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ORIGINAL PAPER

Prognostic value of estimated plasma volume in acute heart failure in three cohort studies

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Abstract

Aims Estimated plasma volume status (ePVS) predicts prognosis in patients with heart failure (HF). It remains unclear whether admission, discharge or change ePVS best predicts post-discharge outcome in patients with acute decompensated heart failure (ADHF).

Methods We retrospectively analyzed three cohort studies: 383 patients admitted at the Tokyo Medical University hospital, 165 patients admitted at the Centro Hospitalar do Porto and 164 patients admitted at the Nancy University Hospital (ICALOR study). ePVS at admission and at discharge as well as its change thereof were, respectively, calculated using the Duarte and Strauss formulas, both derived from hemoglobin and hematocrit ratios. Clinical variables including physical assessment, biological and echocardiographic parameters were recorded. The clinical outcome was a composite of re-hospitalization for worsening HF or all-cause mortality.

Results The primary outcomes occurred in 27.2% at 1 year (in the Tokyo cohort), 45.3% at 6 months (in the Porto cohort) and 53.9% at median terms of 298.3 days (in the ICALOR study). After adjusting for potential confounders including natriuretic peptide, discharge ePVS remained significantly associated with increased rates of composite outcome in the Tokyo and Porto cohorts and ICALOR study [hazard ratio (HR) 1.21 (1.01–1.44), $p = 0.04$; HR 1.45 (1.16–1.81), $p < 0.01$; HR 1.45 (1.16–1.81), $p < 0.01$, respectively]. In addition, a pooled analysis yielded a significant improvement in reclassification with discharge ePVS [net reclassification index 13.6% (5.9–22.7), $p = 0.004$].

Conclusions As validated in three independent ADHF cohorts, ePVS at discharge was independently associated with post-discharge clinical outcomes and improved the risk stratification of patients admitted for ADHF on top of well-established prognostic markers.

Keywords Acute decompensated heart failure · Plasma volume · Prognosis · Congestion

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Introduction

Congestion is one of the most important drivers of heart failure (HF) admission and readmission following index hospitalization [1]. Therefore, decongestive therapy is key to the in-hospital management of acutely decompensated heart failure (ADHF). Although a number of congestion variables such as physical semi-quantitative clinical scores [2], biological assays [3] and imaging parameters [4, 5] were previously associated with post-discharge morbidity and mortality, the recent guidelines have not recommended any particular standardized method with regard to congestion [6, 7].

Estimation of plasma volume using hemoglobin and hematocrit may represent a useful tool to optimize decongestive therapy which has recently gained increasing attention in the field of HF [8–10]. In contrast to invasive or technically demanding methods of quantifying plasma volume such as implanted devices [11] and radioisotope assays [12, 13], plasma volume can be estimated from a routine blood count, using the Strauss and/or Strauss-derived Duarte formula, and thus may be useful for repeat use in clinical practice [9, 10]. Estimated plasma volume status (ePVS) is independently associated with cardiovascular clinical outcomes in patients with de novo HF following acute myocardial infarction or in patients with acute HF and chronic HF [4, 10, 14, 15]. However, data regarding admission, discharge and change from admission to discharge ePVS and subsequent post-discharge outcome in patients with ADHF are currently lacking.

The aims of the present study were: (1) to assess the association between ePVS and post-discharge clinical outcomes following ADHF, and (2) to determine which ePVS measurement (i.e., either admission, discharge or change from admission to discharge) best predicts post-discharge outcomes following ADHF. For this purpose, three independent cohort studies of ADHF patients were analyzed stemming from different patient populations, namely a Cardiology department in Japan and France and an Emergency department in Portugal.

Methods

Studied population

Three independent cohort studies were used for the present analysis:

The Tokyo cohort included patients with ADHF admitted to critical care units or cardiac units of the Tokyo Medical University Hospital, Japan, from August 2009 to December 2015. Comorbidities, medications (at discharge), physical assessment, biological findings including brain natriuretic peptide (BNP) and chest X-ray at both admission and discharge and echocardiographic data from the physical exam performed during the hospitalization were collected retrospectively.

The Porto cohort retrospectively included all patients with ADHF admitted to the emergency room of the tertiary University Hospital Centro Hospitalar do Porto, Portugal [16] from January 2012 to December 2014. All enrolled patients were admitted for ADHF/pulmonary edema. Underlying diseases, medications, physical assessment, biological findings including N-terminal pro-brain natriuretic peptide (NT-proBNP) at both admission and discharge and echocardiography-based left ventricular ejection fraction (LVEF) were recorded.

The ICALOR Study was based on the prospective Insuffisance CARdiaque en LORraine (ICALOR) program enrolling consecutive patients with ADHF in the Institut Lorrain du Coeur et des Vaisseaux in France, from January 2010 to December 2013 as previously described [17]. Of 460 patients with ADHF in this database, 164 patients had complete data with regard to biological findings at admission and echocardiographic assessment during hospital stay. Other clinical data included demographic characteristics, comorbidities and physical examination and blood pressure.

Obesity was defined using body mass index of 30 kg/m^2 or higher. Estimated glomerular filtration rate was determined according to the Modification of Diet in Renal Disease 4-variable formula [18]. In the Tokyo cohort, ADHF was clinically defined based on the presence of congestive signs and symptoms [1] by the treating cardiologists, while in the Porto cohort and ICALOR study, ADHF was diagnosed according to the European Society of Cardiology (ESC) criteria [7]. Patients with acute myocardial infarction, cardiogenic shock, severe sepsis and hemodialysis maintenance were excluded from the analysis reported herein. Each cohort study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Committees.

Outcomes

The primary outcome was a composite of re-hospitalization for worsening HF or all-cause mortality (extracted from electronic health records or database).

Estimated plasma volume status

Estimated plasma volume status at both admission and discharge was calculated from the Strauss-derived Duarte formula using hematocrit and hemoglobin values [10]:

$$\text{ePVS} = (100 - \text{hematocrit}\ (\%))/\text{hemoglobin}\ (\text{g/dl}),$$

while change ePVS was calculated using the Strauss formula [19]:

$$\Delta \text{ePVS} = 100 \times \frac{\text{hemoglobin (g/dl) (before)}}{\text{hemoglobin (after)}} \times \frac{1 - \text{hematocrit (\%) (after)}}{1 - \text{hematocrit (before)}} - 100.$$

Statistical analysis

Data are expressed as mean ± SD for normally distributed variables and as median with interquartile range (IQR) for non-normally distributed data. Categorical data are expressed as numbers (%). Group differences were assessed using Kruskal–Wallis test for continuous variables and Chi square for categorical variables, while unadjusted correlation was expressed using Spearman's correlation coefficient. For descriptive purposes, the cohorts were respectively categorized according to discharge ePVS tertiles.

Linear regression analyses and binary logistic regression analyses were performed to assess the associations of clinical variables with continuous ePVS and upper tertile of ePVS at both admission and discharge. Survival probabilities were estimated using the Kaplan–Meier method and plotted as survival curves. Cox proportional hazards model was used to obtain unadjusted and covariate adjusted hazard ratios (HRs). Proportional hazards assumptions were verified with covariates for adjusted HRs selected from clinically relevant variables including age, sex, coronary artery disease, LVEF, blood urea nitrogen (BUN), estimated glomerular filtration rate (eGFR) and natriuretic peptides.

The increase in discriminative value to predict 1-year composite outcomes following the addition of ePVS variables (admission, discharge and change) in survival models on top of a baseline set of covariates including age, sex, LVEF, BUN, eGFR and natriuretic peptides were evaluated using continuous NRI and IDI in the survIDINRI package [18]. In addition, after matching time to a composite outcome in each cohort (censoring data in the Porto cohort changed to 1 year), the three cohort studies were integrated to assess the association between discharge ePVS as continuous variable and composite outcome in subgroup analysis as well as between additional ePVS variables and risk reclassification.

A p value < 0.05 was considered significant. Statistical analyses were performed using the SPSS package version 24.0 (Chicago, L, USA) and the R software (R Foundation for Statistical Computing).

Results

Patient characteristics

In the Tokyo and Porto cohorts and ICALOR study, a total of 383, 165 and 164 patients were, respectively, included (Tables 1 and 2). In the three cohorts, half of the patients were male. Patients were younger in the Tokyo cohort (71.3 ± 13.5 vs. 76.2 ± 10.3 vs. 72.3 ± 14.7 years) and had lower LVEF (39.8 ± 17.0% vs. 43.8 ± 11.1% vs. 40.3 ± 17.1%). Obesity was infrequent in the Tokyo cohort (< 10%), whereas 50.9% and 26.6% of the patents were obese in the Porto cohort and ICALOR study. New York Heart Association (NYHA) class was III or greater in 80% of cases in both the Tokyo cohort and ICALOR study, while constituting one-third in the Porto cohort. Median length of hospital stay was 18.0 days (13.0–25.0) in the Tokyo cohort, 11.0 days (7.0–15.0) in the Porto cohort and 10.0 days (7.0–15.0) in ICALOR study.

Factors associated with estimated plasma volume at discharge

In the Tokyo cohort, older age and higher LVEF were significantly associated with higher ePVS in multivariable analyses (Table 3, Supplementary Table 1). Conversely, analyses in the ICALOR study showed an association of lower eGFR and prescription of aldosterone antagonist with higher ePVS. In the Porto cohort, higher discharge NT-proBNP was significantly associated with higher ePVS in the logistic regression model.

Associations between ePVS variables and clinical outcomes

During follow-up, the median duration of the follow-up period was 298.3 (77.0–392.5 days) in the ICALOR study. The primary outcome occurred in 28.5% ($N = 109$), 50.3% ($N = 83$) and 53.7% ($N = 88$) of patients in the Tokyo, Porto and ICALOR studies, respectively. In the Tokyo and Porto cohort studies, the upper tertile of discharge ePVS exhibited higher rates of the composite outcome ($p < 0.01$ in both cohorts with the log-rank test, comparatively to $p = 0.09$ in the ICALOR study) (Fig. 1).

In the three cohort studies, higher discharge ePVS values (either used as a continuous or categorical variable) were significantly associated with increased rates of the composite outcome in univariable Cox regression analysis (Table 4). After adjusting for potential confounders, discharge ePVS remained significantly associated with the composite outcome in the Tokyo and Porto cohort studies ($p = 0.01$ and $p < 0.01$ when used as a continuous variable, $p < 0.01$ and $p = 0.04$ when used as a categorical variable, respectively) and in the ICALOR study ($p < 0.049$ when used as a categorical variables). In the Porto cohort, admission ePVS as a continuous variable was also significantly associated with the composite outcome in multivariable analysis. Similarly, when considering worsening HF re-hospitalization as

Table 1 Overall patient characteristics in the three cohort studies

	Tokyo cohort ($n=383$)	Porto cohort ($N=165$)	ICALOR cohort ($n=164$)
Age, years	71.3 ± 13.5	76.2 ± 10.3	72.3 ± 14.7
Male, *n* (%)	245 (64.8%)	84 (50.9%)	92 (55.8%)
Obesity, *n* (%)	28 (8.0%)	85 (51.8%)	33 (26.6%)
Medical history			
Coronary artery disease, *n* (%)	93 (24.3%)	93 (56.4%)	50 (33.3%)
Atrial fibrillation, *n* (%)	174 (45.4%)	80 (47.1%)	/
Hypertension, *n* (%)	279 (72.8%)	145 (87.9%)	49 (32.7%)
Diabetes mellitus, *n* (%)	141 (36.8%)	89 (53.9%)	56 (33.9%)
NYHA ≥ III admission, *n* (%)	304 (80.2%)	49 (29.7%)	93 (89.4%)
Left ventricular ejection fraction, %	39.5 ± 17.1	43.8 ± 11.1	40.3 ± 17.1
Systolic blood pressure, mmHg	143.6 ± 33.2	163.0 ± 33.1	118.7 ± 20.5
Heart rate, bpm	96.5 ± 26.9	108.6 ± 28.2	74.6 ± 14.3
Laboratory data			
Admission hemoglobin, g/dl	12.5 ± 2.4	12.5 ± 2.2	12.1 ± 1.9
Admission hematocrit, %	37.9 ± 6.9	38.7 ± 5.9	38.0 ± 5.5
Admission sodium, mEq/l	141.1 ± 3.8	137.5 ± 5.1	139.6 ± 3.8
Discharge eGFR, ml/min/1.73 m^2	55.1 ± 22.7	62.2 ± 31.1	53.4 ± 23.0
Admission BNP, pg/ml	590 (332–1170)	/	855 (450–1400)
Admission NT-pro BNP, pg/ml	/	3714 (1498–7433)	/
Estimated plasma volume, dl/g			
Admission	5.30 ± 1.81	5.13 ± 1.42	5.33 ± 1.32
Discharge	5.10 ± 1.50	5.53 ± 1.36	5.20 ± 1.31
Change from admission to discharge, %	-0.04 ± 2.91	0.33 ± 8.58	-0.06 ± 2.35
Medications, discharge			
ACE inhibitor/ARB, *n* (%)	291 (77.8%)	98 (59.4%)	136 (84.0%)
Beta blocker, *n* (%)	316 (84.5%)	109 (66.1%)	133 (81.6%)
Aldosterone antagonist, *n* (%)	280 (74.9%)	49 (29.7%)	30 (18.4%)
Furosemide dose, mg	20.0 (0.0–20.0)	80.0 (40.0–80.0)	80.0 (40.0–80.0)
Thiazide diuretics, *n* (%)	14 (3.7%)	2 (1.2%)	10 (6.1%)
Tolvaptan, *n* (%)	33 (8.6%)	0 (0%)	0 (0%)

Values are mean ± SD, *n* (%) or median (25th–75th percentile)

HF heart failure, *NYHA* New York Heart Association, *eGFR* estimated glomerular filtration rate, *BNP* brain natriuretic peptide, *NT-pro BNP* N-terminal pro-brain natriuretic peptide, *ACE inhibitor* angiotensin converted enzyme inhibitor, *ARB* angiotensin II receptor blockers

outcome, discharge ePVS was associated with outcomes in both Tokyo and Porto cohort studies, while in ICALOR study, discharge ePVS tended to be associated with HF re-hospitalization (Supplementary Table 3).

When considering subgroups from the pooled data of the three cohort studies, no significant interactions were identified between discharge ePVS as a continuous variable and age, BMI, anemia, eGFR or LVEF for the composite outcome (Fig. 2). Importantly, a significant interaction between ePVS and NYHA class was identified although the association of greater ePVS with higher event rates remained significant both in patients with NYHA II and NYHA III/IV.

Improvement in reclassification associated with ePVS variables

After merging the three cohort studies, the addition of discharge ePVS both as continuous and categorical variables remained associated with a significant improvement in reclassification to predict a composite outcome [NRI 13.6 (5.9–22.7), $p=0.004$ and IDI 3.4 (1.1–6.6), $p<0.001$ as a continuous variable and NRI 20.3 (4.7–27.8), $p=0.01$ and IDI 2.0 (0.4–4.6), $p<0.001$ as categorical variable) (Fig. 3). Overlapping results were also found in the Tokyo and Porto cohort studies (Supplementary Table 4).

Table 2 Congestive parameters according to discharge-estimated plasma volume tertile in the three cohort studies

	Tokyo cohort				Porto cohort				ICALOR study			
	First [ePVS ≤ 4.23] (*n* = 128)	Second [4.23 < ePVS ≤ 5.67] (*n* = 128)	Third [ePVS > 5.67] (*n* = 127)	*p* value	First [ePVS ≤ 4.82] (*n* = 55)	Second [4.82 < ePVS ≤ 6.10] (n = 54)	Third [ePVS > 6.10] (*n* = 56)	*p* value	First [ePVS ≤ 4.48] (*n* = 55)	Second [4.48 < ePVS ≤ 5.78] (*n* = 54)	Third [ePVS > 5.78] (*n* = 55)	*p* value
LVEF, %	33.5 ± 15.4	40.2 ± 16.4	44.8 ± 17.7	**< 0.001**	43.9 ± 11.3	42.7 ± 11.3	44.8 ± 10.8	0.53	35.1 ± 16.3	40.5 ± 17.5	45.2 ± 16.2	**< 0.001**
PASP, mmHg	40.2 ± 17.7	39.9 ± 18.5	39.7 ± 18.5	0.99	/	/	/	/	32.1 ± 9.9	34.2 ± 10.9	41.0 ± 15.2	**0.008**
IVC, mm	18.4 ± 5.2	17.4 ± 5.7	17.4 ± 5.5	0.34	/	/	/	/	24.0 ± 5.4	20.7 ± 7.1	22.3 ± 6.0	**0.039**
Admission parameters												
NYHA III + IV, *n* (%)	101 (78.9%)	99 (79.2%)	104 (82.5%)	0.72	16 (29.1%)	15 (27.8%)	18 (32.1%)	0.88	32 (91.4%)	33 (91.7%)	28 (84.8%)	0.59
Rales, *n* (%)	60 (46.9%)	66 (52.8%)	81 (64.3%)	**0.018**	/	/	/	/	31 (63.3%)	36 (72.0%)	32 (65.3%)	0.63
S3, *n* (%)	80 (62.5%)	80 (64.0%)	85 (67.5%)	0.7	32 (58.2%)	30 (55.6%)	33 (60.0%)	0.89	/	/	/	/
Pedal edema, *n* (%)	73 (57.0%)	62 (49.6%)	59 (46.8%)	0.24	/	/	/	/	40 (74.1%)	38 (84.4%)	37 (75.5%)	0.42
Systolic BP, mmHg	140.1 ± 32.7	142.0 ± 34.4	148.8 ± 32.1	**0.037**	163.4 ± 32.6	164.1 ± 31.1	161.5 ± 35.8	0.87	114.5 ± 16.0	117.7 ± 19.4	124.4 ± 24.7	0.18
Sodium, mEq/l	141.0 ± 3.5	141.4 ± 4.1	140.9 ± 3.8	0.28	138.0 ± 4.5	137.8 ± 5.0	136.8 ± 5.7	0.52	139.7 ± 3.0	139.2 ± 3.9	140.0 ± 4.3	0.66
BUN, mg/dl	20.1 ± 8.8	23.2 ± 11.9	30.0 ± 16.4	**< 0.001**	26.9 ± 18.3	29.8 ± 16.3	41.2 ± 27.8	**0.002**	32.2 ± 17.3	35.0 ± 19.3	35.0 ± 17.5	0.43
eGFR, ml/min/1.73 m^2	64.3 ± 21.7	56.0 ± 23.1	44.5 ± 26.8	**< 0.001**	64.3 ± 30.4	57.6 ± 30.3	51.1 ± 34.2	0.017	63.1 ± 22.7	53.6 ± 21.3	43.1 ± 17.8	**< 0.001**
BNP, pg/ml	503 (314–1008)	620 (309–1180)	709 (399–1242)	0.079	/	/	/	/	856 (341–1466)	718 (450–1166)	1089 (586–1438)	0.26
NT-pro BNP, pg/ml	/	/	/	/	1812 (704–4338)	4072 (1875–8169)	6114 (3331–10,969)	**< 0.001**	/	/	/	/
ePVS, dl/g	3.8 ± 0.7	5.2 ± 1.5	6.9 ± 1.6	**< 0.001**	3.9 ± 0.7	5.1 ± 0.9	6.4 ± 1.3	**< 0.001**	4.1 ± 0.7	5.3 ± 0.8	6.6 ± 1.0	**< 0.001**
Discharge parameters												
Pedal edema, *n* (%)	7 (5.7%)	11 (10.0%)	16 (16.2%)	**0.038**	11 (21.2%)	6 (13.3%)	17 (34.0%)	0.053	/	/	/	/
Lung congestion, *n* (%)	/	/	/	/	12 (33.3%)	13 (32.5%)	16 (45.7%)	0.43	/	/	/	/
Pleural effusion, *n* (%)	/	/	/	/	4 (7.7%)	9 (19.1%)	8 (16.0%)	0.23	/	/	/	/
Sodium, mEq/l	139.9 ± 3.0	140.3 ± 3.0	139.6 ± 3.6	0.41	139.7 ± 4.5	139.2 ± 3.7	140.1 ± 4.6	0.62	/	/	/	/
BUN, mg/dl	20.3 ± 9.2	24.1 ± 12.7	32.4 ± 18.1	**< 0.001**	29.1 ± 17.0	32.1 ± 21.4	37.8 ± 23.9	**0.043**	31.0 ± 14.7	35.6 ± 22.2	41.8 ± 21.9	**< 0.001**
eGFR, ml/min/1.73 m^2	61.0 ± 19.6	52.6 ± 21.3	39.7 ± 22.1	**< 0.001**	68.9 ± 28.6	64.9 ± 33.4	52.8 ± 29.3	0.012	65.2 ± 23.0	54.0 ± 21.8	41.4 ± 17.8	**< 0.001**
BNP, pg/ml	207 (121–417)	309 (136–454)	377 (164–611)	**< 0.001**	/	/	/	/	/	/	/	/
NT-pro BNP, pg/ml	/	/	/	/	931 (498–2236)	3474 (1329–7486)	3044 (1658–7924)	**< 0.001**	/	/	/	/
ePVS, dl/g	3.5 ± 0.5	4.9 ± 0.4	6.9 ± 0.8	**< 0.001**	4.1 ± 0.5	5.4 ± 0.3	7.1 ± 0.8	**< 0.001**	3.8 ± 0.5	5.1 ± 0.4	6.7 ± 0.7	**< 0.001**

Values are mean ± SD, *n* (%) or median (25th–75th percentile)

Values in bold represent significant values ($p < 0.05$)

ePVS estimated plasma volume status, *LVEF* left ventricular ejection fraction, *PASP* pulmonary artery systolic pressure, *IVC* inferior vena cava, *NYHA* New York Heart Association, *BP* blood pressure, *BUN* blood urea nitrogen, *eGFR* estimated glomerular filtration rate, *BNP* brain natriuretic peptide, *NT-proBNP* N-terminal pro-brain natriuretic peptide

Table 3 Association between clinical characteristics and discharge-estimated plasma volume in the three cohort studies in logistic regression analysis

	Tokyo cohort				Porto cohort				ICALOR study			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Age, years	1.06 (1.04–1.08)	**< 0.001**	1.03 (1.00–1.07)	**0.04**	1.02 (0.99–1.05)	0.31	/	/	1.05 (1.02–1.08)	**0.001**	1.01 (0.97–1.04)	0.80
Male, *n*	0.43 (0.28–0.67)	**< 0.001**	0.58 (0.31–1.09)	0.09	0.61 (0.32–1.17)	0.61	/	/	0.40 (0.21–0.78)	**0.007**	0.56 (0.24–1.29)	0.17
Obesity, *n*	0.24 (0.07–0.82)	**0.02**	0.55 (0.11–2.69)	0.46	0.80 (0.42–1.53)	0.51	/	/	0.72 (0.29–1.79)	0.48	/	/
Coronary artery disease, *n*	2.10 (1.29–3.39)	**0.002**	1.29 (0.63–2.63)	0.49	1.31 (0.68–2.52)	0.42	/	/	2.56 (1.25–5.24)	**0.01**	2.63 (1.14–6.07)	**0.02**
LVEF, % (per 5%)	1.15 (1.08–1.22)	**< 0.001**	1.12 (1.01–1.23)	**0.02**	1.06 (0.92–1.23)	0.42	/	/	1.14 (1.03–1.26)	**0.01**	1.03 (0.91–1.17)	0.61
Leg edema discharge, *n*	2.30 (1.12–4.73)	**0.02**	1.38 (0.58–3.30)	0.47	2.42 (1.11–5.32)	**0.03**	1.79 (0.72–4.50)	0.21	3.68 (0.65–21.00)	0.14	/	/
SBP discharge, mmHg (per 10 mmHg)	1.22 (1.09–1.38)	**< 0.001**	1.06 (0.90–1.26)	0.48	/	/	/	/	/	/	/	/
Sodium discharge, mEq/l	0.95 (0.89–1.01)	0.11	/	/	1.04 (0.96–1.12)	0.34	/	/	/	/	/	/
BUN discharge, mg/dl	1.05 (1.03–1.07)	**< 0.001**	1.02 (0.99–1.06)	0.17	1.02 (1.00–1.03)	**0.048**	0.99 (0.96–1.02)	0.38	1.02 (1.00–1.04)	**0.01**	0.99 (0.97–1.01)	0.45
eGFR discharge, ml/min/1.73 m^2	0.96 (0.95–0.97)	**< 0.001**	0.99 (0.97–1.02)	0.49	0.98 (0.97–0.99)	**0.007**	/	/	0.96 (0.94–0.98)	**< 0.001**	0.97 (0.94–0.99)	**0.02**
BNP discharge, pg/ml (per 100 pg/ml)	1.06 (1.02–1.11)	**0.004**	1.08 (0.99–1.17)	0.08	/	/	/	/	/	/	/	/
NT-pro BNP discharge, pg/ml (per 1000 pg/ml)	/	/	/	/	1.04 (1.00–1.08)	**0.03**	0.98 (0.96–0.99)	**0.02**	/	/	/	/
Aldosterone antagonist, *n*	0.55 (0.34–0.88)	**0.01**	1.05 (0.48–2.30)	0.90	1.19 (0.59–2.40)	0.62	/	/	0.11 (0.03–0.49)	**0.004**	0.18 (0.04–0.87)	**0.03**
Furosemide discharge, mg (per 10 mg)	1.18 (1.07–1.31)	**0.001**	1.05 (0.90–1.22)	0.57	1.02 (0.94–1.09)	0.71	/	/	1.26 (0.72–2.20)	0.41	/	/

Upper overall tertile of discharge ePVS was defined as ≥ 5.67 dl/g in the Tokyo cohort, ≥ 6.10 dl/g in the Porto cohort and ≥ 5.78 dl/g in ICALOR study

Values in bold represent significant values ($p < 0.05$)

LVEF left ventricular ejection fraction, *SBP* systolic blood pressure, *BUN* blood urea nitrogen, *eGFR* estimated glomerular filtration rate, *BNP* brain natriuretic peptide, *NT-proBNP* N-terminal pro-brain natriuretic peptide

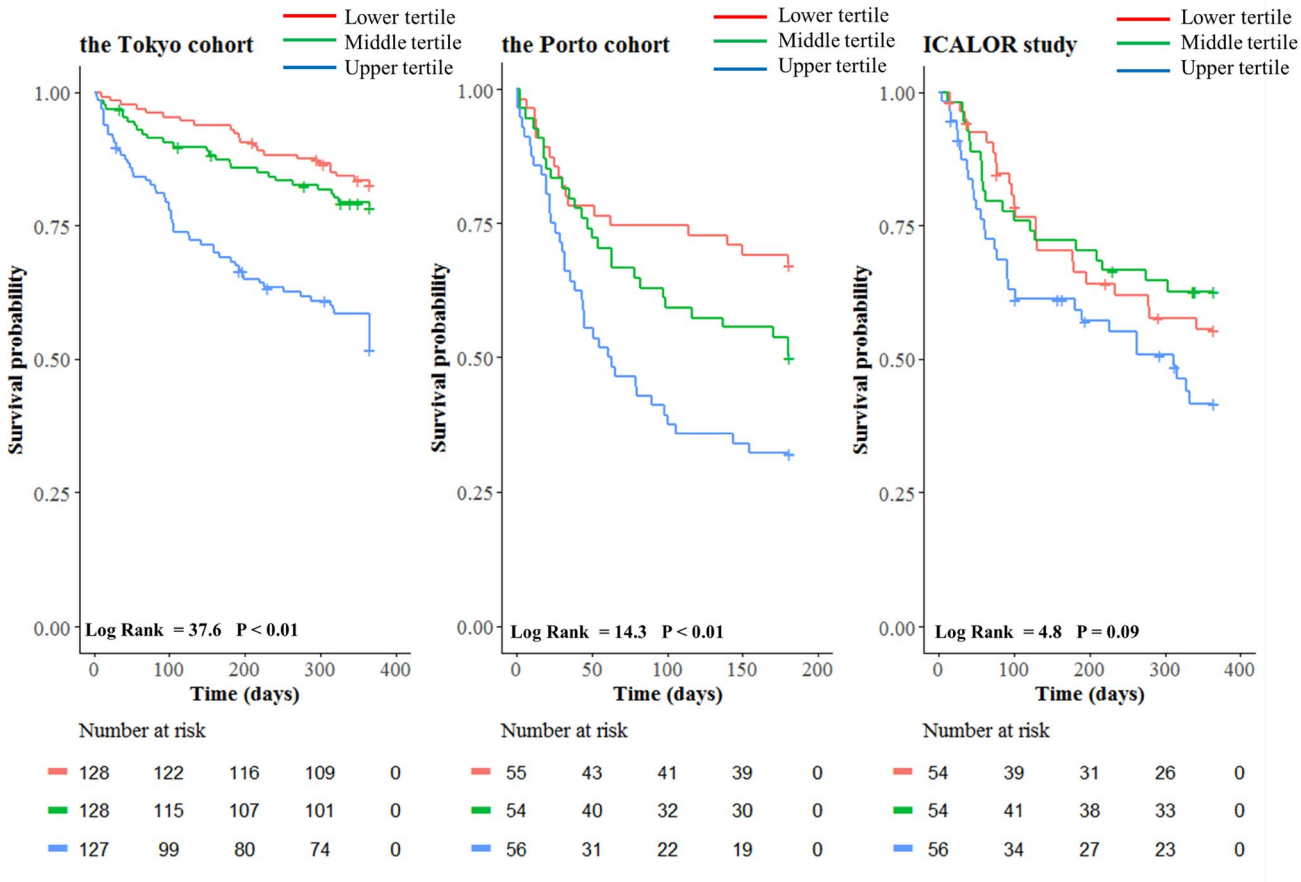

Fig. 1 Survival curves for the composite outcome of all-cause mortality and heart failure re-hospitalization according to estimated plasma volume discharge tertile in the three cohort studies. Estimated plasma volume status (ePVS): (Tokyo cohort) lower tertile: ≤ 4.23 dl/g; middle tertile: 4.23–5.67 dl/g; upper tertile: > 5.67 dl/g (porto cohort), lower tertile: ≤ 4.82 dl/g; middle tertile: 4.82–6.10 dl/g; upper tertile: > 6.10 dl/g (ICALOR study). Lower tertile: ≤ 4.48 dl/g; middle tertile: 4.48–5.78 dl/g; upper tertile: > 5.78 dl/g

Discussion

The results of the three independent cohort studies used for the present analysis showed that discharge ePVS in patients with ADHF was the most informative variable in predicting post-discharge outcomes, independently of traditional clinical variables (e.g., age, ischemic etiology, natriuretic peptides, eGFR and LVEF); of note, discharge ePVS performed better than admission ePVS and change ePVS. These findings, concordant in three independent cohorts, emphasize the prognostic importance of residual congestion in AHF patients as assessed by discharge ePVS beyond and above routine clinical assessment.

ePVS as a prognostic factor in ADHF patients

The present study provides evidence for the strong association between ePVS and post-discharge outcome in ADHF, in concordance with prior publications which focused on patients with chronic or de novo HF. Our group had notably studied the association of short-term changes in ePVS using the Strauss formula and instantaneous ePVS with clinical outcomes in patients with left ventricular systolic dysfunction following acute myocardial infarction from the EPHESUS trial which showed that a higher instantaneous ePVS was significantly associated with poorer outcome independently of routine clinical variables [10]. Ling et al. furthermore reported that higher ePVS (using the Hakim formula which partially relies on dry weight) was significantly associated with poorer outcome even after adjusting for BNP in 5002 patients with chronic HF from the Valsartan in Heart Failure Trial (Val-HeFT) [15]. However, exploring the prognostic value of ePVS measurements in ADHF patients has not been well-established. Other important measurements of congestion, namely echocardiography and bioelectrical impedance [20, 21], may adequately help tailor fluid management in ADHF patients [22]. In addition, admission ePVS using the Hakim formula has previously been associated with post-discharge outcome in ADHF patients [14]. However, dry weight is difficult to ascertain in ADHF, even

Table 4 Univariable and multivariable cox proportional hazard models for a composite outcome of all-cause mortality and heart failure re-hospitalization in the three cohort studies

Tokyo cohort	Composite outcome			
	Univariable analysis		Multivariable analysis	
	HR (95% CI)	*p* value	AHR (95% CI)	*p* value
ePVS admission				
Continuous	1.23 (1.14–1.33)	**< 0.01**	1.11 (0.99–1.25)	0.07
Upper tertile	2.45 (1.68–3.57)	**< 0.01**	1.36 (0.82–2.23)	0.23
ePVS discharge				
Continuous	1.42 (1.26–1.60)	**< 0.01**	1.25 (1.06–1.48)	**0.01**
Upper tertile	3.05 (2.09–4.44)	**< 0.01**	2.15 (1.31–3.53)	**< 0.01**
ePVS change				
Continuous	1.02 (0.93–1.11)	0.75	0.98 (0.90–1.08)	0.69
Lower tertile	0.86 (0.57–1.30)	0.48	0.92 (0.46–1.86)	0.82
Porto cohort				
ePVS admission				
Continuous	1.24 (1.08–1.42)	**< 0.01**	1.26 (1.01–1.56)	**0.04**
Upper tertile	1.96 (1.27–3.05)	**< 0.01**	1.69 (0.97–2.95)	0.06
ePVS discharge				
Continuous	1.45 (1.24–1.70)	**< 0.01**	1.42 (1.18–1.70)	**< 0.01**
Upper tertile	2.12 (1.38–3.28)	**< 0.01**	1.70 (1.03–2.80)	**0.04**
ePVS change				
Continuous	1.00 (0.98–1.03)	0.92	0.99 (0.96–1.03)	0.93
Lower tertile	0.85 (0.53–1.35)	0.48	0.76 (0.44–1.33)	0.34
ICALOR study				
ePVS admission				
Continuous	1.11 (0.95–1.30)	0.18	1.11 (0.92–1.34)	0.29
Upper tertile	1.42 (0.92–2.19)	0.11	1.30 (0.79–2.16)	0.31
ePVS discharge				
Continuous	1.22 (1.03–1.45)	**0.02**	1.21 (0.99–1.48)	0.06
Upper tertile	1.87 (1.22–2.89)	**< 0.01**	1.68 (1.00–2.83)	**0.049**
ePVS change				
Continuous	0.99 (0.91–1.09)	0.95	1.00 (0.90–1.11)	0.99
Lower tertile	0.99 (0.64–1.55)	0.99	0.99 (0.61–1.64)	0.98

Multivariable analysis was adjusted for age, sex, the presence of CAD and LVEF, BUN and eGFR atriuretic peptides (BNP in the Tokyo and ICALOR cohort studies and NT-pro BNP in the Porto study)

(Tokyo cohort) Upper tertile (admission): ≥ 5.82 dl/g; Upper tertile (discharge) ≥ 5.67 dl/g; Lower tertile (change) ≤ − 0.30 dl/g

(Porto cohort), Upper tertile (admission): ≥ 5.71 dl/g; Upper tertile (discharge) ≥ 6.10 dl/g; Lower tertile (change) ≤ − 1.37 dl/g

(ICALOR study) Upper tertile (admission): ≥ 5.85 dl/g; Upper tertile (discharge) ≥ 5.78 dl/g; Lower tertile (change) ≤ − 0.80 dl/g

Values in bold represent significant values ($p < 0.05$)

AHR adjusted hazard ratio, *CAD* coronary artery disease, *LVEF* left ventricular ejection fraction, *BUN* blood urea nitrogen, *eGFR* estimated glomerular filtration rate, *BNP* brain natriuretic peptide, *NT-proBNP* N-terminal pro-brain natriuretic peptide

at the end of hospitalization, as patients can have residual systemic congestion (i.e., have yet to reach their dry weight) [23]. Therefore, in the present analysis, we used the Duarte and Strauss formulas without dry weight for their respective calculation and found that ePVS, which is a simple and non-invasive plasma volume estimation using hemoglobin and hematocrit, was a strong predictor of post-discharge clinical outcomes, on top of traditional clinical assessments (e.g., LVEF, eGFR and natriuretic peptide). Interestingly, in the subgroup analyses, discharge ePVS did not interact with anemia although i did interact with NYHA functional class in patients with ADHF. This finding strengthens the

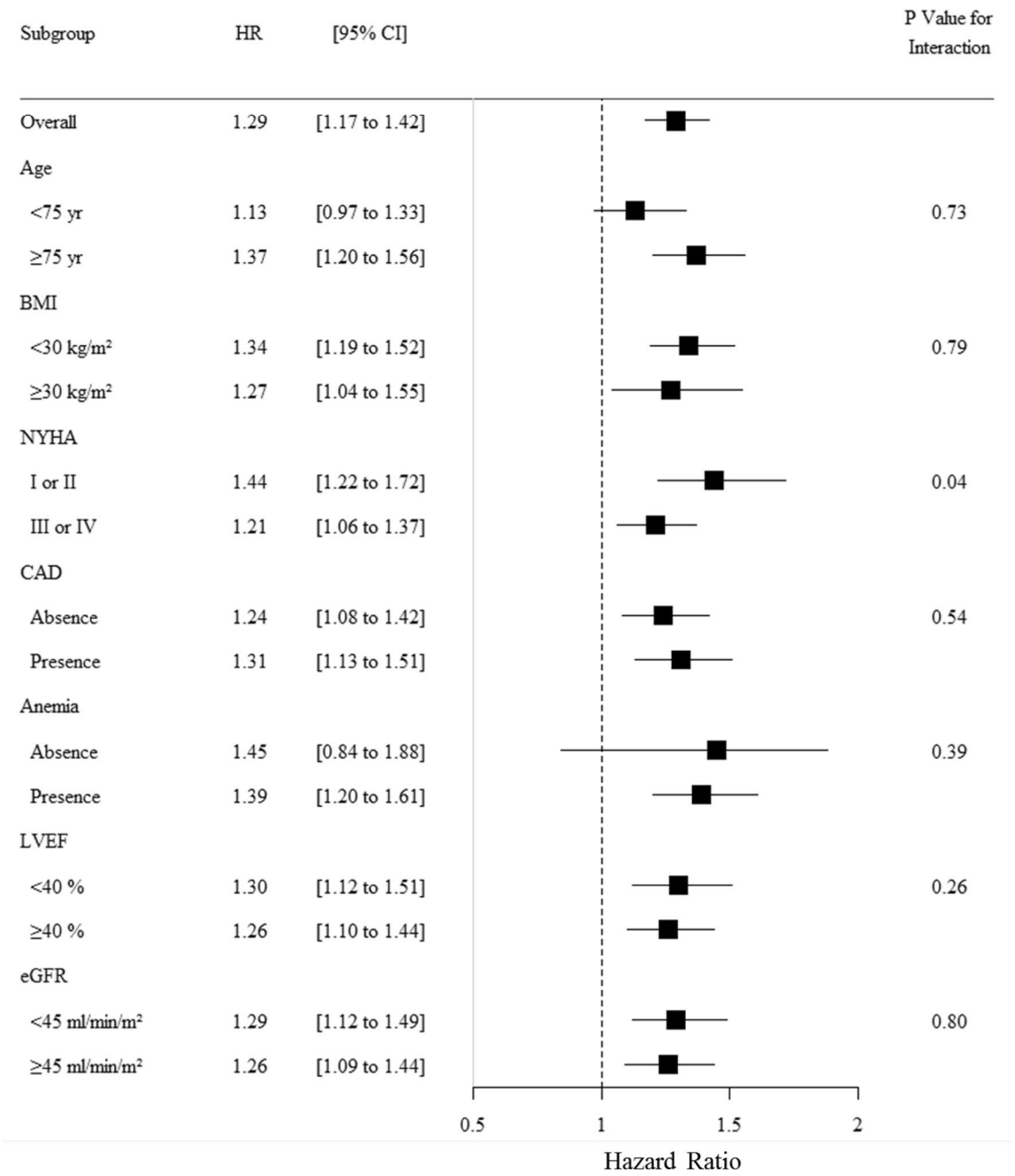

Fig. 2 Subgroup analyses for associations between estimated plasma volume status at discharge and the composite outcome of all-cause mortality and heart failure re-hospitalization from the pooled data of the three cohort studies. Discharge ePVS was analyzed as a continuous variable. Cox proportional hazards model stratified according to subgroups were performed after adjusting for age, sex, the presence of CAD and LVEF, BUN, eGFR and natriuretic peptides (BNP in the Tokyo and ICALOR cohort studies and NT-pro BNP in the Porto study) at discharge. *ePVS* estimated plasma volume status, *HR* hazard ratio, *CI* confidential interval, *CAD* coronary artery disease, *LVEF* left ventricular ejection fraction, *BUN* blood urea nitrogen, *eGFR* estimated glomerular filtration rate, *BNP* brain natriuretic peptide, *NT-proBNP* N-terminal pro-brain natriuretic peptide

notion that ePVS could provide prognostic implication without influence of anemic status as well as reflect the severity of congestion. Indeed, patients with NYHA class III/IV are intrinsically at high risk mostly because of residual congestion and ePVS has less prognostic power in this more homogenously congested subgroup.

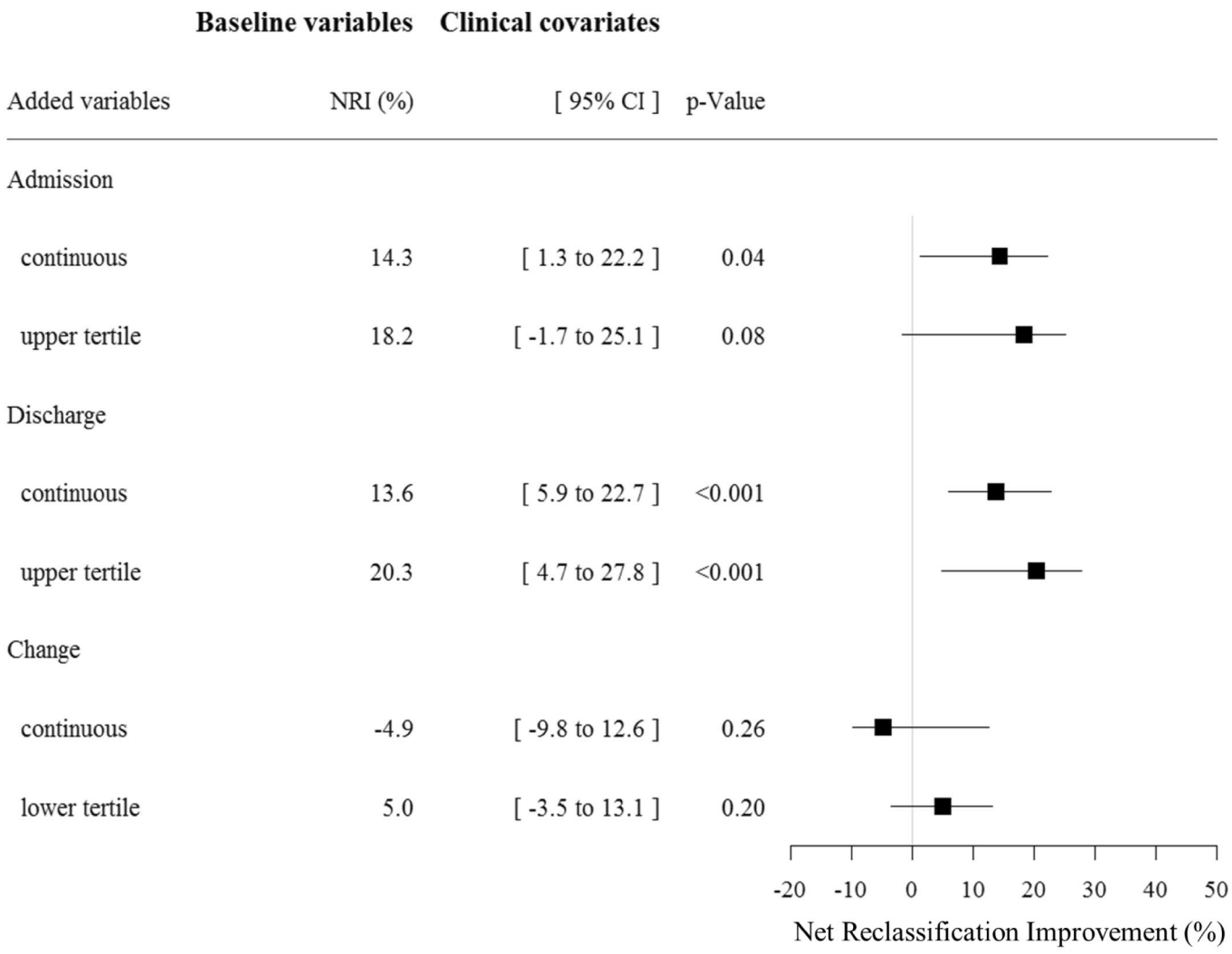

Fig. 3 The additional prediction models for the composite outcome of all-cause mortality and heart failure re-hospitalization from the pooled data of the three cohort studies. Survival models on a baseline set of top* of clinical covariates including age, LVEF, eGFR §, BUN § and natriuretic peptides (BNP in the Tokyo and ICALOR cohort studies and NT-pro BNP in the Porto study) §. *Dichotomized variables were determined as follows; age of (median) in years, LVEF of 40%, eGFR of (median) in ml/min/1.73 m^2, BUN of (median) in mg/dL and natriuretic peptides of (median) in pg/mL. § BUN, eGFR and natriuretic peptides were analyzed in accordance with the timing of ePVS, while change ePVS was analyzed using these variables at discharge. *NRI* net reclassification improvement, *CI* confidential interval, *LVEF* left ventricular ejection fraction, *eGFR* estimated glomerular filtration rate, *BUN* blood urea nitrogen, *BNP* brain natriuretic peptide, *NT-proBNP* N-terminal pro-brain natriuretic peptide

Prognostic performance of discharge ePVS as opposed to admission or change ePVS

Numerous congestion variables have been reported to be associated with post-discharge prognosis in ADHF [2, 4, 24]. However, the impact of the timing of congestion assessment on its usefulness remains a matter of debate. Indeed, changes in congestion and residual congestion have both been reported to have prognostic value. There is obviously interplay between these two approaches since the best means to obtain low levels of residual congestion is to observe substantial decongestion during hospital stay. Using natriuretic peptides, both changes in congestion and residual congestion have been reported to be associated with clinical outcomes [25, 26]. With regard to lung ultrasound-derived congestion assessment, our group similarly reported the association of residual lung congestion with the post-discharge risk for re-hospitalization or death in patients with ADHF [4]. In addition, a sub-analysis of the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) trial reported that hemoconcentration (defined as an increase in hematocrit, albumin and total protein values) was associated with a lower risk of mortality [27].

To the best of our knowledge, this is the first study to compare the prognostic performance of ePVS at different time points of hospital stay in patients with ADHF, thus enabling the determination of the relative contribution of each variable in clinical outcome. Importantly, in the three cohorts, only discharge ePVS was found to be associated with a composite outcome. Conversely, admission ePVS was significantly associated with outcome only in the Porto cohort and not in the Tokyo cohort and ICALOR study. One possible explanation for the discrepancy of prognostic information may be differences in clinical characteristics; patients from the Porto cohort were more likely to have obesity, compared to those in the Tokyo cohort and ICALOR study (51.8% vs. 8.0% vs. 26.6%, respectively) and coronary artery disease (56.6% vs. 24.3% vs. 33.3%), and also had mild HF symptoms at admission (NYHA class III or greater, 29.7% vs. 80.2% vs. 89.4%). Furthermore, change ePVS was not significantly associated with outcome in univariable analysis in either of the three cohorts. This result is in contrast to previous studies which reported a fair prognostic value of short-term changes in hemoglobin [28] and hematocrit [29] during ADHF hospitalization. Because the prognostic value of hemoconcentration/decongestion can be time-dependent [30], the longer length of hospital stay in our cohorts may have affected the prognostic value of change ePVS; indeed, previous studies [median length of hospital stay, 8.0 days (4.0–11.0) in the EVEREST trial and 8.0 days (6.0–14.0) in the PROTECT trial] [31, 32] investigated shorter-term changes in ePVS than in the present cohort [median length of hospital stay 18.0 days (13.0–25.0) in the Tokyo cohort, 11.0 days (7.0–15.0) in the Porto cohort and 10.0 days (7.0–15.0) in the ICALOR study]. In addition, the majority of patients enrolled in the aforementioned trials had LVEF of less than 40%, whereas our study included a population irrespective of LVEF. While there are similarities in the clinical course of decongestion [33], management of HF differs [34, 35] across the LVEF strata. LVEF may influence prognostic implication of hemoconcentration/ePVS due to differing pathophysiological mechanisms [36]. Of note, patients with preserved LVEF have been reported to be particularly susceptible to intravascular volume depletion, which could modify the prognostic value of change ePVS [37].

Limitations

Several limitations should be recognized in our three cohorts. First, this is a three-center, retrospective study with potential bias regarding patient selection and information recording, along with a lack of consistency with regard to certain clinical variables, i.e., actual body weight and prior HF admission. In addition, length of hospital stay differed substantially between the Japan and European cohorts. However, despite these differences, the strong prognostic information derived from discharge ePVS was similar among the three studies and suggests the potential value of assessing the impact of ePVS use in clinical practice. The Duarte/Strauss formula was used in this study and not the Kaplan formula since dry weight could not be determined. These formulas represent estimations of PV, although their correlation with actual/measured values of PV has been insufficiently studied [38], especially in the setting of ADHF. Lastly, the differences observed herein with regard to the association between clinical variables and ePVS may be the result of the different patient settings of the three cohorts (Cardiology department in Japan vs. Emergency department in Portugal vs. Cardiology department in France).

Clinical perspectives

We provide strong evidence for the marked association of ePVS with outcome. ePVS, a marker of subclinical residual congestion, could become an actionable target in the treatment of ADHF and guide ADHF management. Randomized prospective studies are consequently needed to determine whether it is useful to tailor ADHF treatment based on ePVS and other congestion biomarkers integrated in a multimodality approach.

Conclusions

Based on the results from three independent ADHF cohorts, discharge ePVS during ADHF hospitalization—as opposed to admission ePVS or change ePVS—is a strong independent predictor of post-discharge clinical outcome. This simple and widely available biomarker could improve post-discharge risk stratification of patients with ADHF.

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Compliance with ethical standards

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