


Estimation of the plasma volume status of elderly patients with acute decompensated heart failure using bedside clinical, biological, and ultrasound parameters

Xenia Leahova-Cerchez MD¹ | Emmanuelle Berthelot MD²  |
Bastien Genet MD^{3,4} | Olivier Hanon MD, PhD¹ | Patrick Jourdain MD, PhD²

¹Hôpital Broca, Service de Gériatrie, Assistance Publique-Hôpitaux de Paris and EA 4468, Université de Paris, Paris, France

²Department of Cardiology, Université Paris-Saclay, AP-HP, Hôpital Bicêtre, Le Kremlin-Bicêtre, France

³Department of Biostatistics, Université Paris Sud, Le Kremlin-Bicêtre, France

⁴Department of Statistics and Methodology in Biomedical Research, Paris-Saclay University, Gif-sur-Yvette, France

Correspondence

Emmanuelle Berthelot, MD, Department of Cardiology, Hôpital Bicêtre, Université Paris-Saclay, 78 rue du Général Leclerc, 94270 Le Kremlin Bicêtre, France.

Email: emmanuelle.berthelot@aphp.fr

Abstract

Objective: Assessment of intravascular volume status to ensure optimization before hospital discharge could significantly reduce readmissions. It is difficult to evaluate congestion on clinical signs during an episode of acute heart failure (ADHF) in elderly patients.

Hypothesis: There is an association between various volume overload parameters in patients older than 75 years.

Methods: We performed a single-center prospective longitudinal study of patients older than 75 years hospitalized for acute heart failure. We analyzed the association between congestion assessment based on clinical signs, inferior vena cava (IVC) diameter measured by ultrasound, biological evaluation with N terminal pro brain natriuretic peptide (NT-proBNP), and estimated plasma volume (EPV) during decongestive therapy. We also monitored changes in renal function.

Results: Fifty consecutive ADHF patients (85.2 ± 5.9 years, 68% female) were included in the study. At admission, a dilated, noncompliant IVC was found in all patients. The strongest correlations between different parameters of volume overload estimation were found between IVC and jugular vein distention ($r = .8$; $p < .001$), then IVC and oedema ($r = .6$; $p < .001$), IVC and crackles ($r = .3$; $p < .036$), then IVC and NT-proBNP ($r = .3$; $p = .02$). There was no correlation between EPV and signs of congestion. Patients who had no congestive signs on clinical or IVC examination at Day 2, more often presented with acute renal failure.

Conclusion: In ADHF patients older than 75 years, clinical and IVC evaluation of intravascular congestion correlate well. The concomitant assessment of clinical signs and IVC may prevent depletion-related renal failure.

Abbreviations: ACEi, angiotensin-converting-enzyme inhibitor; AF, atrial fibrillation; AHA, American Heart Association; ADHF, acute decompensated heart failure; ALAT, alanine aminotransferase; APE, acute pulmonary edema; ARB, angiotensin II receptor blocker; ARF, acute renal failure; ASAT, aspartate-amino-transférase; BP, blood pressure; CHF, chronic heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; D, diameter; ECG, electrocardiogram; ePVS, estimated plasma volume status; ESC, European Society of Cardiology; GFR, glomerular filtration rate; Hb, hemoglobin; HF-PEF, heart failure with preserved ejection fraction; HF-REF, heart failure with reduced ejection fraction; HJR, hepatojugular reflux; HR, heart rate; HTN, hypertension; IHD, ischemic heart disease; IVC, inferior vena cava; JVD, jugular vein distention; LLE, lower limb edema; LV, left ventricle; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NT-proBNP, N terminal pro brain natriuretic peptide; RAP, right atrial pressure; RV, right ventricle; RV, respiratory variation; SEGA, short emergency geriatric assessment; TTE, transthoracic echocardiogram.

KEYWORDS

acute decompensated heart failure, arrhythmia/all, biomarkers, congestive state, management, older patients, ultrasound

1 | INTRODUCTION

Heart failure is a common disease, with a prevalence of estimates 1,130,000 people in France, with an incidence of more than 120,000 new cases per year.¹ It is a serious disease, burdened with decompensation, with significant consequences on quality of life and soaring costs of public health.² Its incidence and prevalence increase considerably with age, making it the most common cause of hospitalization in the elderly, with more than 50,000 hospitalizations per year in people over 75 in France.³

The assessment of intravascular congestion is paramount in treating acute decompensated heart failure (ADHF) in elderly patients, as it helps optimize diuretic therapy. Such assessment is based on clinical presentation. Elevated jugular venous pressure is a specific sign of overload,⁴ though not a very sensitive one.^{5,6} Natriuretic peptides and chest X-ray are difficult to interpret in the elderly.^{7,8} Transthoracic echocardiography (TTE) remains a method of choice to assess congestion by analyzing left ventricular filling pressures and the inferior vena cava (IVC) variations.⁴ However, access to TTE is limited and it is performed less than one in five patients in geriatric departments.^{9,10}

IVC diameter and compliance as assessed by echocardiography is a fast and effective way to obtain the right-atrial pressure with a threshold of 21 mm and respiratory variation <50% to define hypervolemia.^{11,12} The IVC can guide the clinician in administering effective decongestive treatment and achieving euolemia.^{13,14} In a frail, multimorbid and poly-medicated patient, an ultra-portable ultrasound device at bedside is a valuable, easy-to-use tool.¹⁴

Other parameters have been proposed for the diagnosis and monitoring of volume overload in ADHF patients. The indirect estimation of plasma volume status (ePVS) by the Duarte formula¹⁵ could be useful in diagnosing ADHF.¹⁶

The occurrence of renal failure under diuretic treatment is frequent and increases the length of hospital stay. The use of a blood volume-monitoring tool might be helpful to avoid renal failure¹⁷⁻¹⁹ (Appendix A).

The aim of the study was to determine the relationship between various parameters of blood volume assessment (clinical and laboratory parameters, IVC ultrasound exam, and instantaneous plasma volume) in patients over 75 years of age admitted for ADHF. Then, to determine whether IVC parameters enable identifying patients at risk of functional acute renal failure related to excessive depletion.

2 | METHODS

2.1 | Study presentation

Our study is an observational, longitudinal, prospective, single-center cohort study that was conducted in the cardiology department of

Bicêtre hospital between January 1, 2019, and May 1, 2020. Consecutive patients older than 75 years, hospitalized for ADHF and discharged alive were eligible for the study. The ADHF diagnosis was based on a combination of clinical signs and symptoms, admission N terminal pro brain natriuretic peptide (NT-proBNP) >1500 pg/ml and echocardiographic structural abnormalities (left ventricular ejection fraction [LVEF], filling pressures).^{4,20} The study excluded patients with NT-proBNP <300 pg/ml, cardiogenic shock, acute MI < 1 week, acute pulmonary edema, acute anemia requiring red blood cell transfusions, severe liver failure not related to heart failure with liver enzymes aspartate-amino-transférase and alanine aminotransferase > 4 N, severe chronic kidney disease (CKD) with estimated glomerular filtration rate (eGFR) < 15 ml/min on admission, or on dialysis.

The study complied with the declaration of Helsinki and was approved by the local ethics committee (#20181128163709). All patients gave their informed consent.

2.2 | Data collection

On admission, we collected demographic data including gender and age, and the number of hospitalizations during the previous year.

Medical history included screening for ischemic heart disease (IHD), atrial fibrillation (AF), severe aortic stenosis, arterial hypertension (HTN), LVEF if known, severe CKD with Glomerular filtration rate 30 ml/min, chronic obstructive pulmonary disease (COPD), and diabetes. Data were collected concerning the following medications at admission and discharge: angiotensin-converting-enzyme inhibitors (ACEi), angiotensin II receptor blockers (ARB), diuretics, beta-blockers, and mineralocorticoid receptor antagonists (MRA).

Patient frailty was assessed using the Short Emergency Geriatric Assessment (SEGA) grid part A version approved in 2014.²⁰

2.3 | Management

On admission, patients were treated with loop diuretics such as Furosemide according to the DOSE trial-inspired protocol.²¹ Doses were adjusted according to the doctor's clinical judgment and the patient's frailty.²² The motive for switching to oral diuretic and the cumulative IV dose were recorded.

During hospitalization, a daily clinical examination provided data on weight, heart rate (HR), blood pressure (BP), and the presence of hepatojugular reflux (HJR) or jugular vein distention (JVD) if any. The occurrence of lower limb edema (LLE) was graded according to extent

(none, ankles, knees, and thighs), and similarly for lung crackles (none, lung base, half of the lungs, more than 2/3 of the lungs). Biological data collected daily-included plasma protein levels, hemoglobin, hematocrit, urea and creatinine, with estimated renal function (eGFR according to the CKD-EPI formula) until discharge or up to Day 8. NT-proBNP and plasma albumin were measured at admission.

IVC was measured with the ultra-portable VScan Extend device (GE Healthcare) on hospital admission and on Day 2, and then until the intravenous diuretic was stopped (Day 4 on average) and switched to oral diuretic. Measurements were taken by a resident doctor in charge of the study who was not initially experienced. The training given over 5 days (30 patients total) showed excellent agreement between the assessments performed by an intern and by an experienced operator (Kappa = 0.982 (95% confidence interval [CI]: 0.965–0.991)).

IVC status was defined according to the guidelines²³ as five possibilities: “thin,” “non-dilated with diameter (D) < 21 mm and respiratory variation (RV) > 50%,” “dilated with D < 21 mm or RV < 50%,” “dilated with D > 21 mm and RV < 50%,” “dilated with D > 21 mm and RV < 50% and dilated hepatic veins.”

Estimated plasma volume status was estimated using the Duarte formula:

$$EPVs \left(\frac{dL}{g} \right) = 0.01 \times \frac{1 - 0.01 \times \text{hématocrit}(\%)}{\text{hémoglobine} \left(\frac{g}{dL} \right)}$$

2.4 | Assessment of hypervolemia

Hypervolemia was defined clinically by the presence of at least one clinical sign of congestion (JVD, HJR, LLE associated or not with crackles on lung auscultation).

Hypervolemia was defined by echo by a “dilated IVC > 21 mm and/or RV < 50%.”^{24,25}

The biological definition of hypervolemia was an ePVS score > 5.2 $\frac{dL}{g}$, adapting the results of Chouihed study.²⁶

To monitor follow-up and diuretic treatment and its effect on creatinine levels from D0 to D8, four groups were defined by clinical and IVC evaluation: clinical hypervolemia alone, hypervolemia by IVC alone, hypervolemia by clinical and IVC evaluation, and no hypervolemia at D2. A significant increase in blood creatinine level was defined as a 30% increase from baseline.

2.5 | Statistical analysis

Continuous variables were expressed as mean (standard deviation -SD-), and categorical variables were expressed as a number or frequency (percentage). Differences in patients' clinical characteristics were compared by the χ^2 test (or Fisher test if conditions were not checked) for categorical data and by the Wilcoxon test for continuous data.

A Treemap was used to represent the clinical and ultrasound hypervolemia groups at D1 and D2. A heatmap was used to represent the correlation between clinical, ultrasound, and biological parameters.

A plot over time was used to show the relationships between volume estimations depending on methods and creatinine levels.

A two-sided *p* value < .05 was considered statistically significant. All statistical analyses were performed using RStudio 1.4.1103.

3 | RESULTS

Fifty patients (85.2 ± 5.9 years old, 68% female) were included. Mean SEGA frailty score was 10.4 ± 2.5, each patient presented with an average of five comorbidities, and 18% of patients lived in nursing homes. The main comorbidities were iron deficiency (66%), diabetes (40%), COPD (16%), undernutrition (22%), and severe chronic renal failure with eGFR < 30 ml/min estimated by CKD-EPI (10%). Cardiovascular comorbidities included hypertension (94% of patients), Atrial Fibrillation (66%), Iron deficiency (34%), and severe aortic stenosis (12%). The mean ejection fraction was 44 ± 14%, and 48% of patients had an LVEF ≥ 50%. 42% of patients were hospitalized for acute decompensated HF at least once during the previous year (Table 1).

In the acute phase, the mean duration of intravenous Furosemide treatment was 4.8 ± 1.7 days with a mean dose of 775 ± 1132 mg. Acute renal failure (>30% increase from baseline creatinine) was found in 8% of patients.

98% of patients had ePVS > 5.2 $\frac{dL}{g}$ on admission. Mean NT-proBNP was 11 516 (±12 695) ng/L (Table 2; Figure 1).

On admission, at Day 1 (D1) a dilated, noncompliant IVC correlated well with signs of right heart failure (IVC and JVD/HJR with *r* = .8; *p* < .001, 95% CI: 0.67–0.88; IVC and LLE with *r* = .6; *p* < .001, 95% CI: 0.36–0.74) but correlated slightly with signs of left heart failure (IVC and crackles *r* = .3; *p* = .036).

This result was the same on day 2 (D2). The ePVS did not correlate with either clinical signs or IVC.

There was a correlation between NT-proBNP level at D1 and lung crackles (*r* = .28; *p* = .03) as well as with IVC (*r* = .3; *p* = .02) (Figure 2). Hematocrit and plasma protein levels between D1 and D2 showed no significant variation. Plasma protein levels correlated slightly with LLE and NT-proBNP.

By combining the different means of monitoring volume status at D2 in four groups (clinical hypervolemia alone, hypervolemia by IVC alone, hypervolemia by clinical evaluation and IVC, no hypervolemia), changes in creatinine over the duration of diuretic therapy could be analyzed between D0 and D7 (Figure 3). In the group combining the two parameters (clinical and IVC), a variation in creatinine was found. The six patients who presented functional acute renal failure were those who had a thin, compliant IVC as of Day 2.

4 | DISCUSSION

Our study shows that clinical and ultrasound assessment of the intravascular congestive states of elderly patients with acute heart failure is reliable. There is a significant correlation between JVD/HJR and IVC

TABLE 1 Baseline characteristics

Groups	Overall (D1)
N (%)	50 (100)
<i>Demographic and medical factors</i>	
Age, mean (SD)	85.2 (5.9)
Age groups, n (%)	
75-85 years	25 (50)
>85 years	25 (50)
Female sex, n (%)	34 (68)
SEGA, mean (SD)	10.4 (2.5)
Iron deficiency, n (%)	33 (66)
Coronary heart disease, n (%)	17 (34)
Hypertension, n (%)	47 (94)
eGFR (ml/min), mean (SD)	46 (15)
Chronic kidney disease, n (%) eGFR<30	5 (10)
COPD, n (%)	8 (16)
Atrial fibrillation, n (%)	33 (66)
Diabetes mellitus, n (%)	20 (40)
LVEF (%), mean (SD)	44 (14)
LVEF ≥ 50%, n(%)	24 (48)
<i>Biological factors</i>	
C reactive protein (ng/ml), mean (SD)	32 (62)
Albuminemia (g/dl), mean (SD)	34 (5)
NT-pro BNP (ng/l), mean (SD)	11516 (12695)
<i>Treatments in hospital</i>	
Delay of PO relay, mean (SD)	4.8 (1.7)
PO relay reason	
Euvolemia	38 (76)
Creatinine increase > 30 μmol/l	4 (8)
Other reason	7 (14)
Diuretics cumulative dose, mean (SD)	775 (1132)
<i>Treatments at discharge</i>	
ACEi, n (%)	19 (38)
ARBs, n (%)	8 (16)
Diuretic, n (%)	46 (92)
Diuretic dose, mean (SD)	117 (172)
Beta-blocker, n (%)	34 (68)
MRA, n (%)	2 (4)

Abbreviations: ACEi, angiotensin-converting-enzyme inhibitors; ARB, angiotensin II receptor blockers; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonists; PO, per os; SEGA, Short Emergency Geriatric Assessment.

TABLE 2 Clinical, biological, and ultrasound assessment of congestion, Day 1 and Day 2

Days	Day 1	Day 2
N (%)	50 (100)	47 (94)
<i>Clinical signs</i>		
Weight (kg), mean (SD)	76 (17)	74 (24)
Systolic blood pressure (mmHg), mean (SD)	133 (20)	-
Diastolic blood pressure (mmHg), mean (SD)	70 (14)	-
Heart rate (bpm), mean (SD)	84 (18)	83 (20)
LLE, n (%)	45 (90)	41 (87)
None, n (%)	5 (10)	9 (19)
Wrist, n (%)	14 (28)	16 (34)
Leg, n (%)	18 (36)	11 (23)
Thigh, n (%)	13 (26)	11 (23)
JVD or HJR, n (%)	22 (44)	18 (38)
Crackles, n (%)	47 (94)	42 (89)
None, n (%)	3 (6)	8 (17)
Lung base, n (%)	11 (22)	11 (23)
Half lungs, n (%)	29 (58)	24 (51)
More than 2/3 lungs, n (%)	7 (14)	4 (9)
ePVS, mean (SD)	8.9 (1.4)	9 (1.5)
<i>IVC</i>		
Collapsed and thin, n (%)	0 (0)	1 (2)
D < 21 mm and RV > 50%, n (%)	0 (0)	8 (17)
D > 21 or RV < 50%, n (%)	19 (38)	11 (23)
D > 21 mm and RV < 50%, n (%)	18 (36)	19 (40)
Dilated hepatic veins, n (%)	13 (26)	8 (17)
<i>Hypervolemia</i>		
Clinical hypervolemia, n (%)	46 (92)	40 (85)
Hypervolemia by IVC type 1, n (%)	50 (100)	38 (81)
Hypervolemia by ePVS, n (%)	49 (98)	43 (91)
<i>Biological factors</i>		
Baseline Creatinin (μmol/l), mean (SD)	136 (58)	135 (53)
Increase > 30%, n (%)	-	3 (6)
Plasma protein levels (mg/l), mean (SD)	66 (7)	64 (6)
Hemoglobin (g/dl), mean (SD)	11.4 (1.6)	11.4 (1.7)
Hematocrit (%), mean (SD)	36 (4.5)	35 (5.4)
NT-pro BNP (ng/l), mean (SD)	11 516 (12695)	

Abbreviations: ePVS, estimation of plasma volume status; HJR, hepatojugular reflux; IVC, inferior vena cava; JVD, jugular vein distention; LLE, lower limb edema; RV, respiratory variation.



FIGURE 1 Volemia groups, Day 1 (D1) and Day 2 (D2) (Treemap)

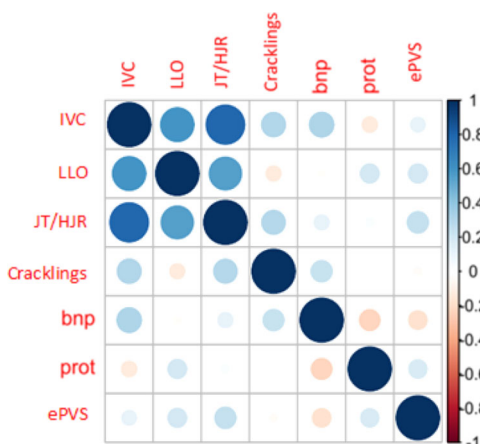


FIGURE 2 Correlation matrix on D1

measurements in the context of hypervolemia. Daily clinical examination, including JVD and IVC assessment, provides a reliable assessment of volume status, and helps quickly adapt the diuretic treatment to avoid functional renal failure.

To our knowledge, our study is one of the first to analyze the association between clinical, biological, and IVC variations, as well as to use both parameters to monitor diuretic treatment of acute heart failure in an elderly patients.

4.1 | Blood volume analysis

Our findings are consistent with previous studies. The clinical evaluation of blood volume showed a good performance of the examination of JVD, which has a class IB recommendation according to American Heart Association (AHA) guidelines.²⁷ In Miller JB's 2012 study,²⁸ the inspiratory collapse of IVC < 33% has a Se of 80% and Sp

of 81% to define hypervolemia. In our study, an IVC > 21 mm and an RV < 50% on admission is superior to clinical evaluation alone and identifies 100% of acutely decompensated patients.

The estimation of plasma volume as a parameter guiding ADHF management has inspired several studies following K. Duarte's 2015 publication¹⁵ of the results on the EPHESES study database.²⁹ A study by Chouihed²⁶ suggests that an ePVS value above 5.12×10^{-4} dL/g at the first blood test in patients presenting with acute dyspnea at the emergency department could help diagnose ADHF. In Kobayashi's study, ePVS is associated with hemodynamic markers of congestion.²⁹ In our study, we did not find any correlation between the selected ePVS value and clinical or ultrasound (IVC) signs of congestion. As for the change in ePVS after the onset of depletion, the results lack differential value. A possible explanation may be that the ePVS may not be as reliable in elderly patients and that the threshold needs adjusting.

In our study, NT-proBNP correlated only slightly with other criteria for hypervolemia. This is consistent with previous studies²⁷ and invites us to retain the use of NT-proBNP for ADHF diagnosis and prognosis only, but not for monitoring patients' congestive states.

Other criteria such as plasma protein levels and hematocrit vary little in the first few days and are poorly correlated with other signs of hypervolemia. This has been shown in other studies.²⁸

4.2 | Managing diuretic therapy

In the study by Yavaşı et al, the authors show that the analysis of IVC collapsibility is useful to manage diuretic therapy.²⁸

In our study, we investigated four ways to monitor patients' blood volume during diuretic therapy, and we found that the combined evaluation of daily clinical signs (JVD) and the ultrasound assessment of IVC was the best method. The combined practice of clinical and ultrasound assessment of congestion allows for early detection of patients whose

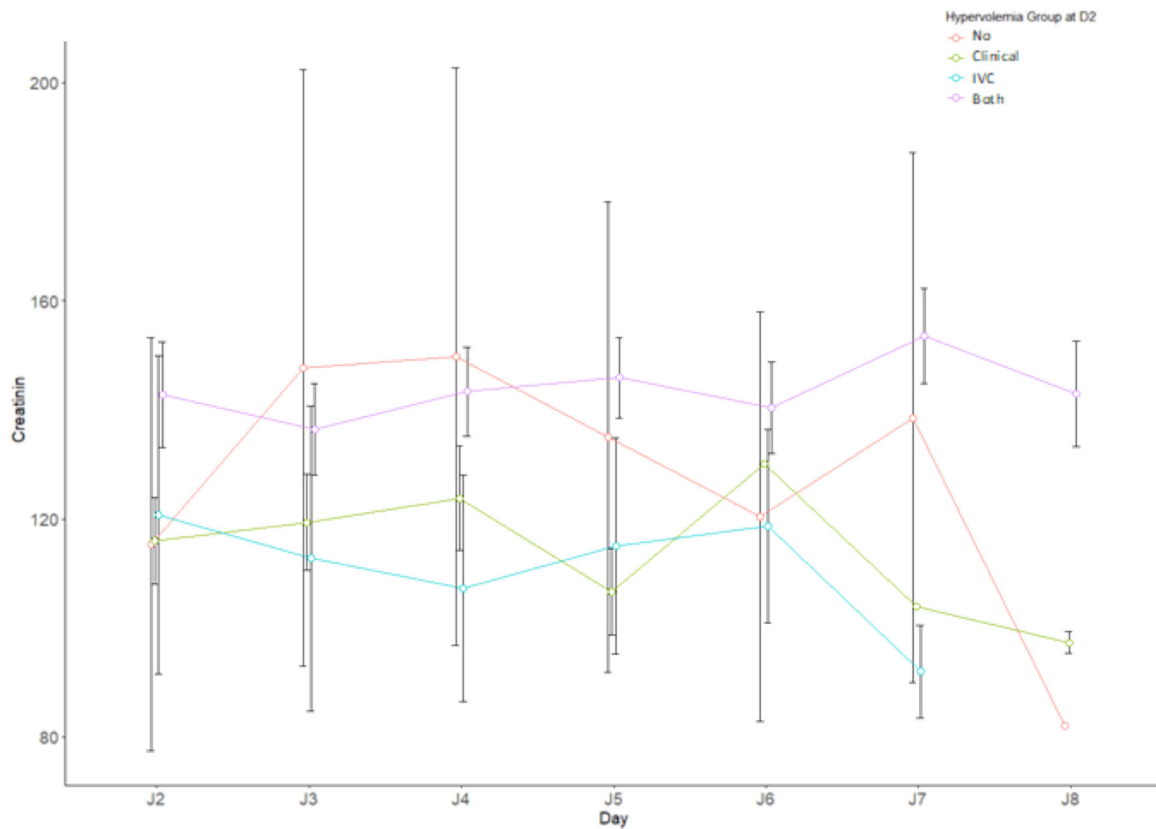


FIGURE 3 Creatinine variation by Volemia groups at D2

renal function is likely to deteriorate due to excess depletion on diuretics. This method may be useful in geriatric departments with limited access to cardiac ultrasound (lack of technical facilities, demented patients difficult to evaluate by standard examination, and long waiting time) for frail patients at risk of developing functional acute renal failure.

4.3 | Limitations of the study

Our study represents a descriptive analysis of the volume status of elderly subjects hospitalized for decompensated HF and explores the combination of different monitoring parameters. The limitations of the study are a small number of patients and the absence of a control group. Therefore, we could not measure diagnostic performance markers (Se, Sp, positive predictive value, negative predictive value).

5 | CONCLUSION

In ADHF patients older than 75 years, clinical evaluation of congestion and the ultrasound examination of IVC correlate well. Evaluation of IVC measurement with an ultraportable device is feasible by a geriatrician. The correlation between JVD/HJR and IVC measurement is good. The combined clinical and ultrasound analysis identifies patients at risk of functional renal failure and should facilitate the adjustment of diuretic doses in elderly patients with acute decompensated HF.

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Not applicable.

CONFLICT OF INTERESTS

The authors declare no conflict of interests.

AUTHOR CONTRIBUTIONS

Xenia Leahova-Cerchez collected data and wrote the main manuscript. Emmanuelle Berthelot Had the idea of the study, reviewed all the data, wrote and edit the main manuscript. Bastien Genet did the statistical analysis, tables and figures, and reviewed and commented the article. Olivier Hanon edit the main manuscript. Patrick Jourdain complete the idea of the study, edit the main manuscript.

DATA AVAILABILITY STATEMENT

Data and materials are not available.

ORCID

Emmanuelle Berthelot  <http://orcid.org/0000-0002-0418-3110>

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APPENDIX A: DIURETIC TREATMENT PROTOCOL

A.1 | Patient naive to loop diuretics

40 mg Furosemide intravenous bolus injection with re-evaluation at 6 h (diuresis and clinical) and continuation at a dose of 40 mg × 2 per 24 h intravenously with a 6 h interval if signs of congestion persist.

A.2 | Patient on long-term loop diuretics

- Intravenous bolus dose of Furosemide equivalent to the usual dose with re-evaluation at 6 h (diuresis and clinical), continuation of usual daily dose doubled divided into two intravenous injections with a 6-h interval over 24 h.
- 60 mg bolus dose of Furosemide then continuation of the double of the usual daily dose by continuous intravenous infusion if quantity exceeds 120 mg.