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Prevalence, predictors and clinical outcome of residual congestion in acute decompensated heart failure

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ABSTRACT

Background: Congestion is the main reason for hospital admission for acute decompensated heart failure (ADHF). A better understanding of the clinical course of congestion and factors associated with decongestion are therefore important. We studied the clinical course, predictors and prognostic value of congestion in a cohort of patients admitted for ADHF by including different indirect markers of congestion (residual clinical congestion, brain natriuretic peptides (BNP) trajectories, hemoconcentration or diuretic response).

Methods and results: We studied the prognostic value of residual clinical congestion using an established composite congestion score (CCS) in 1572 ADHF patients. At baseline, 1528 (97.2%) patients were significantly congested (CCS ≥ 3), after 7 days of hospitalization or discharge (whichever came first), 451 (28.7%) patients were still significantly congested (CCS ≥ 3), 751 (47.8%) patients were mildly congested (CCS = 1 or 2) and 370 (23.5%) patients had no signs of residual congestion (CCS = 0). The presence of significant residual congestion at day 7 or discharge was independently associated with increased risk of re-admissions for heart failure by day 60 (HR [95% CI] = 1.88 [1.39–2.55]) and all-cause mortality by day 180 (HR [95%CI] = 1.54 [1.16–2.04]). Diuretic response provided added prognostic value on top of residual congestion and baseline predictors for both outcomes, yet gain in prognostic performance was modest.

Conclusion: Most patients with acute decompensated heart failure still have residual congestion 7 days after hospitalization. This factor was associated with higher rates of re-hospitalization and death. Decongestion surrogates, such as diuretic response, added to residual congestion, are still significant predictors of outcomes, but they do not provide meaningful additive prognostic information.

1. Introduction

Most patients needing hospital admission for decompensated heart failure present with signs and symptoms of congestion [1]. Relief of signs and symptoms of congestion (i.e. decongestion) is one of the main goals of in-hospital treatment in these patients [2,4,5].

However, adequate decongestion is often not achieved during hospital admission. In a recent post-hoc analysis of DOSE-AHF and CARESS-HF [6,7], only half of the patients were free from signs of congestion at discharge, and these patients had lower rates of death and re-hospitalization at day 60. Similarly, using a composite congestion score (Supplementary Table 1) that comprised orthopnea, jugular

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venous distension (JVD) and peripheral edema, Ambrosy et al. [7] showed that a significant proportion of patients still had residual congestion by day 7 or discharge, and these patients had increased risks of readmission and mortality.

Improved clinical assessment of residual congestion is therefore paramount, and a better understanding of the clinical course of congestion and factors associated with decongestion could play an important role towards the implementation of targeted strategies that can reduce residual congestion and, potentially, improve outcomes [8]. Nonetheless, assessment of decongestion based strictly on clinical findings may be non-sensitive. It has been shown that the change in BNP concentrations [9] and hematocrit during hospitalization [10], as surrogates markers of congestion, add significant prognostic information related with residual congestion. In addition, the metrics of diuretic response seems to be crucial in achieving a safe decongestion [8,11–13,28]. The combination of objective measures of decongestion on top of clinical assessment may help to detect lesser degrees of congestion and lead to a more accurate and safe treatment and follow-up.

We therefore aimed to: (i) characterize the clinical course of congestion (ii) evaluate predictors of residual congestion by day 7 (iii) assess the prognostic value of residual congestion by day 7 and (iiii) evaluate the prognostic value of decongestion markers along with clinical findings of residual congestion in patients hospitalized for decompensated heart failure.

2. Methods

2.1. Study population and procedures

Data from 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) were utilized in this study [14,15]. The PROTECT trial was designed to study rolofylline, an adenosine A1-receptor antagonist as a new treatment for ADHF capable of improving renal function and relieving dyspnea. Main inclusion criteria were persistent dyspnea at rest, impaired renal function, high titers of natriuretic peptides, ongoing intravenous loop diuretic therapy and enrollment within 24 h after admission [11,14]. Other inclusion and exclusion criteria have been previously described [14]. The main findings were neutral with respect to the primary outcome [11].

Clinical assessment of symptoms and signs, including orthopnea, rales, edemas, JVD, dyspnea and body weight was performed daily by clinicians until day 7 or discharge (if earlier), and day 14. Diuretic response was calculated as Δ body weight in the first 72 h/40 mg i.v. furosemide or equivalent [28]. Standard laboratory parameters were measured in a central laboratory (ICON laboratories, Farmingdale, New York).

2.2. Composite congestion score

A composite congestion score was calculated for individual patients at baseline and on days 2, 3, 4, 7 and 14 using a modified algorithm from the one described by Ambrosy et al. [7]. The composite congestion score was calculated by summing the individual scores for orthopnea (0 to 3), peripheral edema (0 to 3) and JVD (0 to 2). In contrast to the previously published composite congestion score [7], the maximum possible score was 8 points in the current study as the coding of JVD was slightly different in the PROTECT trial (Supplementary Table 2).

2.3. Surrogate markers of decongestion

We, thereafter, included several objective measurements of decongestion on top of the aforementioned clinical findings.

Changes in concentration of BNP was defined as (BNP day 7 or discharge-BNP day 1), To calculate percentage change in brain natriuretic peptide (BNP) till day 7 or day 14 from baseline, we used non-commercial plasma BNP measured using a single molecule counting technology with the Erenna® Immunosay System on a microtitre plate assay format from frozen plasma samples (Singulex Inc., Alameda, CA, USA). BNP at baseline was available in 1585 patients. BNP at day 7 was available in 1442 patients. 1248 patients had complete BNP data available on both time points.

Hemoconcentration was defined as the change in hemoglobin at discharge or day 7 and diuretic response was calculated as Δ body weight in the first 72 h/40 mg i.v. furosemide or equivalent [28]. Also, change in estimated plasma volume (delta ePVS) was evaluated [29].

2.4. Study outcomes

Two time-to-event outcomes, heart failure re-hospitalization by day 60 and all-cause mortality by day 180 were assessed. Follow-up for these analyses started at day 7, as the follow-up started before the end of the index hospitalization, we did not report death during hospitalization as these were included in the all-cause mortality by day 180 endpoint. All re-hospitalizations after index hospitalization and all causes of death through day 60 had been adjudicated by an independent clinical events committee.

2.5. Statistical analysis

Baseline clinical characteristics and standard laboratory parameters were summarized and compared in three groups based on composite congestion score on day 7 (0 = no congestion, 1–2 = mild congestion and 3–8 = significant congestion). Continuous variables were summarized as mean ± SD or median (interquartile range) as appropriate. ANOVA (for normally distributed variables) or Kruskall-Wallis (for non-normally distributed variables) tests were used for group comparisons. Categorical variables were compared among groups with the chi-square test. No imputations were performed for missing values.

The clinical course of congestion within the first 14 days of the index hospitalization was graphically assessed by plotting the proportion of patients within each of the three groups over multiple time points; baseline and 2, 3, 4, 7 and 14.

A multivariable explanatory logistic regression model was developed to identify factors independently associated with the presence of significant residual congestion by day 7. Candidate predictors were first selected based on a p-value < 20%, next utilizing an Akaike information criterion (AIC) based backward selection procedure. An internal bootstrap with 1000 replicates of the selected models was performed, testing stability of these models. List of candidate variables considered for this model are included in supplementary material. Before the implementation of the stepwise selection procedure, linearity of association between baseline parameters and residual congestion by day 7 was evaluated using fractional polynomials and appropriate transformations were performed as necessary.

Unadjusted associations between the presence of significant residual congestion by day 7 and clinical outcomes were assessed using univariable cause-specific Cox proportional hazards models. The assumption of proportional hazards was checked and satisfied. Adjusted associations were further evaluated with multivariable cause-specific Cox proportional hazards models that included previously identified predictors for the 180-day all-cause mortality outcome [15]. These encompassed baseline variables including age, peripheral edema, past heart failure hospitalization, systolic blood pressure (SBP), serum creatinine, blood urea nitrogen (BUN), albumin, sodium. For the 60-day heart failure rehospitalization outcome, a baseline model encompassing history of diabetes mellitus, percutaneous intervention (PCI), COPD, coronary artery bypass graft (CABG), heart failure hospitalization within the past year, albumin, BUN, hematocrit, sodium, edema and JVD was developed after implementation of a AIC-based backward selection procedure on a Cox regression model that included candidate predictors associated with outcome at a significance level of 20%. This procedure was performed in multiple bootstrap samples using R package *bootStepAIC*.

Unadjusted and adjusted associations between the other decongestion markers (i.e. change in BNP from baseline to day 7, diuretic response and hemoconcentration) were assessed in univariable and multivariable cause-specific proportional hazards models. Adjusted associations were evaluated in multivariable models that include the previously defined baseline predictors of each outcome and residual clinical congestion at day 7. Added prognostic value was quantified with the gain in the Harrell's C-index.

Estimates are presented with 95% confidence intervals. p-Value < 0.05 was considered statistically significant. Statistical analyses were performed with SPSS version 22.0 (IBM Corp., Armonk, NY) and R: Language and Environment for Statistical Computing, version 3.0.2. (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Baseline characteristics

Of the 2033 patients included in PROTECT, 1572 patients had complete available assessment of orthopnea, JVD and peripheral edema at day 7. Patients with missing values were comparable to patients with available measurements (see Supplementary Tables 3 & 4). The majority of patients were male (67.1%), with a mean age of 70.1 ± 11.5 years, and had a previous history of heart failure hospitalizations (94.8%). hypertension (79.4%), ischemic heart disease (69.7%), hyperlipidemia (51.9%), atrial/flutter fibrillation (54.6%) and diabetes (45.4%) (Table 1).

3.2. Evolution of composite congestion score during 14 days of baseline assessment

Nearly all patients included in the study (97.2%) had moderate to severe congestion at baseline as assessed by the composite clinical congestion score. At baseline, the median [IQR] composite congestion score was 5 [4–6]. A significant reduction in the composite congestion score was observed during the next 7 days after baseline assessment