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ORIGINAL PAPER

Diagnostic and prognostic value of plasma volume status at emergency department admission in dyspneic patients: results from the PARADISE cohort

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Abstract

Background Systemic congestion, evaluated by estimated plasma volume status (ePVS), is associated with in-hospital mortality in acute heart failure (AHF). However, the diagnostic and prognostic value of ePVS in patients with acute dyspnea has been insufficiently studied.

Objectives To assess the association between the first ePVS calculated from blood samples on admission in the emergency department (ED) and discharge diagnosis of AHF and in-hospital mortality in patients admitted for acute dyspnea.

Methods The study included 1369 patients admitted for dyspnea in the ED in 2015. ePVS was calculated from hematocrit and hemoglobin values at admission. Comparisons of baseline characteristics according to ePVS tertiles were carried out and then associations between ePVS and the two outcomes "AHF diagnosis" and "intra-hospital mortality" were assessed using a logistic regression model.

Results 36.6% had a BNP > 400 pg/mL and median ePVS was 4.58 dL/g [3.96–5.55]. Overall in-hospital mortality was 11.1% ($n = 149$). In multivariable analysis, the third ePVS tertile (> 5.12 dL/g) had a significantly increased risk of having AHF (OR = 1.64 [1.16–2.33], $p = 0.005$). In-hospital mortality rose across ePVS tertiles (8.4–13.8% $p < 0.01$). ePVS greater than the first or second tertile threshold (respectively, 4.17 dL/g and 5.12 dL/g) were both significantly associated with a higher risk of in-hospital mortality (OR for 2nd/3rd tertile = 2.06 [1.25–3.38], $p = 0.004$ and OR for 3rd tertile = 1.54 [1.01–2.36], $p = 0.04$).

Conclusion Higher ePVS values determined from first blood sample at admission are associated with a higher probability of AHF and in-hospital mortality in patients admitted in the ED for acute dyspnea.

Keywords Congestion · Estimated plasma volume status · Acute dyspnea · Emergency · Acute heart failure · Mortality

Abbreviations

AHF	Acute heart failure
BNP	Brain natriuretic peptide
CI	Confidence interval
ED	Emergency department
eGFR	Estimated glomerular filtration rate
ePVS	Estimated plasma volume status
HF	Heart failure
Ht	Hematocrit
Hb	Hemoglobin
OR	Odds ratios

Introduction

Heart failure (HF) is a significant public health concern. It is one of the leading causes of hospitalization in Western countries and is associated with a mortality rate at least similar to most cancers [1, 2]. In patients with acute dyspnea, correctly identifying AHF remains a challenge in the emergency department (ED) [3, 4]. These diagnostic difficulties can delay the initiation of adequate therapy, which in turn is

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associated with a higher risk of death [5–7]. As a result, the recent ESC guidelines and other studies have emphasized the importance of early treatment initiation [8, 9].

Assessing congestion is the cornerstone of AHF diagnosis. However, the tools commonly available in ED have suboptimal accuracy [10] and/or their utilization requires a significant amount of time, which further delays adequate treatment initiation. Consequently, simple and rapid diagnostic tools able to better identify patients with AHF and perform early risk stratification of patients with acute dyspnea are drastically needed [11].

Most hemodialysis device currently use hematocrit to monitor volemia during hemodialysis sessions [12]. Recently, Duarte and al. [13], Yoshihisa and al [14] and Bilchick et al. [15] reported a good prognostic value of estimated plasma volume status (ePVS) calculated from simple parameters (hemoglobin and hematocrit measurements) in patients with HF. However, the diagnostic value of ePVS in detecting AHF as well as its prognostic value in an unselected population of patients admitted for acute dyspnea (i.e., due to AHF or another cause) is yet to be fully established. So, the aim of the present study was to investigate the diagnostic and prognostic value of ePVS in patients admitted in the ED for acute dyspnea.

Methods

Population

Patients aged 18 years or older and admitted in the academic ED of the Nancy University Hospital (France) from the PARADISE cohort over a 1-year period from January 1, 2015 to December 31, 2015 were included in this retrospective study. The hospital's electronic charts (Resurgences®) were used to search for the records of all patients admitted for acute dyspnea in the ED. Medical history, clinical parameters, laboratory results, treatment received in the ED, clinical charts during the in-hospital period and the discharge letter were retrieved from patients' electronic records. Patients without available discharge diagnosis ($N = 118/1589$) and without hemoglobin and/or hematocrit measurements ($N = 102/1471$) were not considered in the analysis (Fig. 1).

The PARADISE "Pathway of dyspneic patients in Emergency" cohort was approved by the Commission d'Informatique et Libertés (CIL) (Number R2016-08) and registered on "clinicaltrials.gov" (NCT02800122).

Data acquisition

Two medical physicians (GG and TH) reviewed all electronic charts (including the discharge letter) and entered the data in an eCRF. Homogenous coding was ensured by a trained senior physician (TC) as outlined below. Specifically, acute HF diagnosis, regardless of etiology and systolic function, were coded according to the European Society of Cardiology criteria (clinical, electrocardiographic, echocardiographic and according to BNP levels) [16, 17].

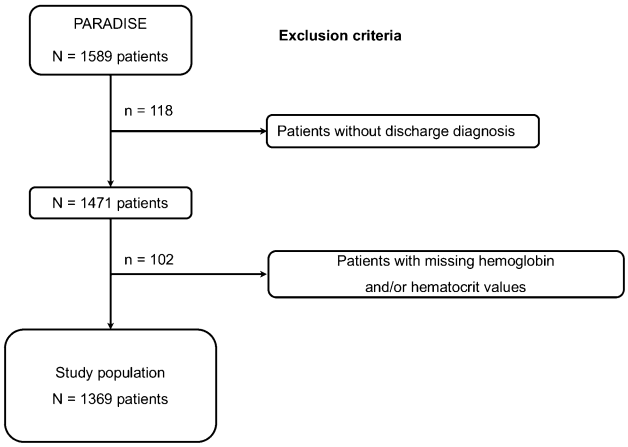

Fig. 1 Flow chart

To ensure coding homogeneity, 20 charts were randomly selected during the early phase of the coding process as well as during the coding process and were reviewed by the senior physician blinded to the initial coding performed by the medical reviewers. A mismatch between the two chart reviews was observed in less than 5% of the items. Our center (Clinical Investigation Center of Nancy, France) data management team performed coherence tests and a senior physician addressed all queries after chart reevaluation.

ePVS quantification

ePVS was calculated from hematocrit and hemoglobin values at admission to the ED as follows [13]:

$$\text{ePVS} = \frac{100 - \text{Ht}\,(\%)}{\text{Hb}\,(\text{g/dL})}.$$

Statistical analysis

All analyses were performed using the R software package (the R foundation for Statistical Computing). Continuous variables are expressed as means ± standard deviation if normally distributed or as median (interquartile range) if skewed, and categorical variables as frequencies (percentages). Odds ratios (OR) are presented with their 95% confidence interval (95% CI). The two-tailed significance level was set at $p < 0.05$.

Comparisons of baseline characteristics according to ePVS tertiles were carried out using one-way ANOVA or non-parametric Kruskal–Wallis test for continuous variables,

as appropriate, and Chi square or Fisher's exact tests for categorical variables.

Associations between ePVS and the two outcomes "AHF diagnosis" and "intra-hospital mortality" were assessed using a logistic regression model. The association with "AHF diagnosis" was adjusted for age, gender, comorbidities (heart failure, hypertension, myocardial infarction, coronary disease, chronic obstructive pulmonary disease), medications (β-blockers, ACE inhibitors, diuretics, oxygen) and clinical status (edema, respiratory distress, crackles, systolic blood pressure [18], heart rate). Assumption of log-linearity was verified using restricted cubic splines. When "intra-hospital mortality" was considered as outcome, the log-linearity hypothesis was not met, and ePVS was subsequently dichotomized using the second tertile as cutoff value. The association with "intra-hospital mortality" was adjusted for age, gender, medications (diuretics, antiaggregants), mode of admission, comorbidities [heart failure, hypertension, flutter/atrial fibrillation, coronary disease, chronic obstructive pulmonary disease (COPD)], clinical status at admission (systolic blood pressure, heart rate) and biological status at admission (hypokalemia < 4 mmol/L [19], corrected natremia, blood glucose, eGFR < 60 mL/min /1.73 m^2, lactate).

The added prognostic value of ePVS was assessed using the calculation of incremental AUC (IAUC), continuous net reclassification improvement (cNRI) and integrated discrimination improvement (IDI) indices.

Results

Patient characteristics (Supplementary Table 1)

A total of 1369 patients admitted to the ED for acute dyspnea with available hemoglobin and hematocrit measurements from the PARADISE cohort were studied. Characteristics of the 102 patients not considered in the analysis due to unavailable hemoglobin and/or hematocrit values primarily differed by a lower risk profile as explained by their high proportion of discharge home (63/102 vs. 277/1369 in patients with available hemoglobin and hematocrit measurements, data not shown).

The comorbidity burden of this elderly cohort (mean age 72 ± 19) was extensive (hypertension 54.9%, chronic heart failure 19.1%, COPD 38.3%). Peripheral edema and bilateral crackles were frequent (respectively, 24.7% and 34.7%). Mean systolic blood pressure (SBP) was 132 ± 26 mmHg and mean heart rate (HR) was 96/min ± 21. The most frequent diagnosis at hospital discharge was pneumonia (41%, $n = 561$) and AHF (21%, $n = 288$). Overall in-hospital length of stay was 11 ± 16 days.

There were 288 patients (21%) with AHF in the PARADISE cohort, including 81 patients (5.9%) without further diagnosis. In the remaining 207 patients with AHF, 12 patients (0.87%) had an associated diagnosis of acute coronary syndrome (ACS). 187 patients (13.6%) had an associated diagnosis of COPD or asthma and 8 patients (0.6%) had an associated diagnosis of atrial fibrillation. For the remainder of the population, 293 patients (21.4%) had COPD or asthma without AHF. There were 561 patients (41%) with pneumonia and only two patients (0.15%) with pulmonary embolism. Finally, 225 patients (16.4%) had other diagnoses (anxiety, pleural effusion, pneumothorax, pain, etc.) (Supplementary Table 2).

BNP values were only available in 37% of the patients in the cohort, while ECG was performed in 51.8% of the cases.

Patient characteristics according to ePVS tertiles (Table 1)

Median ePVS was 4.58 dL/g [3.96–5.55]. The threshold values of ePVS tertile distribution were 4.17 dL/g for the second tertile and 5.12 dL/g for the third tertile. Patients in the third tertile (ePVS > 5.12 dL/g) were more likely to have hypertension (66.4% vs. 43.8% in the 1st tertile, $p < 0.01$), chronic HF (21.7% vs. 15.5% in the 1st tertile, $p < 0.01$) and atrial fibrillation (AF) (28.7% vs. 14.7% in the 1st tertile, $p < 0.01$). In contrast, a higher proportion of COPD patients were observed in the first tertile (43.1% vs. 32.5% in the 3rd tertile, $p < 0.01$).

Patients from the third ePVS tertile were more likely to have clinical signs of congestion (peripheral edema, bilateral crackles) (both $p < 0.05$). There was a gradual and significant increase in BNP values across ePVS tertiles [BNP 1st tertile = 210 (77–493), BNP 3rd tertile = 372 (174–694), $p < 0.01$]. Patients from the third tertile also had a lower eGFR ($p < 0.01$), natremia ($p < 0.01$) and blood pH ($p < 0.01$).

In-hospital length of stay increased from 6 (2–12) days for the first tertile patients to 8 (3–15) days for the third tertile patients, $p < 0.01$.

Association of ePVS with AHF diagnosis (Table 2)

In univariable analysis, the third ePVS tertile was associated with AHF diagnosis (OR (95% CI) 1.71 [1.31–2.23], $p < 0.0001$). A similar association was obtained from the multivariable regression analysis (1.64 [1.16–2.33], $p = 0.005$).

Similar results were also obtained from analyses performed in subsets of patients with available BNP (adjusted OR (95% CI) 1.68 [1.07–2.63], $p = 0.023$). In contrast, in patients who did not have available BNP, in whom the proportion of AHF was much lower (< 10%), ePVS was not

Table 1 Characteristics of the study population according to ePVS and outcomes ($N = 1369$)

	Proportion of available data	Whole population	First tertile ($n = 457$) ePVS[a] ≤ 4.17 dL/g	Second tertile ($n = 456$) 4.17 dL/g < ePVS[a] ≤ 5.12 dL/g	Third tertile ($n = 456$) ePVS[a] > 5.12 dL/g	*p* value
Age (years)	100%	77 (62–86)	70 (55–83)	78 (61–86)	82 (69–88)	< 0.0001
Female	100%	671 (49.0%)	179 (39.2%)	239 (52.4%)	253 (55.5%)	< 0.0001
Medical history	100%					
Chronic heart failure		261 (19.1%)	71 (15.5%)	91 (20.0%)	99 (21.7%)	0.048
Prior hospitalization for HF[b]		94 (6.9%)	24 (5.3%)	24 (5.3%)	46 (10.1%)	0.005
Hypertension		751 (54.9%)	200 (43.8%)	248 (54.4%)	303 (66.4%)	< 0.0001
Coronary disease		166 (12.1%)	47 (10.3%)	58 (12.7%)	61 (13.4%)	0.31
Stroke		157 (11.5%)	47 (10.3%)	60 (13.2%)	50 (11.0%)	0.36
Atrial fibrillation		315 (23.0%)	67 (14.7%)	117 (25.7%)	131 (28.7%)	< 0.0001
Diabetes		307 (22.4%)	82 (17.9%)	105 (23.0%)	120 (26.3%)	0.009
Dyslipidemia		287 (21.0%)	83 (18.2%)	98 (21.5%)	106 (23.2%)	0.16
COPD[c]		524 (38.3%)	197 (43.1%)	179 (39.3%)	148 (32.5%)	0.004
Chronic kidney disease		146 (10.7%)	35 (7.7%)	40 (8.8%)	71 (15.6%)	0.0002
Medications	96.0%					
β-blockers		314 (23.9%)	87 (19.5%)	89 (20.8%)	138 (31.5%)	< 0.0001
ACE inhibitors[d]		250 (19.0%)	62 (13.9%)	89 (20.8%)	99 (22.6%)	0.002
ARBs[e]		211 (16.1%)	58 (13.0%)	73 (17.1%)	80 (18.3%)	0.075
Spironolactone or eplerenone		69 (5.3%)	25 (5.6%)	19 (4.4%)	25 (5.7%)	0.66
Diuretics		374 (28.5%)	96 (21.5%)	113 (26.4%)	165 (37.7%)	< 0.0001
Antiplatelet agents		436 (33.2%)	124 (27.7%)	142 (33.2%)	170 (38.8%)	0.002
Vitamin K antagonist		246 (18.7%)	63 (14.1%)	82 (19.2%)	101 (23.1%)	0.003
Oral anticoagulant therapy		37 (2.8%)	6 (1.3%)	13 (3.0%)	18 (4.1%)	0.036
"Dyspnea/hospitalization" delay (days)	99.6%	1 (0–3)	1 (0–3)	1 (0–3)	2 (1–3)	0.005
Increased JVP[f]	98.6%	43 (3.2%)	13 (2.9%)	16 (3.6%)	14 (3.1%)	0.82
Peripheral edema	100%	338 (24.7%)	105 (23%)	100 (21.9%)	133 (29.2%)	0.025
Respiratory rate	68.4%	24 (20–32)	26 (20–33)	24 (20–30)	24 (20–30)	0.020
SpO_2 (%)	99.8%	95 (93–97)	94 (92–97)	95 (93–97)	95 (93–97)	0.0004
BMI (kg/m^2)[g]	98.9%	26.1 (21.6–27.7)	26.1 (22.2–27.8)	26.1 (21.9–27.9)	25.5 (20.8–27.2)	0.030
Pulmonary auscultation	96.7%					
Bilateral crackles		460 (34.7%)	131 (29.6%)	154 (34.7%)	175 (40.0%)	0.005
Focal auscultatory findings		308 (23.3%)	87 (19.6%)	101 (22.7%)	120 (27.5%)	0.023
Sibilant rale		359 (27.1%)	132 (29.8%)	127 (28.6%)	100 (22.9%)	0.046
Rhonchi		285 (21.5%)	76 (17.2%)	104 (23.4%)	105 (24.0%)	0.021
Systolic blood pressure (mmHg)	100%	132 ± 26	136 ± 26	132 ± 26	129 ± 25	< 0.0001
Heart rate (/min)	99.6%	96 ± 21	98 ± 22	95 ± 20	94 ± 20	0.004
Biology						
BNP[h] (pg/mL)	37.0%	270 (129–586)	210 (77–493)	256 (99–498)	372 (174–694)	< 0.0001
BNP (pg/mL)						< 0.0001
< 100 pg/mL		100 (19.8%)	44 (27.8%)	40 (25.2%)	16 (8.5%)	
100–400 pg/mL		221 (43.7%)	69 (43.7%)	66 (41.5%)	86 (45.5%)	
> 400 pg/mL		185 (36.6%)	45 (28.5%)	53 (33.3%)	87 (46.0%)	
Hyperkalemia (K^+ < 4 mmol/L)	94.5%	473 (36.6%)	154 (35.7%)	163 (38.1%)	156 (35.9%)	0.73
Blood glucose (mmol/L)	97.1%	6.7 (5.7–8.5)	6.7 (5.7–8.4)	6.8 (5.7–8.8)	6.6 (5.6–8.2)	0.63
Serum sodium (mmol/L)	97.3%	137 (134–140)	138 (135–140)	137 (135–139)	137 (134–140)	0.001

Table 1 (continued)

	Proportion of available data	Whole population	First tertile ($n=457$) ePVS[a] ≤ 4.17 dL/g	Second tertile ($n=456$) 4.17 dL/g < ePVS[a] ≤ 5.12 dL/g	Third tertile ($n=456$) ePVS[a] > 5.12 dL/g	p value
Corrected natremia (mmol/L)	97.1%	138 (135–140)	138 (136–140)	137 (135–140)	137 (134–140)	0.001
eGFR MDRD[j] (mL/min/1.73m^2)	96.6%	79 (54–100)	88 (64–101)	80 (57–100)	70 (43–100)	< 0.0001
eGFR MDRD < 60 mL/min/1.73m^2		394 (29.8%)	97 (22.0%)	121 (27.3%)	176 (40.2%)	< 0.0001
pH	80.8%	7.41 (7.34–7.45)	7.39 (7.32–7.44)	7.41 (7.35–7.45)	7.42 (7.35–7.46)	< 0.0001
PaO_2 (mmHg)	80.6%	65.0 (56.0–79.0)	63.0 (56.0–77.0)	64.0 (55.0–81.0)	66.0 (56.0–80.5)	0.34
$PaCO_2$ (mmHg)	80.8%	40.0 (35.0–48.0)	41.0 (35.0–50.0)	40.0 (35.0–48.0)	40.0 (34.0–47.0)	0.14
Lactate (mmol/L)	80.1%	1.1 (0.8–1.6)	1.2 (0.8–1.9)	1.0 (0.8–1.6)	1.0 (0.7–1.4)	< 0.0001
ePVS at admission	100%	4.58 (3.96–5.55)	3.72 (3.38–3.96)	4.59 (4.40–4.85)	6.08 (5.55–6.96)	< 0.0001
Dyspnea diagnosis at discharge	100%					< 0.0001
Heart failure		288 (21.0%)	79 (17.3%)	85 (18.6%)	124 (27.2%)	
COPD		293 (21.4%)	136 (29.8%)	104 (22.8%)	53 (11.6%)	
Pneumonia		561 (41.0%)	149 (32.6%)	200 (43.9%)	212 (46.5%)	
Pulmonary embolism		2 (0.1%)	0 (0.0%)	2 (0.4%)	0 (0.0%)	
Other diagnosis		225 (16.4%)	93 (20.4%)	65 (14.3%)	67 (14.7%)	
Outcomes						
Length of stay (days)	97.5%	7 (2–13)	6 (2–12)	7 (3–12)	8 (3–15)	0.001
In-hospital mortality	97.8%	149 (11.1%)	38 (8.4%)	50 (11.2%)	61 (13.8%)	0.035

[a]*ePVS* estimated plasma volume status

[b]*HF* heart failure

[c]*COPD* chronic obstructive pulmonary disease

[d]*ACE inhibitors* angiotensin-converting enzyme inhibitors

[e]*ARBs* angiotensin receptor blockers

[f]*JVP* jugular venous pressure

[g]*BMI* body mass index

[h]*BNP* brain natriuretic peptide

[i]*eGFR* estimated glomerular filtration rate

[j]*MDRD* modification of diet in renal disease

significantly associated with AHF despite a similar point estimate of the association (OR (95% CI) 1.70 [0.88–3.29], $p=0.11$) (Fig. 2).

A specificity and sensitivity analysis for HF diagnosis was performed based on the ePVS thresholds and detailed in Supplementary Table 3.

Furthermore, using a multivariable analysis of the diagnostic performance of ePVS, an OR = 1.50 (1.06–2.13) $p=0.023$ was obtained for the model without BNP and 1.24 (0.84–1.83) $p=0.28$ when BNP was available (Supplementary Table 4).

Finally, an increase in ePVS diagnostic performance was also detected with a continuous net reclassification improvement (cNRI) of 25.3 95% CI (12.3–38.2) $p=0.0001$ without available BNP values and 22.3 95% CI (9.3–35.3) $p=0.0008$ with available BNP values.

Association of ePVS with in-hospital mortality (Table 3)

In-hospital mortality was 11.1% ($n=149$) and gradually increased across ePVS tertiles, rising from 8.4% ($n=38$) in the first tertile, to 13.8% in the third tertile, $p<0.01$.

In univariable analysis, ePVS was significantly associated with higher in-hospital mortality either using the second tertile threshold or the third tertile threshold (OR for 2nd tertile threshold (95% CI) 1.56 [1.06–2.30], $p=0.024$; OR for 3rd tertile threshold (95% CI) 1.47 [1.04–2.09], $p=0.029$). Similar results were obtained from the multivariable analysis (Table 3).

The association of ePVS with in-hospital mortality, either using the second tertile threshold or the third tertile threshold, was not significantly different in patients with

Table 2 Association between ePVS and discharge diagnosis of heart failure

	N_{AHF}/N (%)	Univariable logistic model		Multivariable logistic model[a]	
		OR (95% CI)	*p*	OR (95% CI)	*p*
Whole population					
ePVS ≤ T2	164/913 (18%)	1.00	< 0.0001	1.00	0.005
ePVS > T2	124/456 (27.2%)	1.71 (1.31–2.23)		1.64 (1.16–2.33)	
According to BNP availability					
In patients without available BNP					
ePVS ≤ T2	38/596 (6.4%)	1.00	0.084	1.00	0.11
ePVS > T2	26/267 (9.7%)	1.58 (0.94–2.67)		1.70 (0.88–3.29)	
In patients with available BNP					
ePVS ≤ T2	126/317 (39.7%)	1.00		1.00	0.023
ePVS > T2	98/189 (51.9%)	1.63 (1.14–2.35)	0.008	1.68 (1.07–2.63)	

AHF acute heart failure, *BNP* brain natriuretic peptide

[a]Multivariable logistic regression analysis with statistical adjustment for age, gender, comorbidities (heart failure, hypertension, myocardial infarction, coronary disease, chronic obstructive pulmonary disease), medications (β-blockers, ACE inhibitors, diuretics, oxygen) and clinical status (edema, respiratory distress, crackles, systolic blood pressure, heart rate). $p < 0.05$

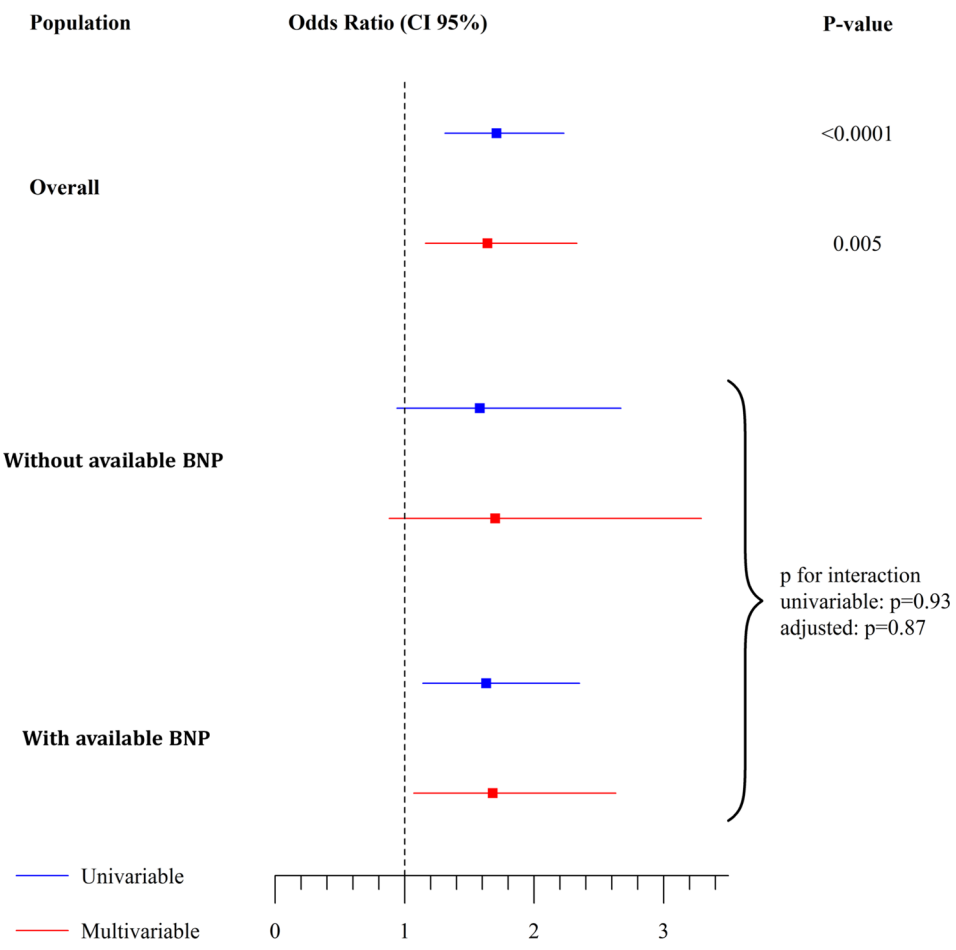

Fig. 2 Univariable and multivariable association between ePVS and discharge diagnosis of heart failure

Table 3 Univariable and multivariable association between ePVS and in-hospital mortality

	N death/*N* (%)	Univariable model		Multivariable model[a]	
		OR (95% CI)	*p* value	OR (95% CI)	*p* value
ePVS		1.15 (1.05–1.32)	0.002	1.23 (1.07–1.41)	0.003
ePVS ≤ T1	38/453 (8.4%)	1.00	–	1.00	–
ePVS > T1	111/887 (12.5%)	1.51 (1.02–2.23)	0.024	2.06 (1.25–3.38)	0.004
ePVS ≤ T2	88/898 (9.8%)	1.00	–	1.00	–
ePVS > T2	61/442 (13.8%)	1.47 (1.04–2.09)	0.029	1.54 (1.01–2.36)	0.047

ePVS estimated plasma volume status

[a]Adjusted for age, gender, medications (diuretics, platelet antiaggregants), mode of admission, comorbidities (heart failure, hypertension, flutter/atrial fibrillation, coronary disease, chronic obstructive pulmonary disease), clinical status at admission (systolic blood pressure, heart rate) and biological status at admission (hypokalemia < 4 mmol/L, corrected natremia, blood glucose, eGFR < 60 mL/min /1.73 m^2, lactate). $p < 0.05$

or without AHF (p for interaction 0.85 and 0.83, respectively) (Fig. 2).

Lastly, the added prognostic value of ePVS was assessed in the multivariable logistic regression model, in which an increase in ePVS prognostic performance was detected with a cNRI of 33.8 95% CI (15.3–52.2) $p = 0.0003$ (Supplementary Table 5).

Discussion

The main findings of our study are that ePVS is significantly associated with AHF diagnosis (OR CI 9% 1.64 [1.16–2.33], $p = 0.005$) and in-hospital mortality (OR 1.23 [1.07–1.41], $p = 0.003$) in patients admitted in the ED for acute dyspnea. Given the wide availability of ePVS, its low cost and very rapid quantification, as well as the standard widespread use of hemogram prescription in the ED, ePVS measurement could represent a valuable additional tool for the early diagnosis and risk stratification of patients with acute dyspnea in an emergency setting.

ePVS for AHF diagnosis in the ED

AHF diagnosis is currently suboptimal in the ED. Accordingly, Ray et al. reported the accuracy of the etiological diagnosis of acute dyspnea to be as low as 76% despite the use of chest X-ray and natriuretic peptides [4]. Importantly, while BNP measurement is indeed important, it does not completely solve the diagnostic issue of the origin of acute dyspnea, as recently highlighted in the study of Pivetta et al., which reported an area under the curve of 0.733 with regard to accuracy of BNP in diagnosing AHF [20]. The BNP and the NTproBNP "gray zone" ultimately translate into diagnostic uncertainty in a number of patients, ranging from 38.5 to 43.5% of patients admitted for acute dyspnea [21].

In addition, several studies have suggested that inadequate initial treatment of heart failure (resulting from an inadequate initial diagnosis) is associated with higher subsequent mortality [4, 5, 7]. For instance, in the ADHERE registry, mortality in patients who received AHF treatment (diuretics and/or vasodilators) while suffering from another cause of dyspnea, had a much higher in-hospital mortality rate than AHF patients (from 3.8 to 13.8%, $p < 0.05$) [22]. In addition, Matsue et al. recently showed that patients with AHF receiving diuretics within 1 h of admission had a 2.3% risk of death, while those treated later had a 6.0% risk of death ($p = 0.002$—adjusted OR: 0.39;95% CI [0.20–0.76]; $p = 0.006$) [7]. This makes targeting an early appropriate diagnosis of acute dyspnea cause particularly beneficial in patients admitted to the ED [23].

Our study suggests that ePVS—using a threshold of 5.12 dL/g—is a useful diagnostic tool to identify AHF in patients admitted for acute dyspnea in the ED (adjusted OR for AHF diagnosis 95% CI 1.64 [1.16–2.33], $p = 0.005$). Importantly, most hemodialysis devices currently use hematocrit to monitor volemia during hemodialysis sessions [12]. To the best of our knowledge, this is the first report investigating the diagnostic value of ePVS in an emergency setting. Of note, the association of ePVS with AHF diagnosis was only significant when not adjusting for BNP (Supplementary Table 4). However, this result can nonetheless have practical implications since ePVS can be determined within a few minutes in the ED, whereas natriuretic peptide quantification usually requires several hours in most hospital settings [24]. This would suggest that ePVS could represent an additional diagnostic tool, along with chest X-ray and lung ultrasound, for the very early identification of AHF in the ED. Importantly, while lung ultrasound has a higher diagnostic value than ePVS for the diagnosis of AHF [20], lung ultrasound is currently not systematically performed in patients with acute dyspnea in most centers worldwide, thus leaving room for

improvement using simple and rapid diagnostic biological tools such as ePVS.

ePVS for risk stratification in patients admitted for acute dyspnea in the ED

Smith et al. showed that severity assessment and hospitalization decision of patients with AHF, based on physician's clinical judgment alone, lead to an overutilization of intensive care unit resources through overestimation of the risk of complication [25]. Such observations have triggered the creation of various risk scores for acute dyspnea including the EHMRG (Emergency Heart Failure Mortality Risk Grade) [26], the Get With the Guidelines-Heart Failure (GWTG-HF) score [27] and the ADHERE score [24]. However, these scores are focused on patients with an initial diagnosis of AHF in the ED, the latter being inadequate in a number of patients as emphasized above [28].

Our data suggest that ePVS has a high prognostic value in patients admitted for acute dyspnea in the ED (adjusted OR for in-hospital mortality in patients with ePVS above the 3rd tertile threshold = 1.47 [1.04–2.09], $p = 0.029$). This further reinforces the prognostic value of ePVS regardless of the setting: our group previously highlighted the post-discharge prognostic value of ePVS following MI with systolic dysfunction in the EPHESUS trial [13]. Hudson et al. furthermore reported that changes in ePVS was an independent predictor of post-discharge death and hospitalization for heart failure even while adjusting for the ADHERE score [29]. Likewise, Yoshihisa et al. reported that admission ePVS was an independent predictor of all-cause mortality in AHF patients (HR for patients above the third tertile = 1.429, $p < 0.001$), cardiac mortality (HR 1.416, $p = 0.001$) and cardiac events (HR 1.207, $p = 0.004$) [14]. However, the study of Yoshihisa et al. used a different formula than the instant ePVS calculation used herein (which is derived from the Strauss formula). The formula previously used by other authors includes patient dry weight, which is difficult to obtain in patients admitted for fluid overload. In addition, in the above previous report, consideration was given to mid-term outcome rather than to in-hospital mortality with the study population being restricted to patients with AHF. Importantly, we found no evidence of heterogeneity in the association of ePVS with mortality in patients with and without AHF (as demonstrated by p values for interaction > 0.80). Our results consequently strengthen the prognostic value of ePVS, showing that admission ePVS (not assessed from patient dry weight, but from the instant ePVS calculation derived from the Strauss formula [30]) is associated with in-hospital outcome in an unselected population of acute dyspnea admitted to the ED, regardless of the underlying cause of dyspnea, and after adjustment for baseline comorbidities and biological abnormalities (lower eGFR, corrected natremia).

Importance of congestion quantification in patients admitted for acute dyspnea in the ED

Congestion during AHF is the key driver of symptoms and is associated with organ dysfunction, in particular worsening renal function [31], which can in turn influence prognosis [32]. Congestion has also been shown to cause dilatation of the left ventricular wall and trigger the production of inflammatory factors, which can contribute to myocardial dysfunction [33]. An early quantification of congestion (including as early as on admission in the ED) consequently appears of importance [34]. Nevertheless, clinical examination is likely less relevant to congestion quantification than congestion identification [10, 35, 36], especially due to its limited capacity to identify and monitor low to moderate levels of congestion [37].

Lung ultrasound has emerged as a useful tool for the identification and quantification of pulmonary congestion, although it is limited to the investigation of only pulmonary congestion per se [38]. Notwithstanding, and as previously emphasized, extra-pulmonary congestion can be mild or absent in the setting of acute pulmonary congestion due to an hypertensive crisis; in these clinical settings, fluid redistribution was preferentially observed as opposed to systemic fluid overload, which obviously cannot be captured by the use of LUS alone.

ePVS, unlike LUS, explores the systemic component of congestion. Other congestion variables can also target systemic congestion assessment, although, in clinical practice, such evaluation is solely based on inferior vena cava assessment using echocardiography. Unfortunately, echocardiography is rarely performed in the ED [3] and its feasibility in patients with acute dyspnea can be very challenging [39]. Consequently, we firmly believe that ePVS could be a useful congestion variable in addition to LUS assessment in the specific setting of patients admitted to the ED.

Limitations

The main limitation of this study is its single-center and retrospective design. However, over 1000 patients were included in this analysis and the single-center nature of our study does translate into a relatively homogenous management of patients with acute dyspnea. Moreover, even if retrospective, our cohort exhibited a low proportion of missing data owing to complete access to electronic charts and the systematic review of all observations by a medical physician.

Secondly, since most of the patients included in this cohort were swiftly transferred to other departments, we did

not have access to changes in ePVS; such changes in ePVS could further add to the prognostic value of ePVS.

Thirdly, ePVS sensitivity and specificity were within the 70 to 80% range at most [the sensitivity and specificity of the 1st tertile threshold (4.17 dL/g) were 72.6% and 34.8% respectively comparatively to 43.1% and 69.2% for the threshold of the 2nd tertile (5.12 dL/g)]. However, importantly, the specificity of natriuretic peptides for AHF diagnosis in the ED has recently been reported by Pivetta et al. to be as low as 61.7% [95% CI 54.6–68.3%] [20]. In addition, the sensitivity of BNP > 500 ng/L has been reported to be as low as 0.35 (0.17–0.56) [21]. These sensitivity and specificity values of biological markers for the diagnosis of AHF in the ED likely suggest that emergency physicians should use the latter in a complementary manner using a multi-marker approach including clinical, biological and imaging markers to improve the accuracy of AHF diagnosis. In keeping with the above, we provide evidence for an added value of ePVS on top of clinical variables as expressed by a significant increase in NRI [25.3 95% CI (12.3–38.2) $p = 0.0001$]. Importantly, BNP and ePVs investigate different congestion features. Whereas BNP represents a "pressure biomarker" and can increase during isolated pulmonary congestion and/or systemic congestion, ePVS, by essence, is a "systemic biomarker" and its diagnostic value is necessarily lower than that of BNP which reflects both congestion settings.

Conclusion

Higher ePVS values determined from first blood sample at admission are associated with a higher probability of AHF and in-hospital mortality in patients admitted in the ED for acute dyspnea. ePVS, whose results are typically available within an hour, may potentially improve AHF diagnosis without substituting BNP measurements and promote early risk stratification in patients with acute dyspnea.

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Compliance with ethical standards

Conflict of interest Dr Chouihed and Dr. Girerd have received board membership fees from Novartis. Dr. Rossignol received fees from Relypsa. Dr. Zannad has received fees for serving on the board of Boston Scientific; consulting fees from Novartis, Takeda, AstraZeneca, Boehringer Ingelheim, GE Healthcare, Relypsa, Servier, Boston Scientific, Bayer, Johnson and Johnson, and Resmed; and speakers' fees from Pfizer and AstraZeneca. He and Dr. Rossignol are cofounders of CardioRenal diagnosticS.

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