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# Association of Estimated Plasma Volume Status with Hemodynamic and Echocardiographic

## Parameters

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**Conflict of interest:** None

## Abstract

**Background:** Estimated plasma volume status (ePVS) has diagnostic and prognostic value in patients with heart failure (HF). However, it remains unclear which congestion markers (i.e., biological, imaging and hemodynamic markers) are preferentially associated with ePVS. In addition, there is evidence of sex differences in both the hematopoietic process and myocardial structure/function.

**Method and results:** Patients with significant dyspnea (NYHA $\geq$ 2) underwent echocardiography and lung ultrasound within four hours prior to cardiac catheterization. Patients were divided according to tertiles based on sex-specific ePVS thresholds calculated from hemoglobin and hematocrit measurements using Duarte's formula.

Among the 78 included patients (median age 74.5 years; males 69.2%; HF 48.7%), median ePVS was 4.1 (percentile<sub>25-75</sub>=3.7-4.9) ml/g in males (N=54) and 4.8 (4.4-5.3) ml/g in females (N=24). Patients with the highest ePVS had more frequently HF, higher NT-proBNP, larger left atrial volume and higher E/e' (all p-values<0.05), but no difference in inferior vena cava diameter or pulmonary congestion assessed by lung ultrasound (all p-values>0.10). In multivariable analysis, higher E/e' and lower diastolic blood pressure were significantly associated with increased ePVS. The association between ePVS and congestion variables was not sex-dependent except for left ventricular end-diastolic pressure, which was only correlated with ePVS in females (Spearman Rho=0.53, p<0.01 in females and Spearman Rho=-0.04, p=0.76 in males; p<sub>interaction</sub>=0.08).

**Conclusion:** ePVS is associated with E/e' regardless of sex, while only associated with invasively measured left ventricular end-diastolic pressure in females. These results suggest that ePVS is preferably associated with left-sided hemodynamic markers of congestion.

## Introduction

Plasma volume is a marker of volume overload and is linked to the regulation between interstitial and intravascular spaces<sup>1, 2</sup>. Estimated plasma volume status (ePVS) derived from hemoglobin and hematocrit has been repeatedly reported to be associated with clinical outcomes in patients with acute or chronic heart failure (HF)<sup>3-6</sup>. Previous reports showed only a moderate association between ePVS using various equations and radiotracer-based quantitative plasma volume measurements<sup>4, 7, 8</sup>. However, the correlation between PV estimated from hemoglobin/hematocrit and measured PV by 125I-human serum albumin in diabetic patients was recently showed to be acceptable (concordance index 0.6,  $P < 0.01$ )<sup>9</sup>. There are only sparse data however regarding the association of ePVS with clinical, biological and echocardiographic congestion as well as with invasive hemodynamic parameters<sup>5, 6, 10-12</sup>. Whether ePVS is more closely associated with pulmonary or systemic congestion markers has yet to be ascertained.

In addition, current evidence suggests that there are underlying sex differences in hematopoiesis<sup>13</sup>, myocardial structure and function<sup>14, 15</sup>. These sex differences may have a substantial impact on the appropriate ePVS thresholds. However, whether the association between congestion markers and ePVS is sex-dependent remains to be established.

The present study aimed to investigate 1) the association of ePVS with clinical, biological, echocardiographic as well as invasive hemodynamic congestion variables and 2) whether these associations are sex-dependent.

## Methods

### Patient Population

This study prospectively included 81 patients with significant dyspnea ( $\text{NYHA} \geq \text{II}$ ) who underwent a coronary angiography with left heart catheterization (LHC) between May 2016 and July 2017<sup>16</sup>. Seventy-eight patients who had available hemoglobin/hematocrit data were included in this subsequent analysis. Exclusion criteria were: mitral stenosis, known pulmonary fibrosis, pneumonia, active lung cancer and history of recent chest trauma. Demographic characteristics, comorbidities and biological profiles were obtained from review of medical records. HF was diagnosed according to the ESC guidelines<sup>17</sup>. Estimated glomerular filtration rate (eGFR) was calculated by the Chronic Kidney Disease Epidemiology Collaboration formula<sup>18</sup>. The study protocol was approved by the local ethics committee (authorization number: 2014-A01331-456).

### Transthoracic Echocardiography

All patients underwent a standard echocardiography using a Vivid S6, E7 or E9 ultrasound system (General Electric Healthcare, Horten, Norway). Images were recorded on a remote station for off-line analysis using a dedicated software (EchoPAC PC, version BT 13, General Electric Healthcare, Horten, Norway). Interpretation was blinded for clinical and hemodynamic data. Left ventricular ejection fraction (LVEF) was measured using the biplane Simpson's method<sup>19</sup>. Diastolic function was assessed from the pattern of mitral inflow by pulsed-wave Doppler. Mitral annular early diastolic velocity (e') was assessed at the septal and lateral sites of the mitral annulus using tissue Doppler imaging. E/A ratio, e' mean and E/e' mean ratio were calculated. Inferior vena cava (IVC), tricuspid annulus plane systolic excursion and left atrial volume (LAV) were obtained as recommended<sup>19</sup>. Pulmonary arterial systolic pressure was estimated using tricuspid velocity and inferior vena cava compliance and diameter<sup>19</sup>. Right ventricular (RV) function was assessed according to recent guidelines<sup>19</sup>.

### **Hemodynamic Data and Lung Ultrasonography**

LHC was performed within four hours following echocardiography. Prior to coronary angiography, transducers were calibrated, with a 0-level set at the mid-axillary line. The left ventricular end-diastolic pressure (LVEDP) was continuously recorded (25 mm/s) with a 5 French Judkin R4 catheter (ICU Medical, San Clemente, CA, USA) placed at the mid-LV cavity. Waveform analysis was blinded from clinical and echocardiographic data. LVEDP was calculated as the mean value of 4 consecutive heart cycles.

Lung ultrasound was performed immediately before echocardiography with patients in supine or near-to-supine position, as previously described<sup>20</sup>. Loops were stored on a remote station for off-line analysis using the same tools as those used for echocardiography. For each lung ultrasound zone, the number of B-lines was quantified from 0 to 10, with resulting LUS scoring ranging from 0 to 80 (8-zone method). An excellent reproducibility of measurements, performed by experienced cardiologists, has previously been reported in this population<sup>16</sup>.

### **Estimated Plasma Volume Status**

ePVS was calculated from the Strauss-derived Duarte formula using hematocrit and hemoglobin values<sup>3</sup> as follows:

$$\text{ePVS (mL/g)} = 100 \times (1 - \text{hematocrit}) / \text{hemoglobin in g/dL}$$

The Hakim formula was also used for calculating plasma volume estimation derived from hematocrit and dry body weight using the following equations<sup>21</sup>:

Actual plasma volume=(1 - hematocrit) × (a + b × body weight in kg)

Ideal plasma volume=c × body weight in kg

(males: a=1530, b=41.0, c=39; females; a=864, b=47.9, c=40),

ePVS=[(actual plasma volume - ideal plasma volume)/ideal plasma volume]×100.

## Statistical Analysis

Continuous data are expressed as median (25 and 75 percentile) and categorical data as numbers (%). Patients were divided into three groups according to sex-specific ePVS tertiles [median (IQR) = 4.07 (3.73-4.93) ml/g in males and 4.76 (4.37-5.27) ml/g in females]. Group differences were assessed using Kruskal-Wallis tests for continuous variables and  $\chi^2$  tests or Fisher's exact test for categorical variables. Unadjusted correlations were expressed using Spearman's correlation coefficients.

Linear regression analyses were performed to evaluate the association of ePVS with clinical, biological, echocardiographic and invasive hemodynamic variables. All variables with a P<0.10 in univariable analysis were used as candidate variables in the multivariable model prior to backward selection procedures. An interaction test was performed to determine whether the associations between ePVS and congestion markers are sex-dependent.

Statistical analyses were performed using R version 3.4.0 (R Development Core Team, Vienna, Austria). A two-sided p-value <0.05 for associations and p < 0.10 for interactions were considered statistically significant.

## Results

### Baseline Characteristics according to Renin and Aldosterone Levels

Among the 78 patients included in this study, 54% were male, median age was 74.5 (67.0-80.0) years, one-fifth (21.8%) of the population had a BMI  $\geq$ 30kg/m<sup>2</sup> and a half (48.7%) had HF and coronary artery (**Table 1**).

Patients in the highest ePVS tertiles had more frequently HF, higher N-terminal pro-B-type natriuretic peptide (NT-proBNP), LAV index, E/e' and lower RV isovolumic acceleration compared to patients in the lowest ePVS tertiles (all p<0.05) (**Table 1**). In contrast, there was no significant difference in IVC, LVEDP and B-line counts across ePVS tertiles.

## Clinical Determinants of Estimated Plasma Volume Status

Univariable linear regression analysis showed that elderly age, female sex, lower BMI, diastolic BP, higher NT-proBNP, larger LAV index and higher E/e' were significantly associated with higher ePVS (**Table 2**). In multivariable linear regression models, only female sex, higher E/e' and lower diastolic BP were significantly associated with higher ePVS (**Table 2**).

Correlation between ePVS and congestion markers across heart rhythm and LVEF strata is shown in **Supplementary table 1**. ePVS significantly correlated with E/e' only in patients with sinus rhythm, whereas similar correlations between ePVS and congestion marker were found across LVEF strata.

## Interplay between Sex, Estimated Plasma Volume Status and other Congestion Markers

ePVS was found to be significantly correlated with NT-proBNP ( $\rho=0.36$ ,  $p=0.01$ ), E/e' ( $\rho=0.33$ ,  $p<0.01$ ) and LAV index ( $\rho=0.31$ ,  $p<0.01$ ). Among congestion markers, only LVEDP was observed to have a sex-specific association with ePVS solely in females ( $\rho=0.53$ ,  $p<0.01$  in females and  $\rho=-0.04$ ,  $p=0.76$  in males;  $p_{\text{interaction}}=0.08$ ) (**Figure 1**). Of note, LVEDP was not associated with higher ePVS in either univariable or multivariable analysis (**Table 2**).

## Estimated Plasma Volume Status Calculated by the Hakim formula

Sex-specific ePVS tertiles derived from the Hakim formula were also applied in the present population [median (IQR)= -9.45 (-15.61 - 1.06) % in males and -7.29 (-10.01 - 4.02) % in females] (**Supplementary table 2**). Patients with the highest ePVS tertiles were older, had lower BMI and were less likely to have atrial fibrillation (all  $p$ -value $<0.05$ ). However, there were no significant differences in biological, echocardiographic and invasive hemodynamic congestion markers across ePVS tertiles.

Multivariable linear regression models showed that ePVS was only associated with BMI and diastolic BP (**Supplementary table 3**).

## Discussion

The current study is the first to assess the association of ePVS with clinical, biological, echocardiographic and invasive hemodynamic congestion markers. Our main findings are that: 1) higher ePVS derived from the Duarte formula was significantly associated with higher E/e' in multivariable analysis; 2) LVEDP was correlated with ePVS using the Duarte formula in females, while not associated with ePVS in the overall population; 3) ePVS derived from the Hakim formula was not associated with usual congestion markers. The above results suggest that ePVS derived

from the Duarte formula may be an easily-accessible surrogate of measured markers of left-sided hemodynamic congestion in routine clinical practice.

### **Estimated Plasma Volume Status – a left-sided congestion variable**

Our findings outline certain underlying features of plasma volume that have not been previously addressed. Among all patients included in our study, results showed that higher E/e' was associated with a higher ePVS level, but not with B-lines or LVEDP. There is growing evidence linking pulmonary interstitial edema quantified by lung ultrasound and elevated invasive measurements of LV filling pressures<sup>16, 22</sup>. In contrast, a recent meta-analysis emphasized the lack of diagnostic value of E/e' ratio in predicting LV filling pressure<sup>23</sup>. This being said, E/e' is nevertheless a recognized congestion marker shown to be associated with clinical outcome in population-based or HF cohorts<sup>24-26</sup>. Given that we did not identify a significant association between ePVS and IVC, our findings further suggest that ePVS is more likely a left-sided congestion marker. This premise is also supported by the biological findings presented herein: patients within the highest ePVS tertiles had higher NT-proBNP, which is also typically considered as a left-sided congestion marker<sup>27, 28</sup>. This result is also in keeping with previous reports in patients with HF and reduced or preserved LVEF<sup>3, 4, 29, 30</sup>. In addition, we observed a better correlation between ePVS and E/e' in patients with sinus rhythm. It may be partly explained by the lack of predictive performance of Doppler echocardiography for LV pressures in patients with atrial fibrillation<sup>19</sup>.

The absence of a strong association between IVC and ePVS may be partly explained by the fact that over two-thirds of the total blood volume resides in the venous circulation, which is relatively unaffected by changes in fluid volume given its high capacitance<sup>31</sup>. Another noteworthy finding of the present study is the strong association between lower diastolic BP and increased ePVS. BP is an important modulator of the complex interaction between interstitial fluid and plasma volume<sup>1</sup>. This could provide some pathophysiological basis for decreased diastolic BP favoring intravascular volume retention, which would translate into higher ePVS.

### **Sex Difference in the association of Estimated Plasma Volume Status with other markers of congestion**

LVEDP was observed herein to be positively correlated with ePVS in females but not in males. Women have been shown to be more prone to impaired LV diastolic reserve<sup>14, 32</sup>. This may partly explain why a higher left volume load (as measured by ePVS) was better correlated with LVEDP since the left ventricle in women (particularly in older women) is unable to mitigate intravascular pressure. The same amount of volume could indeed translate into different pressure levels according to the intrinsic diastolic properties of the heart. Irrespectively, these findings suggest that increased ePVS may be a more relevant marker of cardiopulmonary congestion in females<sup>33, 34</sup>. In contrast, there was



no sex-dependent interaction of ePVS with other congestion markers such as NT-proBNP and E/e'. Both congestion markers were reported to have sex-dependency<sup>35-37</sup>, which may influence this sex-dependent interaction. The pathophysiological mechanism which may explain the sex-different association of ePVS with LVEDP needs to be further evaluated in future studies. Both clinical studies and animal studies would be interesting to refine our understanding of these differences in association between congestion variables.

### **Clinical Perspectives**

Hemodynamic congestion can precede symptoms of congestion by several days. Plasma volume, estimated from hemoglobin/hematocrit using Duarte's formula or hematocrit/body weight using the Hakim formula, could represent easy-to-use markers in routine clinical practice. In contrast, we observed no significant association between congestion markers and ePVS derived from the Hakim formula. This differential association could be related to the Hakim formula incorporating "dry" body weight. There is a complex interplay of congestion and cachexia in HF patients which may explain that PV estimated from Hakim formula becomes less effective in this clinical setting<sup>38, 39</sup>. Importantly, previous reports showed moderate associations between ePVS derived from Duarte/Hakim formula and radiotracer-based quantitative plasma volume measurements which could explain variations of association between ePVS and other congestion markers. In contrast, Duarte-derived ePVS was significantly associated with E/e' (in the whole population) and LVEDP (in females) in the current study (**Figure 2**).

ePVS using Duarte's formula may be a useful integrative marker of left-sided hemodynamic congestion. Other congestion markers such as E/e' and LVEDP often cannot be repeatedly measured especially in the context of ambulatory patients with HF<sup>28</sup>. Therefore, PV estimated from Duarte formula could potentially become a useful congestion marker in the management of HF given its low cost and practicability. Large-scale multicenter studies are invariably needed to determine whether ePVS-guided treatment can improve clinical outcome in HF patients.

### **Limitations**

First, this is a single-center cohort study; thus, there may be residual confounding and generalizability is not unequivocal. The moderate size of our cohort only yielded moderate statistical power. Second, we had no direct measurement of plasma volume by conventional radioisotope-labeled albumin or red blood cell assays, although these techniques are relatively impractical in routine clinical practice. The concordance between estimated and measured PV is still a matter of debate. Adequation for ePVS in the specific context of HF, especially in patients with large variations in body weight, should be further studied. In addition, Patients did not undergo catheterization with a high-fidelity micromanometer-tip catheter. Third, ambulatory patients were recruited in this study and consequently

experienced less severe degrees of congestion than patients typically included in acute HF registries: Our results are thus only relevant for these lower risk patients.

Lastly, the sex-specific association identified herein could also be a chance finding. Further investigations are needed to determine whether a reproducible sex-specific pattern is observed for the association between ePVS and other congestion markers.

## Conclusion

ePVS is associated with E/e' regardless of sex difference and is associated with invasively-measured LV filling pressure only in females. These results suggest that ePVS may be a marker of left-sided hemodynamic congestion rather than pulmonary interstitial edema or systemic congestion.

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### **Table 1. Patient Characteristics according to Sex-specific Tertiles of Estimated Plasma Volume Status**

\* Sex-specific tertiles indicate the tertiles derived from males and females separately.

M, male; F, female; COPD, chronic obstructive pulmonary disease; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; BP, blood pressure; eGFR, estimated glomerular filtration rate; NT proBNP, N-terminal prohormone brain natriuretic peptide; ePVS, estimated plasma volume status; LVSV, left ventricular systolic volume; LAV, left atrial volume; LVEF, left ventricular ejection fraction; E/A, ratio of peak early and late diastolic velocities; e', mean value of early diastolic velocity at the septal and lateral sites of the mitral annulus; E/e', ratio of early mitral inflow velocity and mitral annular early diastolic velocity; RAV, right atrial volume; TAPSE, tricuspid annular plane systolic excursion; IVA, isovolumic acceleration; IVC, inferior vena cava; PASP, pulmonary artery systolic pressure; LVEDP, left ventricular end-diastolic pressure.

### **Table 2. Multivariable Model for the Association of Clinical, Biological and Hemodynamic Parameters with Estimated Plasma Volume Status**

NYHA, New York Heart Association; BP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; NT proBNP, N-terminal prohormone brain natriuretic peptide; LVSV, left ventricular stroke volume; LAV, left atrial volume; E/A, ratio of peak early and late diastolic velocities; E/e', ratio of early mitral inflow velocity and mitral annular early diastolic velocity; RAV, right atrial volume; TAPSE, tricuspid annular plane systolic excursion; IVA, isovolumic acceleration; IVC, inferior vena cava; PASP, pulmonary artery systolic pressure; LVEDP, left ventricular end-diastolic pressure.

**Table 1. Patient Characteristics according to Sex-specific Tertiles of Estimated Plasma Volume Status**

	Global	Low	Intermediate	High	p-value	p-Value 1 vs. 3	p-Value 2 vs. 3
	(N=78)	M, <3.8 ml/g; F, <4.4 ml/g (N=26)	M, 3.8-4.5 ml/g; F, 4.4-5.0 ml/g (N=26)	M, >4.5 ml/g; F, >5.0 ml/g (N=26)			
Age, yrs	74.5 (67.0 - 80.0)	73.5 (64.0 - 78.0)	71.5 (67.0 - 78.0)	77.5 (70.0 - 82.0)	0.15	0.11	0.08
Males, N (%)	54 (69.2 %)	18 (69.2 %)	18 (69.2 %)	18 (69.2 %)	NA	NA	NA
Body mass index, kg/m <sup>2</sup>	25.7 (22.9 - 29.5)	27.9 (24.7 - 32.6)	25.9 (23.3 - 28.9)	23.6 (20.7 - 26.7)	<b>&lt;0.01</b>	<b>&lt;0.01</b>	0.12
Medical history, N (%)							
Hypertension	53 (67.9 %)	16 (61.5 %)	18 (69.2 %)	19 (73.1 %)	0.66	0.38	0.76
Dyslipidemia	35 (44.9 %)	12 (46.2 %)	10 (38.5 %)	13 (50.0 %)	0.70	0.78	0.4
Diabetes mellitus	16 (20.5 %)	2 (7.7 %)	7 (26.9 %)	7 (26.9 %)	0.14	0.08	0.99
Coronary artery disease	38 (48.7 %)	9 (34.6 %)	12 (46.2 %)	17 (65.4 %)	0.08	<b>0.03</b>	0.17
Heart failure	38 (48.7 %)	8 (30.8 %)	13 (50.0 %)	17 (65.4 %)	<b>0.04</b>	<b>0.01</b>	0.26
Atrial fibrillation	23 (29.5 %)	10 (38.5 %)	7 (26.9 %)	6 (23.1 %)	0.45	0.23	0.75
COPD	6 (7.7 %)	2 (7.7 %)	4 (15.4 %)	0 (0 %)	0.11	0.99	0.99
Smoking	30 (38.5 %)	10 (38.5%)	12 (46.2 %)	8 (30.8 %)	0.52	0.56	0.26
Medications, N (%)							
ACEi/ARB	48 (61.5 %)	15 (57.7 %)	16 (61.5 %)	17 (65.4 %)	0.85	0.57	0.77
Calcium channel blocker	4 (5.1 %)	1 (3.8 %)	1 (3.8 %)	2 (7.7 %)	0.77	0.56	0.56
Beta-blocker	44 (56.4 %)	17 (65.4 %)	13 (50.0 %)	14 (53.8 %)	0.51	0.40	0.78
MRA	8 (10.3 %)	2 (7.7 %)	2 (7.7 %)	4 (15.4 %)	0.57	0.39	0.39
Clinical profile							
NYHA III+IV, N (%)	21 (26.9 %)	6 (23.1 %)	8 (30.8 %)	7 (26.9 %)	0.82	0.75	0.76
Systolic BP, mmHg	134.0 (118.0 - 148.0)	139.0 (130.0 - 144.0)	133.0 (119.0 - 148.0)	130.0 (110.0 - 147.0)	0.48	0.27	0.64
Diastolic BP, mmHg	72.5 (65.0 - 84.0)	76.0 (68.0 - 90.0)	75.0 (67.0 - 81.0)	67.0 (65.0 - 80.0)	0.17	0.06	0.20
Heart rate, bpm	70.5 (61.0 - 83.0)	70.0 (61.0 - 86.0)	76.5 (59.0 - 83.0)	67.0 (62.0 - 75.0)	0.69	0.82	0.35
Laboratory measurements							
Hemoglobin, g/dl	13.6 (12.5 - 14.7)	15.0 (14.3 - 15.4)	13.9 (13.3 - 14.3)	11.9 (10.9 - 12.5)	<b>&lt;0.01</b>	<b>&lt;0.01</b>	<b>&lt;0.01</b>
Sodium, mmol/l	140.0 (137.0 - 141.0)	140.0 (138.0 - 141.0)	140.0 (138.0 - 142.0)	138.0 (137.0 - 141.0)	0.22	0.18	0.12
eGFR, ml/min/1.73m <sup>2</sup>	70.0 (53.0 - 85.0)	67.1 (57.2 - 88.0)	75.3 (48.0 - 85.0)	71.0 (49.0 - 81.0)	0.66	0.44	0.53
NT proBNP, pg/ml	1025 (283 - 2384)	668 (112 - 2168)	576 (172 - 1472)	2327 (1025 - 5752)	<b>0.03</b>	<b>0.04</b>	<b>0.01</b>
ePVS, ml/g	4.4 (3.8 - 5.0)	3.7 (3.5 - 3.8)	4.2 (4.0 - 4.5)	5.4 (5.0 - 6.1)	<b>&lt;0.01</b>	<b>&lt;0.01</b>	<b>&lt;0.01</b>
LV function							
LVSV index, ml/m <sup>2</sup>	31.4 (19.3 - 50.6)	29.6 (18.3 - 42.7)	34.8 (23.2 - 59.1)	42.7 (20.9 - 69.2)	0.18	0.08	0.99
LAV index, ml/m <sup>2</sup>	47.7 (33.4 - 62.3)	47.3 (31.8 - 58.9)	41.9 (33.3 - 52.3)	55.4 (44.4 - 65.5)	<b>0.046</b>	0.06	<b>0.02</b>
LVEF, %	52.0 (33.0 - 62.0)	54.0 (43.0 - 63.0)	50.5 (31.0 - 58.0)	50.4 (31.0 - 62.0)	0.25	0.25	0.76
LVEF<40%, N (%)	26 (33.3 %)	4 (15.4 %)	10 (38.5 %)	12 (46.2 %)	<b>0.049</b>	<b>0.02</b>	0.58
LVEF≥50%, N (%)	42 (53.8 %)	16 (61.5 %)	13 (50.0 %)	13 (50.0 %)	0.63	0.40	1.00
Global longitudinal strain, %	-12.9 (-18.4 - -8.6)	-15.2 (-19.0 - -10.0)	-13.2 (-19.4 - -8.6)	-10.2 (-16.9 - -7.4)	0.24	0.08	0.40
E/A ratio (N=61)	0.9 (0.7 - 1.6)	0.9 (0.6 - 1.6)	0.9 (0.7 - 1.5)	1.1 (0.7 - 1.8)	0.58	0.49	0.90
e' mean, cm/s	6.5 (4.5 - 8.5)	6.8 (5.5 - 10.0)	6.5 (5.0 - 9.0)	6.0 (3.5 - 7.0)	0.11	<b>0.04</b>	0.14
E/e' mean	12.5 (9.3 - 18.3)	10.9 (8.5 - 15.0)	11.7 (8.6 - 15.6)	16.3 (11.6 - 22.6)	<b>0.02</b>	<b>0.01</b>	<b>0.03</b>
RV function							
RAV index, ml/m <sup>2</sup>	25.4 (19.5 - 34.4)	29.4 (19.4 - 44.8)	22.8 (19.5 - 28.8)	26.3 (19.5 - 34.4)	0.27	0.29	0.52
TAPSE, mm	22.8 (18.0 - 25.3)	23.0 (19.0 - 26.0)	24.0 (20.0 - 30.0)	20.5 (18.0 - 24.0)	0.12	0.16	<b>0.047</b>
RV IVA, m/sec	1.4 (0.9 - 2.1)	1.3 (0.9 - 1.6)	1.9 (1.4 - 2.3)	1.1 (0.8 - 1.9)	<b>0.03</b>	0.71	<b>0.03</b>
IVC dimension, mm	13.0 (8.0 - 16.7)	13.0 (6.0 - 16.0)	12.0 (7.5 - 16.0)	13.5 (10.0 - 20.5)	0.29	0.20	0.15
estimated PAPS, mmHg	34.0 (26.0 - 45.0)	34.0 (26.0 - 38.0)	30.0 (25.0 - 42.0)	35.0 (26.0 - 50.0)	0.38	0.21	0.28
Other parameters							

<b>LVEDP, mmHg</b>	16.0 (12.0 - 22.0)	15.5 (11.0 - 20.0)	16.0 (13.0 - 21.0)	17.0 (12.0 - 23.0)	0.77	0.52	0.79
<b>LV-PreA, mmHg (N=61)</b>	10.0 (7.0 - 16.0)	10.0 (5.0 - 12.0)	10.0 (6.5 - 16.0)	12.0 (8.0 - 16.0)	0.33	0.15	0.54
<b>Total B-Lines</b>	3.0 (0.0 - 12.0)	2.5 (0.0 - 12.0)	1.0 (0.0 - 9.0)	4.0 (0.0 - 19.0)	0.52	0.46	0.29

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**Table 2. Multivariable Model for the Association of Clinical, Biological and Hemodynamic Parameters with Estimated Plasma Volume Status**

Variables	Univariable model		Multivariable model	
	$\beta$ (95%CI)	p-Value	$\beta$ (95%CI)	p-Value
<b>Clinical parameters</b>				
Age, yrs (per 5 yrs)	0.15 (0.04 - 0.26)	<b>0.01</b>	—	—
Male sex	-0.54 (-0.99 - -0.08)	<b>0.02</b>	-0.67 (-1.25 - 0.08)	<b>0.03</b>
Body mass index, kg/m <sup>2</sup> (per 5 kg/m <sup>2</sup> )	-0.20 (-0.39 - -0.01)	<b>0.04</b>	—	—
Hypertension	0.16 (-0.31 - 0.62)	0.50	—	—
Diabetes mellitus	0.44 (-0.09 - 0.97)	0.09	—	—
Coronary artery disease	0.27 (-0.16 - 0.70)	0.21	—	—
Heart failure	0.52 (0.10 - 0.94)	<b>0.02</b>	—	—
NYHA III+IV	0.41 (-0.07 - 0.89)	0.09	—	—
Diastolic BP, mmHg (per 5 mmHg)	-0.13 (-0.21 - -0.05)	<b>&lt;0.001</b>	-0.22 (-0.41 - -0.02)	<b>0.03</b>
<b>Biological parameters</b>				
Sodium, mmol/l (per 5 mmol/l)	-0.14 (-0.44 - 0.16)	0.35	—	—
eGFR, ml/min/1.73m <sup>2</sup> (per 5 ml/min/1.73m <sup>2</sup> )	-0.03 (-0.08 - 0.03)	0.34	—	—
Log NT proBNP	0.24 (0.04 - 0.43)	<b>0.02</b>	—	—
<b>Left ventricular function</b>				
LVS index, ml/m <sup>2</sup> (per 5 ml/m <sup>2</sup> )	0.02 (-0.02 - 0.05)	0.43	—	—
LAV index, ml/m <sup>2</sup> (per 5 ml/m <sup>2</sup> )	0.05 (0.01 - 0.10)	<b>0.03</b>	—	—
LV ejection fraction, % (per 5%)	-0.02 (-0.09 - 0.04)	0.46	—	—
LV ejection fraction <40%	0.42 (-0.03 - 0.87)	0.07	—	—
Global longitudinal strain, %	0.02 (-0.02 - 0.06)	0.24	—	—
E/A ratio	0.02 (-0.25 - 0.28)	0.91	—	—
E/e' mean	0.04 (0.01 - 0.06)	<b>&lt;0.001</b>	0.03 (0.01 - 0.06)	<b>0.03</b>
<b>Right ventricular function</b>				
TAPSE, mm	-0.02 (-0.06 - 0.02)	0.27	—	—
RV IVA, m/sec	-0.09 (-0.29 - 0.12)	0.40	—	—
IVC dimension, mm	0.01 (-0.03 - 0.05)	0.51	—	—
estimated PAPS, mmHg (per 5 mmHg)	0.06 (-0.02 - 0.13)	0.15	—	—
<b>Other parameters</b>				
LVEDP, mmHg	0.01 (-0.02 - 0.04)	0.37	—	—
Total B-Lines	0.02 (-0.01 - 0.04)	0.18	—	—



## Graphic abstract

### Figure 1. Scatterplots of Congestion Markers with Estimated Plasma Volume Status according to Sex Difference

ePVS, estimated plasma volume status; NT proBNP, N-terminal prohormone brain natriuretic peptide; E/e', ratio of early mitral inflow velocity and mitral annular early diastolic velocity; LAV, left atrial volume; IVC, inferior vena cava; LVEDP, left ventricular end-diastolic pressure

### Central Illustration. Association between Congestion Markers and Estimated Plasma Volume Status

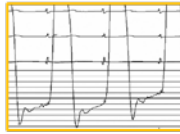
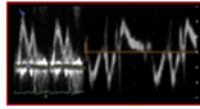
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# Graphic abstract

## STUDY DESIGN

78 patients with dyspnea undergoing

- Echocardiography (E/e' etc)
- lung ultrasound
- routine biological measurements
- cardiac catheterization (LVEDP etc)



ePVS derived from Duarte formula

$$\frac{1-Hct}{Hb} \times 100$$

## OBJECTIVE

- 1) To study the association of ePVS with clinical, biological, echographic and invasive hemodynamic congestion variables
- 2) To investigate whether these associations are sex-dependent

## RESULTS

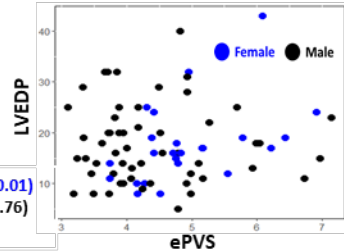
### Multivariable association with ePVS

	$\beta$	95% CI
<b>E/e'</b>		
Male	-0.67	-1.25 - 0.08
DBP	-0.22	-0.41 - -0.02
E/e'	0.03	0.01 - 0.06

### Sex-dependent association with ePVS

LVEDP

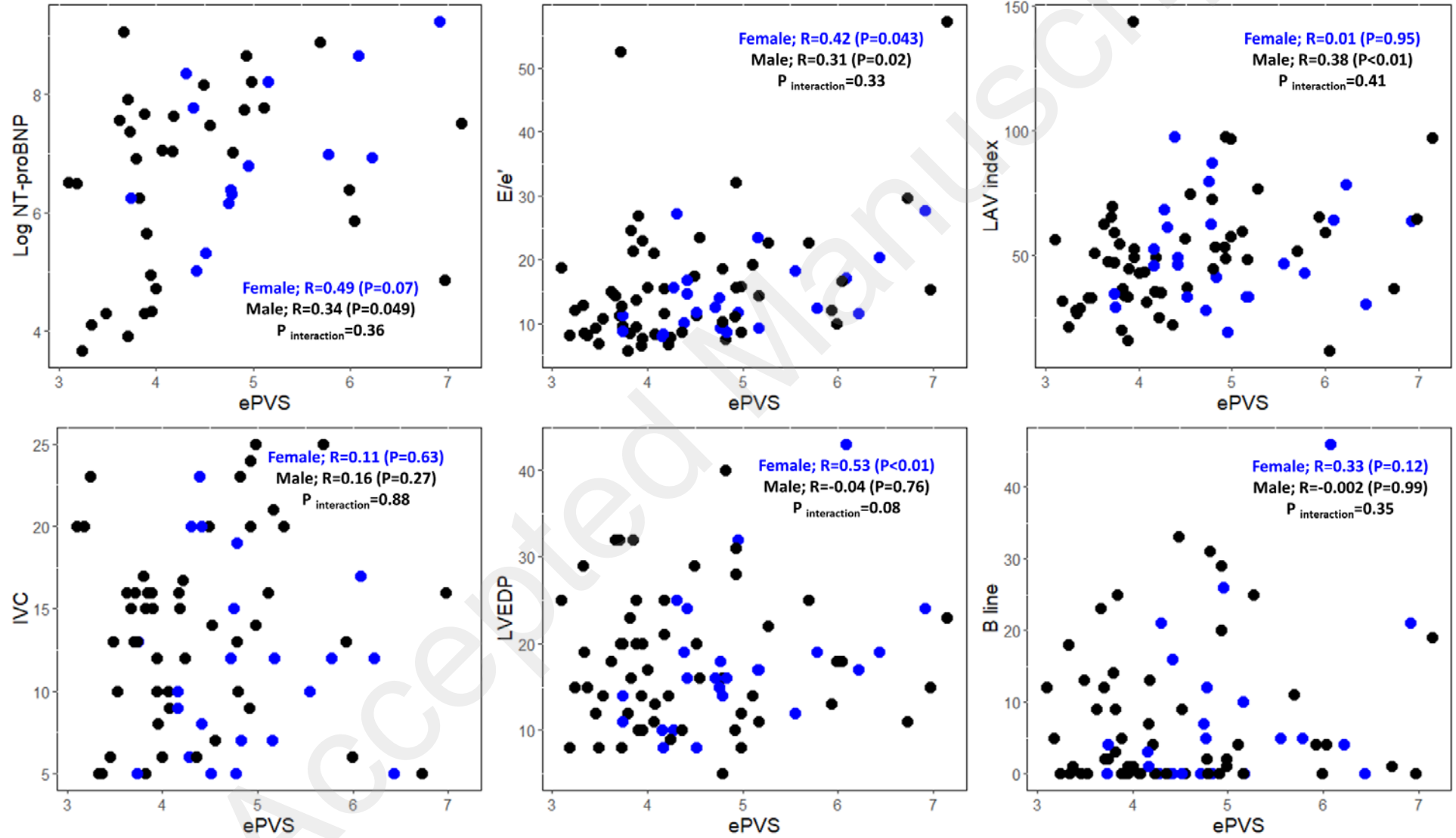
Female; R=0.53 (P<0.01)  
Male; R=-0.04 (P=0.76)  
P<sub>interaction</sub>=0.08



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Figure 1. Scatterplots of Congestion Markers with Estimated Plasma Volume Status according to Sex Difference

● Female ● Male



**Estimated Plasma Volume Status**

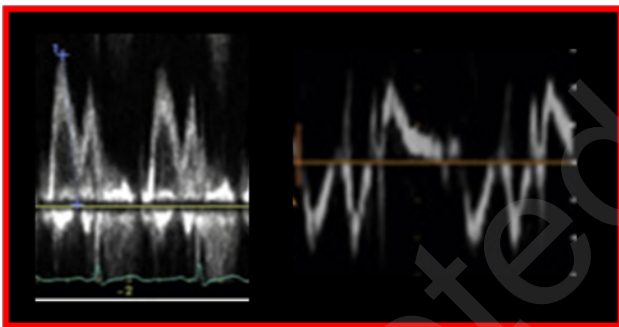
$$\frac{1-Hct}{Hb} \times 100$$

**Independent association**

**Sex-dependent association**

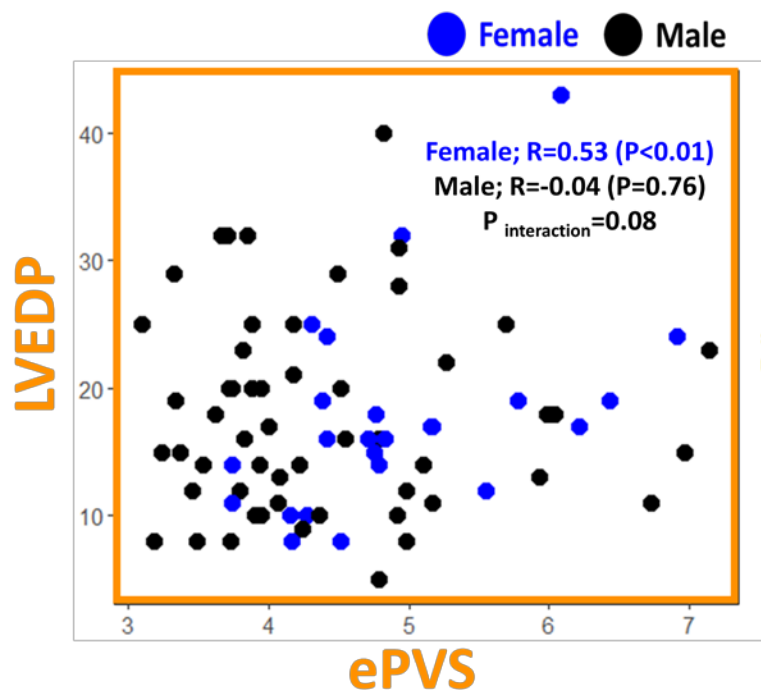
**E/e'**

**LVEDP**



**Multivariable association with ePVS in linear regression**

	$\beta$	95% CI
<b>Male</b>	-0.67	-1.25 - 0.08
<b>DBP</b>	-0.22	-0.41 - -0.02
<b>E/e'</b>	<b>0.03</b>	<b>0.01 - 0.06</b>



**Supplementary table 1. Correlation Matrix between Estimated Plasma Volume Status and Congestion Markers across Heart Rhythm and Left Ventricular Ejection Fraction Strata**

	Sinus rhythm (N=61)		Atrial fibrillation (N=17)		p-value for interaction	LVEF $\geq$ 50% (N=42)		LVEF<50% (N=36)		p-value for interaction
	rho	p-value	rho	p-value		rho	p-value	rho	p-value	
<b>Log NTproBNP</b>	0.49	<b>0.002</b>	0.26	0.43	0.93	0.47	<b>0.01</b>	0.44	0.06	0.57
<b>E/e' mean</b>	0.39	<b>0.002</b>	0.06	0.82	<b>0.02</b>	0.33	<b>0.03</b>	0.31	0.06	0.30
<b>LAV index</b>	0.31	<b>0.01</b>	0.36	0.16	0.84	0.25	0.11	0.34	<b>0.04</b>	0.34
<b>IVC dimension</b>	0.11	0.41	0.19	0.48	0.60	-0.06	0.72	0.25	0.14	0.84
<b>LVEDP</b>	0.08	0.56	0.14	0.60	0.91	0.14	0.38	0.04	0.81	0.73
<b>Total B-lines</b>	0.13	0.30	-0.13	0.62	0.60	0.07	0.67	0.12	0.49	0.86

Correlations were analyzed using Spearman's correlation.

NT proBNP, N-terminal prohormone brain natriuretic peptide; E/e', ratio of early mitral inflow velocity and mitral annular early diastolic velocity; LAV, left atrial volume; IVC, inferior vena cava; LVEDP, left ventricular end-diastolic pressure.

**Supplementary table 2. Patient Characteristics according to Sex-specific Tertiles of Estimated Plasma Volume Status (Hakim formula)**

	Sex specific ePVS tertiles				p-value
	Global (N=78)	Low M, <-12.9%; F, <-9.7% (N=26)	Intermediate M, -12.9 - -3.4%; F, -9.7 - 0.2% (N=26)	High M, -3.4%>; F, 0.2%> (N=26)	
Age, yrs	74.5 (67.0 - 80.0)	71.5 (64.0 - 76.0)	75.0 (67.0 - 79.0)	78.0 (70.0 - 83.0)	<b>0.02</b>
Males, N (%)	54 (69.2 %)	18 (69.2 %)	18 (69.2 %)	18 (69.2 %)	NA
Body mass index, kg/m <sup>2</sup>	25.7 (22.9 - 29.5)	29.8 (25.9 - 32.7)	25.3 (22.9 - 28.7)	23.1 (20.7 - 25.2)	<b>&lt;0.001</b>
Medical history, N (%)					
Hypertension	53 (67.9 %)	18 (69.2 %)	17 (65.4 %)	18 (69.2 %)	0.94
Dyslipidemia	35 (44.9 %)	10 (38.5 %)	13 (50.0 %)	12 (46.2 %)	0.70
Diabetes mellitus	16 (20.5 %)	2 (7.7 %)	9 (34.6 %)	5 (19.2 %)	0.06
Coronary artery disease	38 (48.7 %)	8 (30.8 %)	14 (53.8 %)	16 (61.5 %)	0.07
Heart failure	38 (48.7 %)	11 (42.3 %)	11 (42.3 %)	16 (61.5 %)	0.28
Atrial fibrillation	23 (29.5 %)	12 (46.2 %)	4 (15.4 %)	7 (26.9 %)	<b>0.048</b>
COPD	6 (7.7 %)	3 (11.5 %)	3 (11.5 %)	0 (0 %)	0.20
Smoking	30 (38.5 %)	9 (34.6 %)	12 (46.2 %)	9 (34.6 %)	0.61
Medications, N (%)					
ACEi/ARB	48 (61.5 %)	15 (57.7 %)	17 (65.4 %)	16 (61.5 %)	0.85
Calcium channel blockers	4 (5.1 %)	1 (3.8 %)	1 (3.8 %)	2 (7.7 %)	0.77
Beta-blocker	44 (56.4 %)	17 (65.4 %)	11 (42.3 %)	16 (61.5 %)	0.20
MRA	8 (10.3 %)	2 (7.7 %)	4 (15.4 %)	2 (7.7 %)	0.57
Clinical profile					
NYHA III+IV, N (%)	21 (26.9 %)	7 (26.9 %)	8 (30.8 %)	6 (23.1 %)	0.82
Systolic BP, mmHg	134.0 (118.0 - 148.0)	138.0 (130.0 - 145.0)	133.0 (119.0 - 153.0)	132.0 (110.0 - 147.0)	0.55
Diastolic BP, mmHg	72.5 (65.0 - 84.0)	76.0 (65.0 - 90.0)	75.0 (67.0 - 80.0)	70.0 (65.0 - 80.0)	0.24
Heart rate, bpm	70.5 (61.0 - 83.0)	75.0 (64.0 - 90.0)	72.5 (60.0 - 83.0)	66.0 (60.0 - 75.0)	0.36
Laboratory measurements					
Hemoglobin, g/dl	13.6 (12.5 - 14.7)	14.8 (14.0 - 15.4)	13.8 (12.8 - 14.6)	12.2 (10.9 - 12.7)	<b>&lt;0.001</b>
Sodium, mmol/l	140.0 (137.0 - 141.0)	140.0 (137.0 - 141.0)	140.0 (138.0 - 141.0)	138.5 (137.0 - 141.0)	0.37
eGFR, ml/min/1.73m <sup>2</sup>	70.0 (53.0 - 85.0)	68.5 (56.0 - 91.1)	66.1 (49.0 - 84.4)	72.2 (52.0 - 81.0)	0.60
NT proBNP, pg/ml	1025 (283 - 2384)	661 (113 - 2384)	595 (204 - 2074)	1777 (1025 - 3738)	0.10
ePVS, %	-20.6 (-29.9 - -9.7)	-33.0 (-37.7 - -16.6)	-26.9 (-28.4 - -8.7)	-12.8 (-16.8 - 4.0)	<b>&lt;0.001</b>
LV function					
LVSV index, ml/m <sup>2</sup>	31.4 (19.3 - 50.6)	30.3 (19.5 - 47.8)	31.6 (18.8 - 48.8)	35.7 (20.9 - 69.2)	0.67
LAV index, ml/m <sup>2</sup>	47.7 (33.4 - 62.3)	44.2 (28.5 - 52.4)	48.9 (33.8 - 62.3)	53.3 (36.6 - 65.5)	0.06
LVEF, %	52.0 (33.0 - 62.0)	48.0 (40.0 - 62.0)	53.3 (37.0 - 61.4)	50.4 (31.0 - 62.0)	0.78
LVEF<40%, N (%)	26 (33.3 %)	6 (23.1 %)	8 (30.8 %)	12 (46.2 %)	0.20
LVEF≥50%, N (%)	42 (53.8 %)	12 (46.2 %)	17 (65.4 %)	13 (50.0 %)	0.34
Global longitudinal strain, %	-12.9 (-18.4 - -8.6)	-13.6 (-18.0 - -8.6)	-15.2 (-19.2 - -9.8)	-10.3 (-16.9 - -7.4)	0.28
E/A ratio (N=61)	0.9 (0.7 - 1.6)	0.9 (0.6 - 1.5)	0.9 (0.7 - 1.9)	1.0 (0.8 - 1.8)	0.60
e' mean, cm/s	6.5 (4.5 - 8.5)	6.8 (5.0 - 9.5)	6.5 (5.0 - 9.0)	6.5 (3.5 - 7.0)	0.36
E/e' mean	12.5 (9.3 - 18.3)	10.4 (8.4 - 14.7)	13.1 (9.4 - 18.5)	15.5 (11.1 - 22.6)	0.054
RV function					
RAV index, ml/m <sup>2</sup>	25.4 (19.5 - 34.4)	27.6 (19.6 - 34.1)	24.8 (19.3 - 35.6)	25.6 (19.5 - 31.2)	0.77
TAPSE, mm	22.8 (18.0 - 25.3)	22.5 (19.0 - 25.0)	23.5 (18.0 - 30.0)	21.5 (18.0 - 24.0)	0.24
RV IVA, m/sec	1.4 (0.9 - 2.1)	1.4 (0.9 - 1.7)	1.7 (1.1 - 2.2)	1.2 (0.8 - 2.1)	0.16
IVC dimension, mm	13.0	12.0	14.5	12.5	0.54

	(8.0 - 16.7)	(6.0 - 16.7)	(9.0 - 16.0)	(9.5 - 20.0)	
<b>estimated PAPS, mmHg</b>	34.0 (26.0 - 45.0)	34.0 (23.0 - 40.0)	30.0 (27.0 - 45.0)	35.0 (26.0 - 50.0)	0.38
<b>Other parameters</b>					
<b>LVEDP, mmHg</b>	16.0 (12.0 - 22.0)	14.5 (10.0 - 20.0)	16.0 (14.0 - 21.0)	17.0 (12.0 - 23.0)	0.40
<b>LV-PreA, mmHg (N=61)</b>	10.0 (7.0 - 16.0)	8.5 (5.0 - 10.0)	12.0 (8.0 - 17.0)	11.0 (8.0 - 16.0)	0.08
<b>Total B-Lines</b>	3.0 (0.0 - 12.0)	2.0 (0.0 - 9.0)	4.5 (0.0 - 12.0)	4.0 (0.0 - 19.0)	0.80

\* Sex specific tertiles indicate the tertiles derived from male and female separately.

M, male; F, female; COPD, chronic obstructive pulmonary disease; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; BP, blood pressure; eGFR, estimated glomerular filtration rate; NT proBNP, N-terminal prohormone brain natriuretic peptide; ePVS, estimated plasma volume status; LVSV, left ventricular systolic volume; LAV, left atrial volume; LVEF, left ventricular ejection fraction; E/A, ratio of peak early and late diastolic velocities; e', mean value of early diastolic velocity at the septal and lateral sites of the mitral annulus; E/e', ratio of early mitral inflow velocity and mitral annular early diastolic velocity; RAV, right atrial volume; TAPSE, tricuspid annular plane systolic excursion; IVA, isovolumic acceleration; IVC, inferior vena cava; PAPS, pulmonary artery systolic pressure; LVEDP, left ventricular end-diastolic pressure.

**Supplementary table 3. Multivariable Model for the Association of Clinical, Biological and Hemodynamic Parameters with Estimated Plasma Volume Status (Hakim formula)**

	Univariable model		Multivariable model	
	$\beta$ (95%CI)	p-Value	$\beta$ (95%CI)	p-Value
<b>Clinical parameters</b>				
Age, yrs (per 5 yrs)	1.81 (0.59 - 3.03)	<b>0.004</b>	—	—
Male sex	-3.01 (-8.21 - 2.20)	0.25		
Body mass index, kg/m <sup>2</sup> (per 5 kg/m <sup>2</sup> )	-6.07 (-7.75 - -4.38)	<b>&lt;0.001</b>	-6.07 (-8.26 - -3.89)	<b>&lt;0.001</b>
Hypertension	-0.34 (-5.54 - 4.85)	0.90		
Diabetes mellitus	0.90 (-5.10 - 6.90)	0.77		
Coronary artery disease	2.41 (-2.41 - 7.23)	0.32		
Heart failure	4.19 (-0.57 - 8.94)	0.08	—	—
NYHA III+IV	1.26 (-4.19 - 6.72)	0.65		
Diastolic BP, mmHg (per 5 mmHg)	-1.84 (-3.63 - -0.06)	<b>0.043</b>	-2.45 (-4.22 - -0.68)	<b>0.008</b>
<b>Biological parameters</b>				
Sodium, mmol/l (per 5 mmol/l)	-1.88 (-5.20 - 1.45)	0.26		
eGFR, ml/min/1.73m <sup>2</sup> (per 5 ml/min/1.73m <sup>2</sup> )	-0.16 (-0.75 - 0.43)	0.59		
Log NT proBNP	1.91 (-0.13 - 3.95)	0.07	—	—
<b>Left ventricular function</b>				
LVS <sub>V</sub> index, ml/m <sup>2</sup> (per 5 ml/m <sup>2</sup> )	0.27 (-0.14 - 0.68)	0.20		
LAV index, ml/m <sup>2</sup> (per 5 ml/m <sup>2</sup> )	0.75 (0.24 - 1.26)	<b>0.005</b>	—	—
LV ejection fraction, % (per 5%)	-0.10 (-0.84 - 0.63)	0.78		
LV ejection fraction <40%	4.15 (-0.90 - 9.20)	0.11		
Global longitudinal strain, %	0.22 (-0.21 - 0.65)	0.31		
E/A ratio	-0.02 (-2.88 - 2.85)	0.99		
E/e' mean	0.32 (0.06 - 0.59)	<b>0.02</b>	—	—
<b>Right ventricular function</b>				
TAPSE, mm	-0.25 (-0.68 - 0.18)	0.25		
RV IVA, m/sec	-0.11 (-2.37 - 2.16)	0.93		
IVC dimension, mm	0.10 (-0.32 - 0.52)	0.64		
estimated PAPS, mmHg (per 5 mmHg)	0.59 (-0.29 - 1.47)	0.18		
<b>Others</b>				
LVEDP, mmHg	0.05 (-0.27 - 0.37)	0.75		
Total B-Lines	0.15 (-0.10 - 0.39)	0.24		

NYHA, New York Heart Association; BP, diastolic blood pressure; eGFR, eGFR, estimated glomerular filtration rate; NT proBNP, N-terminal prohormone brain natriuretic peptide; LVS<sub>V</sub>, left ventricular stroke volume; LAV, left atrial volume; E/A ratio of peak early and late diastolic velocities; E/e', ratio of early mitral inflow velocity and mitral annular early diastolic velocity; RAV, right atrial volume; TAPSE, tricuspid annular plane systolic excursion; IVA, isovolumic acceleration; IVC, inferior vena cava; PAPS, pulmonary artery systolic pressure; LVEDP, left ventricular end-diastolic pressure.