	4.3 [3.9–4.7]	4.4 [4.0–4.8]	<0.001
Chloride (mEq/L) on day 7/discharge	101 [97.0–103]	99.0 [96.0–102]	100 [96.0–103]	99.0 [95.8–102]	<0.001
Biomarker measurements					
BNP (pg/ml) on day 1	441 [258–774]	432 [262–884]	454 [224–902]	626 [311–952]	0.004
BNP (pg/ml) on day 7/discharge	225 [125–414]	293 [178–543]	343 [165–642]	516 [245–817]	<0.001
Change in BNP between day 1 and 7	−156.79 [−365.77 to −48.80]	−132.42 [−345.26 to −18.43]	−74.20 [−290.45 to −7.27]	−93.31 [−307.63 to 12.4]	0.002
Bio-ADM (pg/ml) on day 1	38.1 [23.8–65.6]	43.9 [24.5–91.8]	61.5 [40.8–115]	76.3 [45.0–151]	<0.001
Bio-ADM (pg/ml) on day 7/discharge	27.5 [18.9–46.8]	39.9 [24.6–63.8]	47.4 [30.1–100]	81.8 [42.2–148]	<0.001
Change in bio-ADM between day 1 and 7	−7.79 [−21.89 to 1.46]	−6.22 [−26.19 to 5.65]	−7.98 [−24.17 to 2.46]	−1.68 [−31.05 to 19.0]	0.328
CA125 (U/ml) on day 1	60.9 [25.8–169]	77.3 [34.8–164]	113 [49.0–273]	156 [68.1–307]	<0.001
IL-6 (pg/ml) on day 7/discharge	8.94 [5.37–15.8]	11.1 [6.11–19.1]	13.1 [8.76–23.7]	20.3 [12.2–39.2]	<0.001

Data are presented as mean (standrad deviation), median [interquartile rabge] or *n* (%).
bio-ADM, bioactive adrenomedullin; BMI, body mass index; BNP, B-type natriuretic peptide; CA125, cancer antigen-125; Hb, haemoglobin; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; IL-6, interleukin-6; RC, residual congestion.

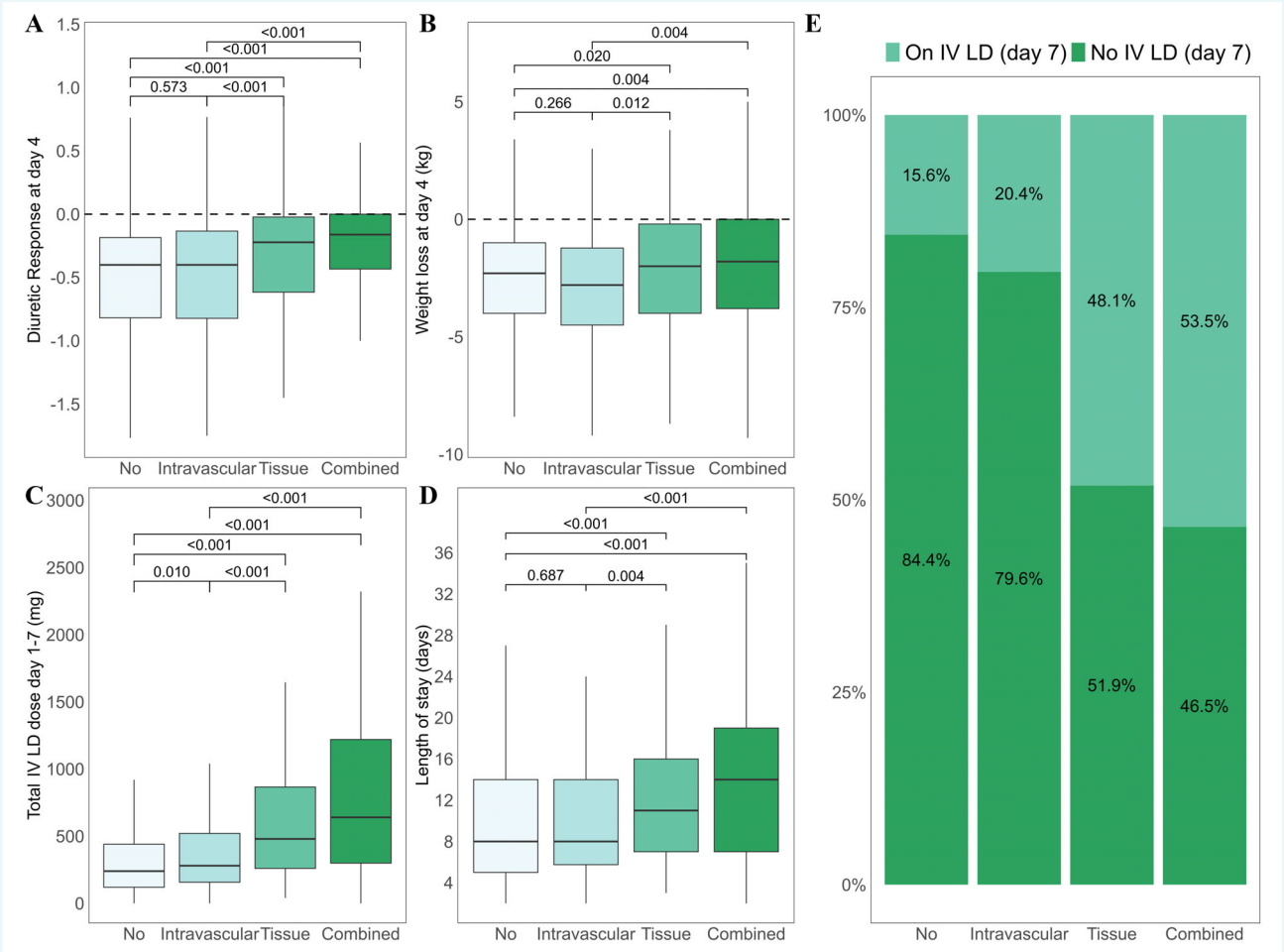


Figure 2 In-hospital outcomes in the index cohort per residual congestion phenotype. (*A*) Diuretic response in kilogram change per 40 mg furosemide equivalent dose. (*B*) Weight loss during first 4 days of hospitalization. (*C*) Total intravenous (IV) loop diuretic (LD) dose given between day 1 and 7. (*D*) Total length of stay. (*E*) Presence of IV LD treatment at day 7/discharge. *P*-values were calculated using pairwise Wilcoxon test, adjusted for multiple testing using the Benjamini–Hochberg method.

Table 2 In-hospital outcomes in the replication (RELAX-AHF-2) cohort

	No RC ($n = 386$)	Intravascular RC ($n = 62$)	Tissue RC ($n = 20$)	*p*-value overall	*p*-value no RC vs. tissue RC	*p*-value intravascular RC vs. tissue RC	*n*
Diuretic response (kg weight change by day 4/40 mg furosemide equivalent administered on days 1–3)	−0.44 [−0.82 to −0.18]	−0.47 [−0.88 to −0.14]	−0.20 [−0.54 to 0.03]	0.047	0.041	0.041	457
Cumulative total diuretic dose (mg) from day 1 to 5	320 [230–438]	355 [265–578]	435 [311–602]	0.005	0.019	0.292	468
Weight change from baseline to day 4	−3.0 [−5.0 to −1.1]	−3.2 [−5.7 to −1.2]	−2.4 [−4.2 to 0.4]	0.129	0.156	0.156	457
Length of stay (days)	7.6 [6.1–9.8]	7.8 [6.3–10.7]	9.5 [7.0–15.9]	0.066	0.074	0.209	468

RC, residual congestion.
Pairwise comparisons were adjusted using the Benjamini–Hochberg method.

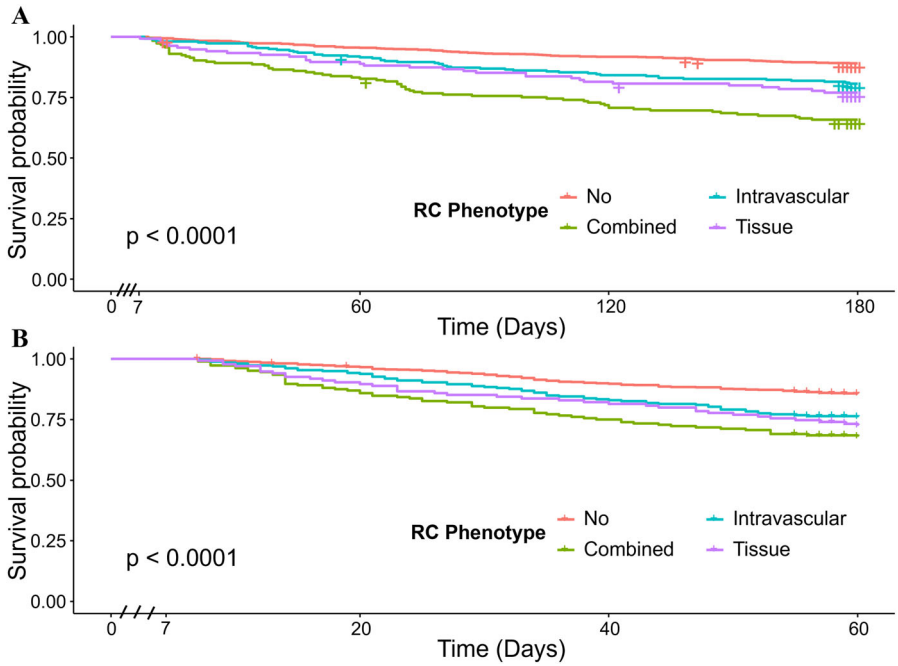


Figure 3 Adverse outcomes in the index cohort. (*A*) All-cause mortality at 180 days. (*B*) All-cause mortality or heart failure rehospitalization at 60 days. Any patients with events prior to 7 days were excluded from the analysis. RC, residual congestion.

Table 3 Adverse outcomes per residual congestion phenotype

Phenotype	HR	95% CI	*p*-value	Event rate (%)
All-cause mortality at 180 days				
No RC	Ref.			10.8
Intravascular RC	1.69	1.15–2.49	0.007	19.2
Tissue RC	2.07	1.25–3.41	0.005	23.0
Combined RC	2.18	1.44–3.30	<0.001	34.1
All-cause mortality or HF rehospitalization at 60 days				
No RC	Ref.			14.3
Intravascular RC	1.53	1.08–2.17	0.018	23.9
Tissue RC	1.76	1.13–2.75	0.013	27.4
Combined RC	1.54	1.04–2.28	0.032	32.1

BMI, body mass index; BNP, B-type natriuretic peptide; CI, confidence interval; HF, heart failure; HR, hazard ratio; RC, residual congestion.
Corrected for age, previous HF hospitalization, systolic blood pressure, plasma sodium, log-blood urea nitrogen, log-creatinine, albumin and rolofylline treatment, in addition to log-BNP and log-BMI. Patients with an event prior to 7 days were excluded from the analysis for that outcome ($n = 6$ for death or rehospitalization).

These results highlight the importance of identifying RC to identify patients at risk of adverse outcomes and provides the first evidence that specific RC phenotypes are associated with differential responses to decongestive therapy.

Our findings suggest that RC at discharge may reflect both the extent of congestion at baseline and differences in diuretic response or treatment intensity during hospitalization, in addition to underlying disease severity/duration, comorbidities and inflammation.[17,18] Patients with an adequate diuretic response may have successfully been decongested or transitioned to intravascular RC, whereas those with a poor response may have developed/maintained tissue or combined RC. Recognizing RC at discharge is therefore critical to inform post-discharge treatment, as it remains a key predictor of adverse outcomes in ADHF, which has previously been investigated in both the PROTECT and RELAX-AHF-2 cohorts.[5,17] Further, congestion phenotypes may reflect distinct pathophysiological mechanisms that affect diuretic response and could guide post-discharge therapy.

Congestion phenotypes and diuretic response

Previous studies have proposed possible mechanisms between congestion phenotypes and diuretic response. Boorsma *et al.*[2] suggested that chronic sodium saturation in the glycosaminoglycan network disrupts its ability to function as a buffer for sodium and water, impairing the structure of the interstitium. This could be exacerbated by the reduced lymphatic drainage observed in patients with acute HF, which also has been linked to lower diuretic responses.[19] These disruptions lead to increased interstitial fluid accumulation and worsen tissue congestion. Additionally, increased vascular permeability due to conditions like diabetes or inflammation further contributes to (residual) tissue congestion.[2,20] These mechanisms may contribute to diuretic resistance in longstanding/residual tissue congestion by decreasing mobilization of fluid

from the extravascular to the intravascular compartment, possibly due to a reduced osmotic gradient, making it more challenging to resolve than intravascular RC.[2,20] These patients may benefit from other diuretic agents, like thiazide diuretics, sodium–glucose co-transporter 2 inhibitors, and vasopressin antagonists rather than higher doses of loop diuretics.[2,6] Recent findings suggest that anti-inflammatory treatments might also play a role. An open-label pilot study demonstrated that prednisone burst therapy reduced the 90-day risk of worsening HF or HF hospitalization and tended to lessen signs and symptoms of congestion in ADHF, especially among patients with high IL-6 levels.[21,22] Our findings, where we saw a trend that IL-6 at day 7 was higher in patients with combined and tissue RC compared to those with intravascular RC, suggest that these patients might benefit from anti-inflammatory treatments to reduce vascular permeability and improve decongestion. However, further mechanistic/experimental studies are needed to clarify the association between tissue RC and increased inflammation, vascular permeability or glycosaminoglycan saturation and how this relates to diuretic response.

In contrast to patients with tissue RC, patients with intravascular RC may have had better mobilization of extravascular water and salt into the circulation, resulting in more diuresis and better diuretic response as observed in this study. This suggests that patients with intravascular RC may represent those with partial resolution of congestion despite an initial favourable diuretic response, as almost 80% of patients with residual intravascular congestion had already switched from IV to an oral loop diuretic. Consequently, these patients may still benefit from higher doses of loop diuretics to achieve further decongestion. A possible explanation could be that jugular venous distension and intravascular congestion are less likely to be noticed by clinicians or patients compared to pulmonary and/or peripheral oedema. Although standardized JVP assessments in research settings have acceptable sensitivity (0.61–0.97), specificity (0.75–0.94), and interobserver reliability, in routine clinical practice JVP is often measured less rigorously, potentially limiting its accuracy.[23,24] Furthermore, patients with intravascular RC exhibited similar, if not greater, weight reduction and diuretic response compared to those who were completely decongested, which may contribute to this phenotype being underrecognized at discharge. Still, intravascular RC carries residual risk, as it was associated with an increase in mortality. This is in line with a recent study investigating patients with chronic HF, which found that elevated JVP was the strongest predictor of HF rehospitalizations and positioned it as a strong marker for RC.[25] Our study showed that, despite a milder clinical presentation, biomarkers such as bio-ADM were elevated in patients with intravascular RC, suggesting they may help identify this underrecognized phenotype.

It is important to note that, although recent trials that sought to enhance decongestion, such as ADVOR, CLOROTIC, and PUSH-AHF successfully increased diuresis, natriuresis, and in some cases reduced length of stay and dyspnoea, these trials did not demonstrate improvements in HF rehospitalization or all-cause mortality.[6,26–28] A substantial proportion of these patients still had RC at discharge: 21% of those receiving acetazolamide and 38% of those managed with standard of care in ADVOR.[26,27] Therefore, unless there is complete decongestion, an increased risk remains regardless of intensified therapy. Adequately powered trials are needed to give a conclusive answer on whether more effective decongestive therapies can combat the increased risk for adverse outcomes related to RC. This will give insight into whether RC indeed drives adverse events in HF or is merely a marker of severity or disease progression.[6]

Limitations

This study is a post-hoc analysis, and the results are hypothesis-generating. It remains uncertain to what extent congestion phenotypes mediate the relationship between congestion and outcomes, or act as confounders reflecting underlying HF severity, comorbidities, and discharge practice variability. Additionally, patients with true hypertensive intravascular congestion at baseline may have been excluded, as those with systolic blood pressure ≥160 mmHg were not enrolled in the PROTECT trial. Furthermore, due to their specific inclusion and exclusion criteria, the PROTECT and RELAX-AHF-2 trials may not fully represent the heterogeneity of the real-life acute HF population. Bio-ADM, CA125 and IL-6 measurements were unavailable in the RELAX-AHF-2 cohort, and discharge congestion assessments were only available in a subset of patients, limiting the ability to replicate results across both cohorts. Additionally, the trial populations differed in clinical characteristics, including ejection fraction, age, and sex, as well as in the mechanisms of action of the study drugs which may affect neurohormonal activation and diuretic response. Nonetheless, the consistency of results across cohorts supports the robustness of our findings. Physical examination has inherent inaccuracies, and no confirmatory test was performed (e.g. ultrasound or invasive pressure measurement). Although previous studies showed strong correlations between JVP and right atrial pressure, elevated JVP remains an imperfect surrogate for intravascular volume and pressure.[23,24,29] Still, it is likely any resulting misclassification resulting from physicians' errors would bias the results toward the null hypothesis.[30] Therefore, the fact that congestion phenotypes based on these basic clinical signs were preceded by distinct diuretic responses lends credence to the potential impact of congestion phenotypes. Improved phenotyping, potentially by imaging (i.e. inferior vena cava, lung ultrasound and near-infrared spectroscopy), invasive pressure measurements, and biomarkers could improve the discrimination of congestion phenotypes further and should be investigated by future studies.[31–33] This could enable phenotype-specific management strategies, such as tailored diuretic regimens guided by objective and easy-to-implement tools (e.g. biomarkers or imaging), allowing more precise adjustment of decongestive therapy, reducing RC, and ultimately advancing toward more personalized care and improved outcomes in acute HF.

Conclusion

This analysis highlights the heterogeneity of RC in ADHF and its impact on outcomes. Further, our results suggest that residual intravascular congestion is most common at discharge and is

associated with higher mortality despite a good diuretic response during admission, while residual tissue congestion is associated with poor diuretic response and the highest mortality. These results highlight the importance of identifying RC to identify patients at risk of adverse outcomes. Future trials should evaluate tailored treatments for specific RC phenotypes at or prior to discharge.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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