



# Evaluation Tools to Quantify Congestion and Prognostic Implication in Patients with Heart Failure

Masatake Kobayashi

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**Evaluation Tools to Quantify Congestion and Prognostic Implication**

**in Patients with Heart Failure**

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## Synthèse (en français)

La congestion réfère aux œdèmes pulmonaires et systémiques habituellement observés dans un contexte d'augmentation des pressions intracardiaques. C'est un prédicteur majeur de mauvais pronostic en insuffisance cardiaque. Une meilleure évaluation et quantification de la congestion au cours du parcours de soins (en amont d'une décompensation, aux urgences, en cours d'hospitalisation et en contexte ambulatoire) est souhaitable pour améliorer la stratification du risque et aider à la prise en charge de ces patients. Des outils d'évaluation de la congestion facilement accessibles et d'utilisation simple seraient utiles dans ce contexte.

Au cours de ce doctorat, nous avons étudié un score de congestion estimé à partir de la radiographie pulmonaire (dénommé dans la littérature « congestion score index ») ainsi que le volume plasmatique estimé à partir de l'hémoglobine et de l'hématocrite sanguine. **Notre but était d'évaluer la pertinence de ces paramètres de congestion en insuffisance cardiaque.**

Nous avons donc évalué :

1. la capacité diagnostique et pronostique du score de congestion pulmonaire radiographique dans le contexte de la dyspnée aigue,
2. les implications cliniques et pronostiques de la quantification du volume plasmatique estimé en insuffisance cardiaque et,
3. l'utilité de la combinaison de ces 2 variables en insuffisance cardiaque décompensée.

*Dans le cadre de ce doctorat, j'ai écrit 7 articles en qualité de premier auteur, dont 5 sont publiés et 2 soumis.*

La **première partie** de ce doctorat était centrée sur le score radiographique de congestion, initialement développé par une autre équipe dans le contexte de l'insuffisance cardiaque chronique. Nous avons dans un premier temps étudié la valeur diagnostique de ce score radiologique de congestion pulmonaire chez des patients admis pour dyspnée aigue aux urgences au sein de la cohorte PARADISE (1<sup>er</sup> article – *en cours de soumission*). La radiographie pulmonaire reste très utilisée aux urgences,



principalement pour écarter un diagnostic différentiel. Sa performance diagnostique en utilisant une approche non systématisée est modérée. Nos résultats issus de l'analyse de 1333 patients de la cohorte PARADISE (âge moyen  $72 \pm 19$ ) montrent que le score radiologique a une bonne performance diagnostique pour l'insuffisance cardiaque aigue lorsque qu'utilisé seul (C-index=0.84, 0.82-0.86) ou concomitamment de variables cliniques (C-index=0.87, 0.85-0.90). Nous avons aussi montré que ce score radiographique de congestion améliore la performance diagnostique en plus de l'utilisation de variables cliniques. Chez les patients ayant eu un dosage des peptides natriurétiques, le score de congestion radiographique présente une capacité diagnostique non significativement différente de celle du BNP. Par ailleurs, la valeur diagnostique de ce score radiologique ne semblait pas affecté par les caractéristiques cliniques des patients, notamment par l'âge, la présence d'une obésité ou d'une bronchite chronique. Nous avons pu valider ces résultats dans une cohorte indépendante 224 patients.

Nous avons ensuite (2<sup>ème</sup> article – *publié dans International Journal of Cardiology*) étudié la valeur pronostique de ce score radiologique dans une cohorte de 292 patients (âge moyen  $71 \pm 14$  ans) admis pour insuffisance cardiaque aigue à Tokyo. Nous avons observé que la congestion pulmonaire radiographique résiduelle (plutôt que la congestion initiale) était associée au pronostic des patients. Par ailleurs, nous avons observé que l'association du score de congestion pulmonaire radiographique était significativement associé au pronostic même après ajustement sur les peptides natriurétiques, et améliorait la capacité de prédiction (telle qu'évaluée par le Net Reclassification Index) en plus des variables cliniques.

La **deuxième partie** de notre doctorat s'est centré sur le volume plasmatique estimé. Nous avons évalué l'association du volume plasmatique estimé à partir de l'hémoglobine et l'hématocrite, en utilisant la formule de Duarte (publiée dans le cadre d'un précédent doctorat réalisé au sein de l'Université de Lorraine), avec des variables biologiques, échographiques et hémodynamiques de congestion (3<sup>ème</sup> article, *publié dans Clinical Research in Cardiology*). Cette étude conduite chez 78 patients (âge moyen 74 ans) admis pour réalisation d'un cathétérisme gauche suggère que le volume plasmatique estimé est un marqueur de congestion préférentiellement gauche (comme le rapport E/e', les peptides natriurétiques et les pressions de remplissage ventriculaire telles qu'estimées en cathétérisme). Par ailleurs, nous avons identifié dans

cette analyse que le lien entre le volume plasmatique estimé et ces variables semble partiellement dépendant du sexe : La corrélation entre le volume plasmatique estimé et les pressions télé-diastoliques ventriculaires gauches était en effet plus importante chez les femmes.

Nous avons ensuite étudié l'association du volume plasmatique estimé avec le risque d'évènements cliniques dans différents contextes (en IC décompensée et en IC ambulatoire avec fraction d'éjection préservée). La première analyse a été réalisée dans 3 cohortes internationales de patients admis pour insuffisance cardiaque décompensée réalisées dans des contextes cliniques et géographiques différents (deux cohortes japonaise et française en service de cardiologie et une cohorte portugaise aux urgences) permettant une bonne validité externe de nos résultats. La cohorte fusionnée comportait 712 patients, dont 383 étaient issus de la cohorte de Tokyo (âge moyen  $71 \pm 14$  ans), 165 de la cohorte ICALOR (âge moyen  $76 \pm 10$  ans) et 164 de la cohorte de Porto (âge moyen  $72 \pm 15$  ans). La deuxième analyse a été réalisée dans l'essai clinique TOPCAT (évaluant l'effet de la Spironolactone en IC à fraction d'éjection préservée). Ces travaux ont montré l'association indépendante du volume plasmatique estimé par la formule de Duarte avec les évènements cliniques à moyen terme et sa valeur ajoutée (telle qu'évaluée par le Net Reclassification Index) dans la stratification du risque des patients insuffisants cardiaques dans des contextes très différents ; Ils ont donné lieu à deux articles (4<sup>ème</sup> et 5<sup>ème</sup> article), tous les deux *publiés dans Clinical Research in Cardiology*.

Suite à ces travaux, nous avons réalisé une revue de la littérature centrée sur l'estimation du volume plasmatique, incluant donc nos premiers articles publiés, dans le but de mettre en avant l'intérêt de cette approche chez les patients insuffisants cardiaques en pratique de routine (6<sup>ème</sup> article – *en cours de soumission*).

Dans la troisième partie de ce doctorat, nous avons exploré la valeur pronostique combinée du score radiographique de congestion pulmonaire et du volume plasmatique estimé par la formule de DUARTE chez des patients hospitalisés pour aggravation d'IC en service de cardiologie issus de la cohorte ICALOR (7<sup>ème</sup> article – *publié dans International Journal of Cardiology*). La cohorte ICALOR comporte des patients inclus dans le réseau d'insuffisance cardiaque ICALOR, et suivi dans ce cadre. Nous avons trouvé que,

dans cet échantillon de 117 patients (âge moyen  $74 \pm 14$  ans, fraction d'éjection moyenne  $40\% \pm 16\%$ ), une approche bivariable avait une valeur importante pour la stratification du risque intra-hospitalier et dans les suites de l'hospitalisation. Après ajustement, les patients ayant à la fois un score radiologique de congestion pulmonaire et un volume plasmatique estimé élevés avaient une durée de séjour significativement plus importante et un risque 5 fois plus important de décès ou réhospitalisation pour insuffisance cardiaque à 90 jours. Les patients ayant seulement un marqueur augmenté (score radiologique de congestion pulmonaire ou volume plasmatique estimé) ne semblaient pas avoir d'augmentation importante du risque d'événements. L'utilisation combinée du score radiographique de congestion pulmonaire et du volume plasmatique estimé permettait une augmentation significative de la discrimination du modèle pour le risque de décès ou de réhospitalisation (telle qu'évaluée par le Net Reclassification Index).

Notre travail souligne l'utilité clinique du score radiologique de congestion pulmonaire, du volume plasmatique estimé et de leur évaluation conjointe dans le champ de l'IC. Par ailleurs, nous montrons la bonne performance d'une approche mêlant marqueurs d'imagerie et marqueurs biologiques évaluant différentes composantes de la congestion.

Les limites de notre travail sont principalement celles issues des études observationnelles et retrospectives (hormis l'analyse réalisée dans l'essai TOPCAT). En particulier, la version de la cohorte PARADISE utilisée dans ce doctorat est mono-centrique, ce qui limite la validité externe de nos analyses. Cependant, nous avons, chaque fois que cela était possible, utilisé des cohortes de validation indépendantes pour confirmer les résultats obtenus dans PARADISE. Par ailleurs, concernant les analyses sur l'estimation du volume plasmatique, une des forces de notre travail est la diversité des cohortes utilisées, issues des services d'urgence et de cardiologie français, portugais et japonais. L'utilisation à l'avenir de cohortes prospectives comportant plus de variables de congestion (notamment échocardiographiques) permettra de dépasser les limites rencontrées dans notre travail.

Dans la lignée de ces travaux, une intégration des marqueurs de congestion au sein d'une démarche multi-paramétrique pourrait apporter une meilleure caractérisation du profil congestif individuel des patients insuffisants cardiaques. Des travaux futurs utilisant de grandes bases de données comportant des informations relatives à des variables variées de congestion pourrait aider à l'intégration de ces variables à

des modèles diagnostiques et pronostiques en IC. Dans la lignée du travail effectué en thèse, de futur travaux sur des cohortes multicentriques de patients admis pour dyspnée, comme la cohorte PARADISE-multicentrique et la cohorte PURPLE (Pathway and Urgent care of dyspneic Patient at the emergency department in LorrainE district) et des cohortes de patients admis pour insuffisance cardiaque aigue précisément phénotypes (telles que la cohorte AHF-CORE - Acute Heart Failure -COngestion Repeated Evaluation), pourraient explorer des approches d'évaluation multimodales de la congestion. Ces analyses permettront d'identifier la meilleure combinaison de variables pronostiques et de préciser la meilleure stratégie d'évaluation de la congestion en routine. Cette intégration passera vraisemblablement par l'utilisation d'outils de type intelligence artificielle, afin d'obtenir des algorithmes intégrés et personnalisés, prenant en compte les caractéristiques des patients (notamment les antécédents et comorbidités). Cette approche flexible semble plus adaptée à la complexité de la situation d'analyse. Enfin, à terme, pour permettre une large diffusion de ces approches aboutissant le plus souvent à des algorithmes complexes, une intégration de ces outils au système d'information des structures de soins serait nécessaire. L'implémentation de ces algorithmes dans les dossiers informatisés des patients permettrait une évaluation en temps réelle de l'évolution des états congestifs, et pourrait à terme aider à la prise en charge thérapeutique des patients insuffisants cardiaques.

## Table of contents

Synthèse (en français) .....	2
Table of contents .....	7
<b>1. Introduction.....</b>	<b>10</b>
<b>2. Congestion evaluation tools: Description and association with diagnosis/prognosis.....</b>	<b>12</b>
2.1. Clinical congestion markers .....	12
2.1.1. Leg edema .....	12
2.1.2. Jugular venous distention and hepatojugular reflex .....	12
2.1.3. Pulmonary rales.....	13
2.1.4. Body weight.....	13
2.1.5. Dyspnea .....	14
2.1.6. Clinical congestion score.....	15
2.2. Biological congestion markers.....	17
2.2.1. Natriuretic peptide.....	17
2.2.2. Carbohydrate antigen 125 .....	18
2.2.3. Estimated plasma volume status .....	19
2.3. Imaging congestion markers .....	21
2.3.1. Transthoracic echocardiography .....	21
2.3.2. Lung ultrasound .....	23
2.3.3. Renal Venous Doppler .....	25
2.3.4. Chest radiography .....	26
2.4. Other congestion markers .....	28
2.4.1. Directly measured plasma volume .....	28
2.4.2. Right heart catheterisation and pulmonary artery pressure monitoring.....	28
<b>3. Integrative approach to systemic and pulmonary congestion.....</b>	<b>29</b>
3.1. Systemic congestion in right-sided heart failure.....	29
3.2. Pulmonary congestion in left-sided heart failure.....	29
3.3. Conceptualized figure of congestion profile.....	30
<b>4. Hypothesis and objectives .....</b>	<b>32</b>
4.1. Objectives .....	32
4.2. Hypothesis.....	32
<b>5. Articles in thesis .....</b>	<b>33</b>
5.1. Radiographic congestion score index.....	34
5.1.1. Congestion Score Index Evaluated from Chest Radiography for Diagnosing Acute Heart Failure in the Emergency Department: insights from the PARADISE cohort (1 <sup>st</sup> paper).....	34
5.1.2. Mid-term prognostic impact of residual pulmonary congestion assessed by radiographic scoring in patients admitted for worsening heart failure (2 <sup>nd</sup> paper) .....	63
5.2. Estimated plasma volume status .....	70

5.2.1. Association of Estimated Plasma Volume Status with Hemodynamic and Echocardiographic Parameters (3 <sup>rd</sup> paper) .....	71
5.2.2. Prognostic value of estimated plasma volume in acute heart failure in three cohort studies (4 <sup>th</sup> paper) .....	82
5.2.3. Prognostic Impact of Plasma Volume Estimated from Hemoglobin and Hematocrit in Heart Failure with Preserved Ejection Fraction (5 <sup>th</sup> paper) .....	96
5.2.4. Estimated plasma volume status in heart failure: Clinical implications and future directions (6 <sup>th</sup> paper) .....	107
5.3. Radiographic congestion score index and estimated plasma volume status .....	137
5.3.1. Chest X-ray Quantification of Admission Lung Congestion as a Prognostic Factor in Patients Admitted for Worsening Heart Failure from the ICALOR Cohort Study (7 <sup>th</sup> paper) .....	137
6. Discussion of the thesis .....	145
6.1. Limitations .....	145
6.2. Strengths .....	146
7. Perspectives .....	148
7.1 Cohorts to be used within the integration process .....	149
7.1.1 The Pathway of dyspneic patients in Emergency (PARADISE) .....	150
7.1.2 Pathway and Urgent caRe of Dyspneic Patient at the Emergency Department in Lorraine District (PURPLE) .....	151
7.1.3 Acute Heart Failure -COngestion Repeated Evaluation (AHF-CORE) .....	151
7.1.4 Pooled patient data from the European countries (Nancy, Perugia, Pisa and Siena cohorts) .....	152
7.2. Integration of all evaluation tools of congestion using machine learning approach .....	154
7.2.1 Outline of the machine learning approach .....	154
7.2.2 Diagnosis value for acute heart failure of machine learning based integration of congestion markers .....	157
7.2.3 Prognostic value of integrated congestion approach derived from machine learning methods .....	158
7.3. Artificial intelligence approach to Congestion Score index .....	159
7.4. Integration of congestion markers in electronical healthcare records .....	159
8. Conclusion .....	162
9. Articles .....	163
References .....	164
Abstract (English version) .....	179
Abstract (Version française) .....	179

## **Abbreviations and acronyms**

HF=heart failure

CHF=chronic heart failure

AHF=acute heart failure

ADHF=acutely decompensated heart failure

HFrEF=heart failure with reduced ejection fraction

HFpEF=heart failure with preserved ejection fraction

CXR=chest radiography

CSI=congestion score index

PV=plasma volume

ePVS=estimated plasma volume status

NYHA=New York Heart Association

JVD=jugular venous distention

JVP=jugular venous pressure

HJR=hepatojugular reflex

BNP=brain type natriuretic peptide

NTproBNP=N-terminal pro-B-type natriuretic peptide

LV=left ventricular

RV=right ventricular

RAP=right atrial pressure

PASP=pulmonary artery systolic pressure

PCWP=pulmonary capillary wedge pressure

LUS=lung ultrasound

## 1. Introduction

Congestion is defined as a high left ventricular (LV) filling pressure associated with signs and symptoms of heart failure (HF) <sup>1</sup>. Elevated filling pressure leads to the imbalance of Starling's equilibrium in the alveolar capillary barrier, resulting in the development of lung edema, i.e. pulmonary congestion. Elevated LV filling pressure also leads to retrograde increased right arterial pressure (RAP) and central venous pressure, leading to systemic congestion such as leg edema <sup>2,3</sup>. The presence of systemic or pulmonary congestion is theoretically related to an elevation in right- or left-sided intracardiac pressure. Of note, patients with pulmonary hypertension without left-sided HF may have isolated systemic congestion.

Development of congestion is one of the main causes leading to urgent hospitalization for HF and subsequent poor prognosis <sup>4,5</sup>. A recent European survey showed that more than 40% of patients admitted for worsening HF died or were readmitted to hospital within 1 year <sup>6-8</sup>. Furthermore, 30% of patients hospitalized for worsening HF still have residual congestion at discharge, which is strongly associated with increased risk of subsequent cardiovascular events <sup>9</sup>. Therefore, it is of paramount importance to correctly evaluate congestion to rightfully assess the degree of decongestion and favor the optimal tailoring of HF medications at each point of patient management (i.e., before progression to decompensation, emergency department, hospital index, prior discharge assessment and outpatient clinic) <sup>4</sup>. In addition, serial assessment of congestion may identify patients who have higher risk of cardiovascular events. Furthermore, a quantitative assessment of congestion has been reported to provide better prognostic information even in patients with absent or minimal residual congestion <sup>10</sup>. Therefore, the quantification and monitoring of congestion using new imaging/biological approaches may be useful for the clinical management and risk-stratification of patients with HF. Clinical, biological and imaging assessment of congestion can help the diagnosis of acute HF (AHF) and (sometimes) guide decision-making <sup>11-13</sup>. The availability, however, of these congestion markers may limit their clinical utility. Indeed, recent data showed that less than 20% of patients underwent lung ultrasound (LUS) and/or echocardiography to diagnose AHF in the emergency department <sup>14</sup>.



Readily and widely available evaluation tools are warranted to quantify and/or monitor congestion and eventually improve risk-stratification. In this thesis, we investigated several types of congestion markers (i.e., clinical, biological, imaging and invasive markers) and determine whether these additional congestion markers could be useful in various setting of patients with heart failure.

## **2. Congestion evaluation tools: Description and association with diagnosis/prognosis**

### **2.1. Clinical congestion markers**

#### **2.1.1. Leg edema**

Leg edema may reflect higher intravascular pressure, leading to fluid transmission from the intravascular space to interstitial tissues. Leg edema is one of the most simple and common signs in patients with worsening HF<sup>15</sup>. Previous studies showed that more severe leg edema in patients hospitalized for worsening HF were associated with longer hospital stay and a higher risk of post-discharge cardiovascular mortality<sup>16-18</sup>; thus, leg edema may be a clinically useful measure of systemic congestion. Leg edema, however, may be often influenced by non-cardiac causes such as venous insufficiency, obesity, lymphedema, nephrotic syndrome or cirrhosis<sup>19</sup>. In patients with a known history of HF, rapid accumulated bilateral leg edema associated with a significant increase in body weight may be often considered as a surrogate of volume expansion<sup>20</sup>. The combined assessment of leg edema and jugular venous distention may provide better identification of patients with a higher risk of poor outcomes<sup>21</sup>.

#### **2.1.2. Jugular venous distention and hepatojugular reflex**

Jugular venous distention (JVD) is defined as a significant increase in estimated jugular venous pressure (JVP)<sup>22</sup>, and is a useful congestion sign which can contribute to diagnose HF or manage patients with HF<sup>23-26</sup>. Recent registry data showed that 35% of patients admitted for worsening HF have a significant increase in JVP<sup>27</sup>. In a post-hoc analysis of Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial, patients hospitalized for worsening HF were categorized into 4 groups according to JVP (<8, 8 to 12, 13 to 16, >16mmHg). In this study, JVP was associated with significantly elevated pulmonary capillary wedge pressures (>22mmHg) and a higher risk of cardiovascular events<sup>25</sup>. In a post-hoc analysis of Study of Left Ventricular Dysfunction (SOLVD) trial, in patients with symptomatic HF and a reduced ejection fraction (HFrEF), JVD, a third heart sound or their combination were associated with the composite of mortality and/or hospitalization for HF<sup>28</sup>. In this study, the presence of both clinical signs increased the risk of

the composite of mortality and/or development of HF in patients with asymptomatic HFrEF<sup>29</sup>. Worse prognostic value of JVD was also reported in 1,376 patients with HFrEF and atrial fibrillation in a post-hoc analysis of Atrial Fibrillation and Congestive Heart Failure (AF-CHF) trial<sup>30</sup>.

A positive hepato-jugular reflux (HJR) sign is defined as an increased JVP of greater than 3cm sustained during 10 seconds of continuous pressure on the abdomen<sup>31</sup>, and predicts a significant increase in pulmonary capillary wedge pressure (PCWP) (>15mmHg) in the absence of isolated right ventricular (RV) dysfunction<sup>32</sup>. Several studies confirmed the association of the presence of HJR with elevated PCWP<sup>26 33</sup> and diagnostic utility of HJR for AHF<sup>34</sup>. Furthermore, in a post-hoc analysis of ESCAPE trial, patients with persistent HJR at discharge were at a higher risk of 6-month mortality<sup>33</sup>, suggesting that HJR may identify AHF patients who persist residual congestion.

When assessed properly by experienced clinicians, JVD and HJR may have better accuracy, thus practical tips to assess this congestion parameter is needed<sup>20, 25, 35</sup>.

### **2.1.3. Pulmonary rales**

Pulmonary rales may reflect increased lung interstitial fluid but have low sensitivity for HF<sup>1</sup>. Patients with advanced CHF often have no rales even if these patients had elevated LV filling pressures<sup>19, 26, 30</sup>. A post-hoc analysis of the Placebo-Controlled Randomized Study of the Selective A1 Adenosine Receptor Antagonist Rolofyl line for Patients Hospitalized with Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function (PROTECT) trial showed that severe pulmonary rales ( $\geq 2/3$  area) were significantly associated with 180-day mortality in 2,033 patients with HF and significant signs/symptoms of volume overload<sup>36</sup>. If patients have persisting rales without any other congestion sign/symptom at the time of discharge, this sign may be due to other lung conditions such as pneumonia, chronic bronchitis, asthma or interstitial fibrosis.

### **2.1.4. Body weight**

Development of congestion is most often based on sodium and water retention, leading to an increase in body weight. Important daily variation in body weight most likely reflects changes in volume status. However, there are several potential factors such as cardiac cachexia<sup>37</sup> and dehydration related to aggressive decongestion therapy, which may be plausible contributors of rapid changes in body

weight. An acute change in body weight has been known to parallel the development of congestion <sup>1</sup>. The well-known barrier to body weight-based congestion assessment is that its fluctuations may not always express changes in intravascular volume <sup>38</sup>.

The Tele-HF trial randomly assigned patients hospitalized for HF either to telemonitoring (N=826) or to usual care (n=827) <sup>39</sup>. The telemonitoring system collected information about symptoms and daily body weight. Their results consistently showed no benefit of this telemonitoring on mortality or any rehospitalization within 180 days. In a report from TIM-HF trial comparing telemonitoring (i.e. daily body weight and blood pressure) (N=354) and usual care (N=356) in patients with CHF, no benefit of telemonitoring was observed <sup>40</sup>. This suggest that weight monitoring alone is not enough to prevent HF hospitalization.

#### **2.1.5. Dyspnea**

Various types of dyspnea (i.e., dyspnea with exertion, orthopnea and paroxysmal nocturnal dyspnea) are central to HF patients as emphasized by the Framingham Heart Study <sup>41</sup>. Orthopnea was found to be associated with elevated pulmonary capillary wedge pressure in the ESCAPE trial <sup>25</sup>. This type of dyspnea is one of the simplest assessments of LV filling pressures in our patients. Optimal HF medications may reduce the presence of orthopnea in HF patients, which is associated with improved ejection fraction and favorable prognosis <sup>42</sup>.

Bendopnea, which Thibodeau et al. recently defined in an advanced HF population, is a symptom of dyspnea when patient bent forward during 30 seconds in sitting in a chair and touching one's feet with one's hands <sup>20,43</sup>. Previously published study showed that bendopnea was associated with increases in ventricular filling pressure but not reduction in cardiac index, especially in the context of HF patients with low cardiac index <sup>43</sup>. Additional data confirmed that bendopnea is associated with elevated filling pressure, subsequent exercise tolerance <sup>44-46</sup> and prognostic <sup>45,47</sup>.

### 2.1.6. Clinical congestion score

Despite somewhat limited diagnostic/prognostic value of clinical congestion markers, clinical scores that combine clinical congestion markers improve their performance (**Table 1**).

The Brest score has been proposed to diagnose AHF in acute dyspneic patients in the emergency department. The Brest score is calculated from clinical parameters such as age, comorbidities (*i.e.* prior history of heart failure, myocardial infarction and chronic obstructive pulmonary disease), pattern of dyspnea, ST segment abnormalities and signs/symptoms of congestion (*i.e.* rales and leg edema), showing good diagnostic value (AUC=0.86)<sup>48</sup>.

In a post-hoc analysis of the (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan) EVEREST trial, 2,061 patients hospitalized for worsening HF and a reduced ejection fraction were calculated a composite congestion by summing the individual scores for orthopnea, JVD, rales and leg edema from the time of enrolment until discharge or hospital day 7<sup>10</sup>. This congestion score substantially improved during hospital index, and the discharge value of this score was significantly associated with poor prognosis. These findings suggest that quantification of clinical congestion may provide better identification of patients at higher risk even in those with marginally increased congestion status. Furthermore, Gheorghiade et al. proposed a congestion score integrating bedside clinical bedside parameters, dynamic parameters, and natriuretic peptides<sup>1</sup>. This scoring may improve the objective assessment of the congestion severity; however, some assessments (*e.g.* 6-min walk test) incorporated in this model may have less availability in clinical routine.

In contrast, (too) simple scoring systems may have sometimes limited clinical utility. In a sub-study of the (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure) ASCEND-HF trial with 884 patients hospitalized for worsening HF, an increase in in-hospital congestion scoring derived from orthopnea, pedal edema and NTproBNP levels was associated with a higher risk of short-term mortality and/or re-hospitalization for HF, but did not improve traditional risk-stratification<sup>49</sup>. Holistic congestion scorings, integrated from readily and widely available congestion variables, with better diagnostic and prognostic performance are warranted.

**Table 1. Summary for clinical congestion score**

	Diagnostic score	Prognostic score		
	Brest score <sup>48</sup>	EVEREST Score <sup>10</sup>	Gheorgiade Score <sup>1</sup>	ASCEND-HF score <sup>49</sup>
<b>Settings</b>	Acute dyspneic patients in the emergency department	Discharge from HF hospitalization		Admission at HF hospitalization
<b>Dyspnea</b>	1=Night outbreak 2=Sudden dyspnea	0=None 1=Seldom 2=Frequent 3=Continuous		
<b>Orthopnea</b>	1=Orthopnea	0=None 1=Seldom 2=Frequent 3=Continuous	0=None 1=Mild (1 pillow) 2=Moderate (>1 pillow) 3=Severe (sleeps sitting)	Orthopnea 2+
<b>JVD</b>		0≤6 1=6-9 2=10-15 3≥15	-1≤8 and no hepatojugular reflux 1=8-10 or hepatojugular reflux 2=11-15 3≥16	
<b>Rales</b>	2=Pulmonary crackle	0=None 1=Bases 2=Up to <50% 3≥50%		
<b>Edema</b>	1=Pitting leg edema	0=Absent/trace 1=Slight 2=Moderate 3=Marked	0=None 1=1+ 2=2+ 3=3+/4+	0=None 1=edema up to shins 2=edema up to knees 3=edema up to sacrum
<b>Other bedside parameters</b>	1=ST segment abnormalities	Fatigue: 0=None 1=Seldom 2=Frequent 3=Continuous	Hepatomegaly: -1=Absent in the setting of normal JVP 0=Absent 1=Liver edge 2=Moderate pulsatile enlargement 3=Massive tender enlargement extending to midline	
<b>Dynamic parameters</b>			Orthostatic testing: -1=Significant SBP decrease or HR increase 0=No change in SBP or HR and no difficulty 1=Mild difficulty/ 2=Moderate/ 3=Severe/worst  6-min walk test: -1≥400m/ 0=300-400m/ 1=200-300m 2=100-200m/ 3≤100m  Valsalva maneuver: -1=Normal response/ 1=Absent overshoot pattern 2=Square wave pattern	
<b>Nonclinical parameters</b>			BNP (pg/ml): 0≤100/ 1=100-299/ 2=300-500/ 3≥500  NT-proBNP (pg/ml): 0≤400/ 1=400-1,500/ 2=1,500-3,000/ 3≥3,000	NT-proBNP (pg/ml): Measured between 48 and 72hrs after admission [median= 3278 (1344-7033)] 1= tertile 1 2= tertile 2 3= tertile 3
<b>Medical history</b>	2=prior CHF episode 2=Myocardial infarction 1=Atrial fibrillation/flutter -2=Chronic pulmonary disease			

## 2.2. Biological congestion markers

### 2.2.1. Natriuretic peptide

Natriuretic peptides (NPs), such as B-type natriuretic peptide (BNP), N-terminal fragment pro-B-type natriuretic peptide (NT-proBNP) are recognized circulating biomarkers in HF. NPs are recommended to support the diagnosis of AHF as Class I, Level of Evidence A, in recent clinical practice guidelines<sup>50</sup>. Previously published data showed that, in acute dyspneic patients, cutoffs of BNP <100pg/ml and NTproBNP <300pg/ml efficiently ruled out HF, and that BNP (AUC=0.91) and NTproBNP (AUC=0.94) provided high diagnostic accuracy of HF<sup>51, 52</sup>. A recent published including 1,461 acute dyspneic patients with 277 AHF patients showed that age-stratified NTproBNP had good diagnostic performance for AHF<sup>53</sup>. However, one possible concern is that elevated levels of NPs do not automatically diagnose AHF. Indeed, recent practical guidelines emphasized that NPs should be used to rule-out HF rather than ascertain HF. A number of underlying cardiac-related diseases can be associated with raised levels of NPs (p.e. prior heart failure hospitalization, atrial fibrillation, acute coronary syndrome and depressed systolic dysfunction) or reduced levels (p.e. decompensated end-stage HF, flash pulmonary edema or right-sided HF). In addition, the levels of NPs may be influenced by several patient characteristics such as age, sex, obesity and renal function<sup>54</sup>.

Elevated NPs is also associated with poor patient outcome in both acute and chronic settings<sup>55-58</sup>. BNP provides important prognostic information with every 100-pg/ml increase being associated with a 35% increase in the risk of mortality. In a report of post-hoc analysis of the (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) OPTIMIZE-HF trial, the association of BNP on admission, discharge and its in-hospital change with 1-year cardiovascular event was assessed in 7,039 patients hospitalized for worsening HF had BNP. Discharge BNP best predicts 1-year mortality and/or rehospitalization, highlighting the central prognosis importance of residual congestion<sup>59</sup>.

Similarly, in patients with CHF, NP levels provide powerful prognostic information. In a post-hoc analysis of (Valsartan Heart Failure Trial) Val-HeFT study including 4,300 outpatients with CHF, elevated BNP (despite standardized therapy) was associated with high morbidity and mortality.

Importantly, it should be emphasized that NPs are often surrogate of hemodynamic congestion<sup>60</sup>, and persistent elevation in NPs despite resolution of symptomatic congestion during hospital index has been reported<sup>10</sup> and is associated with worse prognosis<sup>61, 62</sup>, suggesting that improving underlying hemodynamic congestion rather than alleviating symptomatic congestion may be the key to optimize patients' outcome.

Determining which of the NPs (BNP or NTproBNP) is the best surrogate with regards to HF diagnosis and prognostication needs further research<sup>63</sup>. However, sacubitril/valsartan have been shown to influence levels of BNP. Although this treatment is not used in a majority of patients with chronic HFrEF in the most recent registry data<sup>64</sup>, NTproBNP is more likely to become the standard of care.

### **2.2.2. Carbohydrate antigen 125**

Carbohydrate antigen-125 (CA125), which is usually used to monitor ovarian cancer therapy<sup>65</sup>, is synthesized by serosal cells in response to the presence of serosal effusions, and can serve as a surrogate for fluid retention in AHF<sup>66</sup>. A recent randomized control trial comparing outcomes of a CA125-guided strategy vs standard care in 380 HF patients showed that CA125 levels below 35 U/ml reduced the risk of 1-year adverse outcomes, which is mainly driven by a significantly reduction in the rate of HF rehospitalizations<sup>67</sup>. These results highlighted that CA125 is likely to be a clinically relevant congestion marker. However, inflammation status also stimulates the production of CA125<sup>68</sup>. A recent data confirmed that, through a cluster analysis, CA125 grouped with recognized biomarkers with congestion and inflammation<sup>69</sup>. The applicability of CA125 use may be limited since clinicians may not be able to ascertain which clinical condition, congestion or inflammation, determines the level of CA125 in patients with HF<sup>70</sup>. Furthermore, several pleural effusion-related diseases such as malignancies, pneumonia, pelvic inflammatory diseases and peritonitis are associated with increased level of CA125, which limit the accuracy of CA125 to detect HF worsening<sup>66, 71</sup>.



### 2.2.3. Estimated plasma volume status

All fluid compartments are balanced, and plasma volume (PV) can interact with the interstitial and intracellular compartments<sup>72-75</sup>. Patients with HF often have fluid volume accumulation due to several underlying conditions or have fluid redistribution from splanchnic venous system to the pulmonary circulation, both of which may contribute to expand PV and subsequently to urgent hospitalization for HF<sup>72, 76, 77</sup>. Despite this pathophysiological plausibility of measuring PV, the procedure of direct PV measurement requires specialized equipment with relatively high cost and exceedingly high logistical issues to implement, which may not be readily available for clinicians. Recent published data introduced two available formulas for estimating PV, which are derived from clinical routine parameters and could provide better diagnostic and prognostic performance.

#### Strauss Formula

In 1950's, Strauss firstly addressed the concept of estimation of PV and demonstrated the association between the infusion of saline into human bodies and rapid changes in their estimated PV<sup>78</sup>. This formula was validated with a radiolabeled gold standard method, and has been used over decades<sup>79, 80</sup>.

To estimate relative changes in PV between two-time points, the Strauss formula incorporates changes in hemoglobin and hematocrit<sup>78</sup>:

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

In a recent report, Duarte et al. used an instantaneous-derived measurement of plasma volume (Duarte's formula) for estimating PV derived from the Strauss formula as follows<sup>81</sup>:

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

A recent published study comparing Strauss/Duarte derived PV and <sup>131</sup>I-labeled albumin-based PV in 110 patients with CHF and NYHA III/IV showed that Strauss-derived ePVS was weakly correlated with measured PV ( $r=0.29$ ,  $p=0.003$ )<sup>82</sup>. However, a more recent report comparing Strauss-derived ePVS and measured PV by <sup>125</sup>I-human serum albumin in 10 patients with type 2 diabetes showed

good correlation (Lin's concordance index of 0.6 ( $p < 0.01$ ))<sup>83</sup>. Further research is needed to determine the concordance between estimated and measured PV in HF.

Patients with higher ePVS are usually older, had more frequent ischemic heart disease, more severe clinical congestion, poorer renal function, higher natriuretic peptide, and are less likely to be on HF medications; in addition, they experience higher subsequent rates of death and cardiovascular events<sup>84-87</sup>. Importantly, in a post-hoc analysis of the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) trial, Rossignol et al. showed that changes from baseline to 1 month in ePVS were significantly correlated with those in BNP ( $r = 0.284$ ;  $p < 0.001$ ), independently of study drug and renal function variations, and that elevated ePVS changes were associated with worse prognosis in patients with *de novo* HF followed by myocardial infarction<sup>88</sup>. In a more recent analysis from the EPHESUS trial, Duarte et al. assessed the prognostic value of instantaneous ePVS at 1 month as well as ePVS change from baseline to 1 month<sup>81</sup>. They found that instantaneous ePVS at 1 month was a better predictor of cardiovascular events than change in ePVS from baseline to 1 month over a follow-up period of 6 months.

### Hakim Formula

The Hakim formula is also used for calculating actual and ideal PV and ePVS derived from hematocrit and dry body weight using the following equations<sup>89</sup>:

$$\text{actual PV} = (100 - \text{hematocrit (\%)}) / 100 \times [a + (b \times \text{weight (kg)})]$$

$$\text{ideal PV} = c \times \text{weight (kg)}$$

(males:  $a=1530$ ,  $b=41$ ,  $c=39$ ; females:  $a=864$ ,  $b=47.9$ ,  $c=40$ ),

Relative PV status, an index of the extent to which patients have deviated from their ideal PV, was subsequently calculated from the following equation:

$$\text{ePVS} = [(\text{actual PVS} - \text{ideal PV}) / \text{ideal PV}] \times 100\%$$

Several reports have shown a moderate correlation between Hakim-derived ePVS and the conventional radioisotope-labeled albumin or red blood cell assays in patients with stable CHF<sup>82, 85, 90</sup>.

Previously published data showed that Hakim-derived ePVS may have prognosis in patients with AHF or CHF. The Hakim formula, however, has several caveats. It indeed relies on dry body weight which may be influenced by several factors such as obesity, cardiac cachexia and congestion/decongestion therapy<sup>85, 87, 90, 91</sup>.

## **2.3. Imaging congestion markers**

### **2.3.1. Transthoracic echocardiography**

Transthoracic echocardiography (TTE) is the gold standard for the assessment of congestion severity, through the estimation of fluid volume (p.e. inferior vena cava) and intracardiac pressures (p.e., pulmonary artery pressure and transmitral flow pattern)<sup>8, 50, 92</sup>. TTE may help clinicians diagnose AHF, identify associated underlying causes, and assess the treatment response, subsequently predicting a risk of mortality or cardiovascular events<sup>93-98</sup>. Particularly, this tool is the most available method to measure left ventricular ejection fraction (EF), which is used to categorize patients as HF with reduced EF, mid-range EF or preserved EF, providing relevant information about their management.

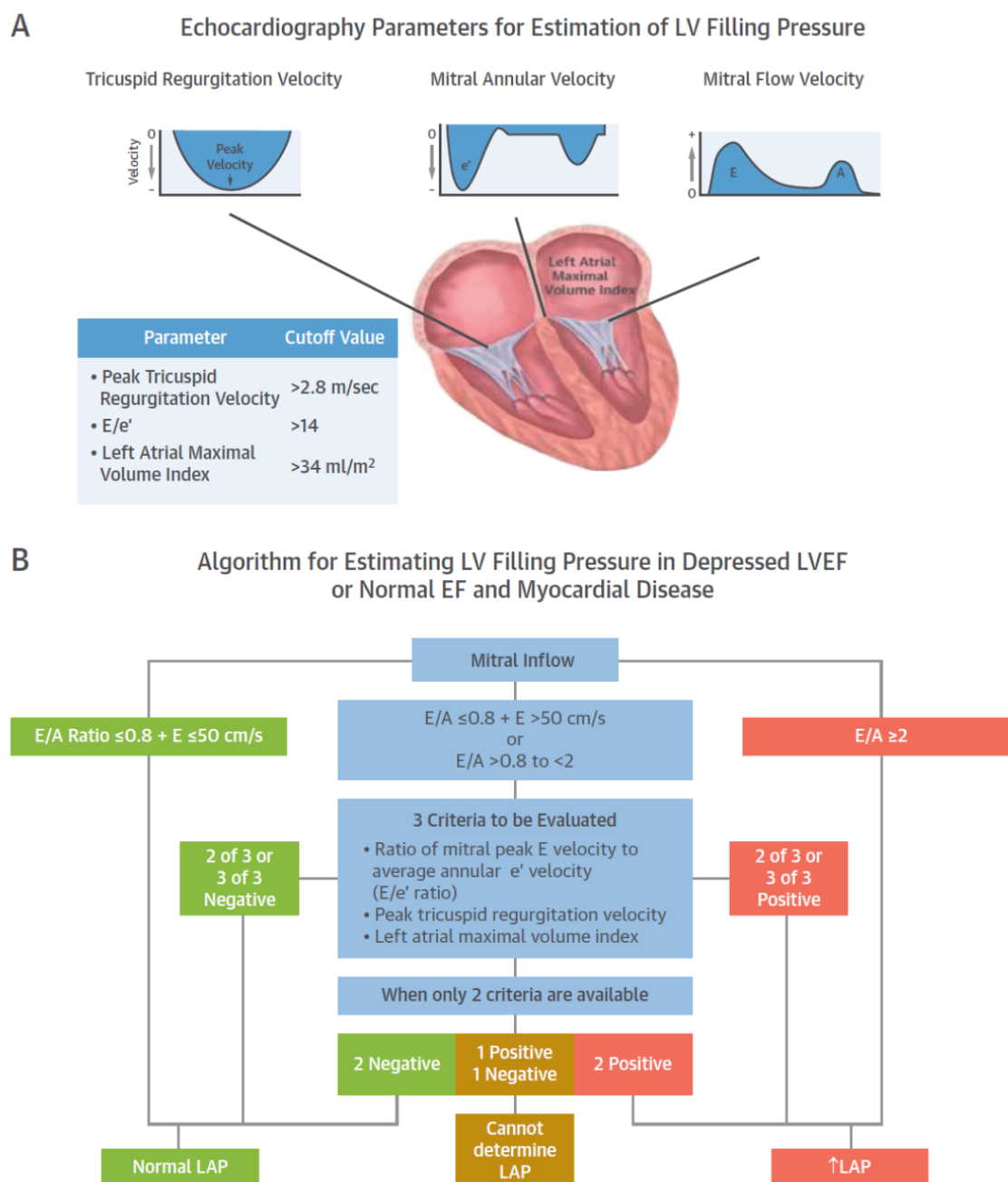
Measurement of the inferior vena cava (IVC) diameter and its changes with respiration shows a modest approximation of right atrial pressure<sup>99, 100</sup>. The diameter of the IVC is recommended to be measured with a phased array or curvilinear transducer with the patient in supine position in the subcostal view at 1.0 to 2.0 cm from the junction with the right atrium, using the long-axis view<sup>101</sup>. IVC diameter might be a sensitive tool to assess changes in intravascular volumes, and persistent dilation of the IVC during hospital index predicts a poor outcome in patients with acutely decompensated HF<sup>102-104</sup>. Furthermore, even in ambulatory HF patients with few symptoms and signs of congestion, such patients with dilated IVC had elevated NPs and poor prognosis<sup>105, 106</sup>. These data suggested that measurement of IVC may help monitoring congestion, although guidelines do not recommend its routine use in ambulatory HF patients.

The assessment of mitral inflow, mitral annulus motion by tissue Doppler imaging and left atrial volumes provide relevant estimates of left ventricular filling pressures<sup>107</sup>, but universal algorithm to combine these parameters are debated especially in cases of preserved EF<sup>50, 92, 108, 109</sup>. E/e' ratio is used frequently to assess intracardiac pressure and estimate hemodynamic congestion<sup>98, 110, 111</sup>. A recent meta-

analysis, however, emphasized the lack of diagnostic value of E/e' ratio to predict elevated LV filling<sup>112</sup>. In this regard, a recent report showed that isolated echocardiographic parameters such as E/e', tricuspid regurgitation velocity and left atrial volume had good accuracy for LV filling pressure prediction, and that this accuracy was actually better than the algorithm of the 2016 guidelines, irrespective of ejection fraction (**Figure 1**)<sup>113</sup>. In addition, elevated E/e' ratio has been a well-known predictor of cardiovascular outcomes in patients with chronic HF and those with acutely decompensated HF<sup>114, 115</sup>.

These congestion echocardiographic variables may have high inter-intra observer correlation but a long training period is usually needed to measure these parameters accurately. Recently, relatively easily portable, pocket-sized ultrasound devices have been made available which can favor the repeated assessment of congestion status measuring inferior vena cava diameter, ejection fraction and the right atrial volume index.

**Figure 1. Algorithm for estimating left ventricular filling pressure (Adapted from Andersen et al.<sup>113</sup>)**



### 2.3.2. Lung ultrasound

In the context of HF, Lung ultrasound (LUS) often provides comet-like images also called, “B-line”, which are related to extravascular lung water. The number of B-line is proportional to the amount of lung water, and consequently provide a semi-quantitative assessment of the severity of pulmonary congestion; the normal lung is black (no signal); the abnormal wet lung with interstitial lung edema is black and white; and the lung with alveolar pulmonary congestion is white. A curvilinear or phased array transducer in 6-8 intercostal spaces [3 (or 4) on each hemithorax] can be used to assess for the

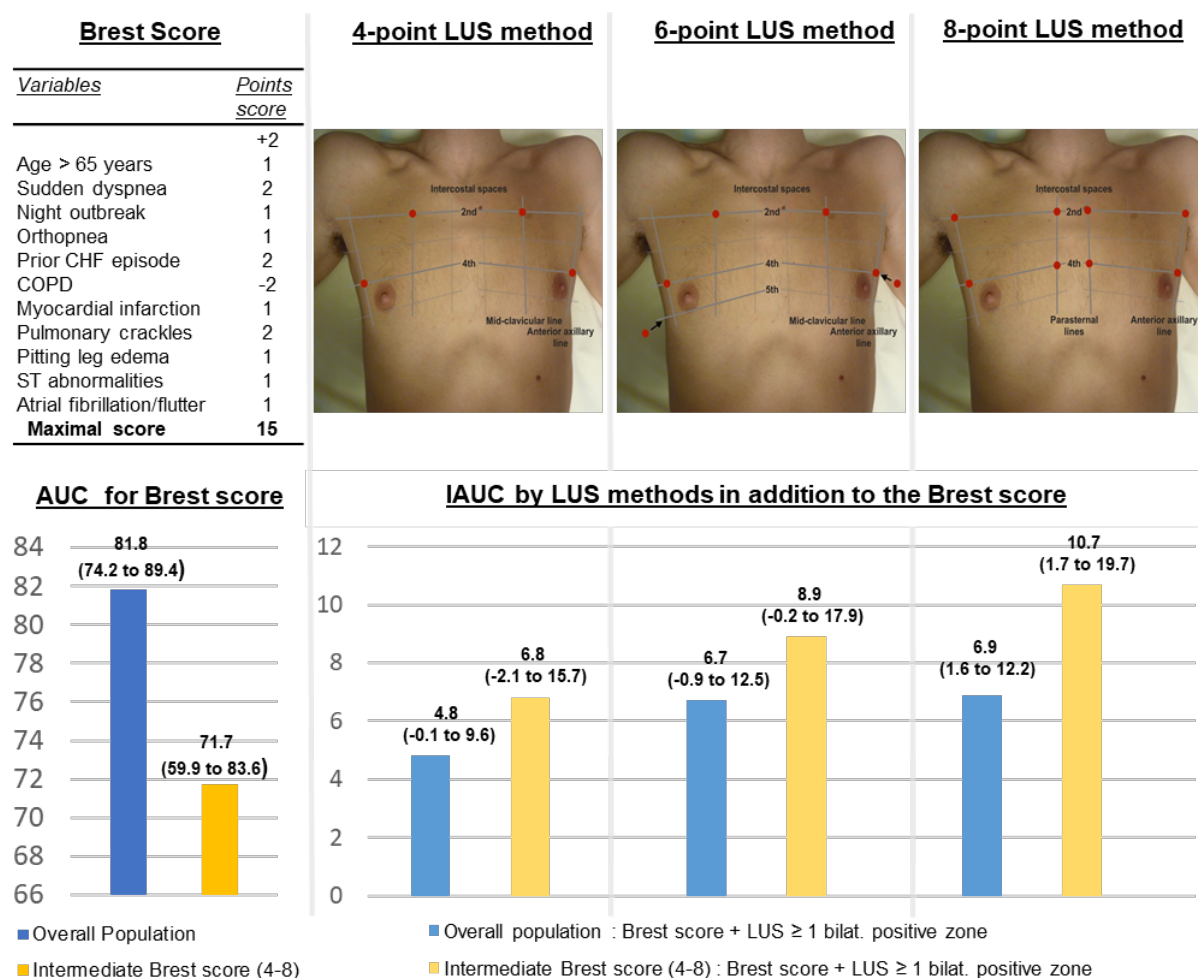
presence of B-lines at an imaging depth of  $\sim 18$ cm. There are mainly four types of imaging protocols (the 4-, 6-, 8-, and 28-point method). The presence of  $\geq 3$  B-lines per zone in at least two zones on each hemithorax is considered as pulmonary congestion in patients with suspected AHF<sup>116, 117</sup>. Several studies confirmed the clinical utility of LUS to diagnose AHF in dyspneic patients with high specificity and high sensitivity<sup>12, 13, 118</sup>. Pivetta et al. randomly assigned 518 patients in acute dyspnea to undergo LUS (N=258) or CXR/NTproBNP (N=260) to diagnose acutely decompensated HF (ADHF). Their results showed that the addition of LUS had higher diagnostic accuracy than clinical model alone (AUC=0.95 in LUS plus clinical model, AUC=0.88% in clinical model alone, p-value<0.01), whereas CXR/NTproBNP did not<sup>12</sup>, thus suggesting that the best diagnostic protocol should include both LUS and clinical assessment. Interestingly, Buessler et al. compared diagnostic value of LUS based on the 4-, 6-, 8-, and 28-point methods in 117 dyspneic patients, and showed that the 8-point-based LUS provided the highest increase in the C-index on top of clinical diagnostic model (AUC=90.6%;NRI=6.9%, p-value=0.010) followed by 6-point method<sup>119</sup> (**Figure 2**). These results suggested diagnostic reliability of 6-/8-point-based LUS, which can be pragmatic and easily implemented methods in the emergency department.

The accurate detection of pulmonary congestion based on LUS has predicted poor prognosis in patients with AHF and CHF. Coiro et al. assessed prognostic value of discharge pulmonary congestion assessed by LUS in 60 patients hospitalized for worsening HF, and showed that an increase in B-line count at discharge was associated with a higher rate of the composite of mortality and cardiovascular events<sup>120</sup>. Other reports also confirmed worse prognosis of residual congestion assessed by LUS<sup>121, 122</sup>. Platz et al. assessed the association of number of B-lines with the composite of mortality and HF hospitalization in 185 patients with CHF, showing a good risk-stratification when using B-lines regardless of their ejection fraction<sup>123</sup>. These data suggest that a high number of B-lines identifies patients at greater risk for subsequent HF hospitalization and mortality regardless of the clinical setting.

The main limitation of LUS is its availability. The proportion of patients who have an ultrasound evaluation in the emergency department, at the end of hospital stay or during an outpatient clinical assessment is likely minimal.

**Figure 2. Lung ultrasound for diagnosing acute heart failure according to different protocols**

### Diagnostic performance of the Brest score and LUS methods

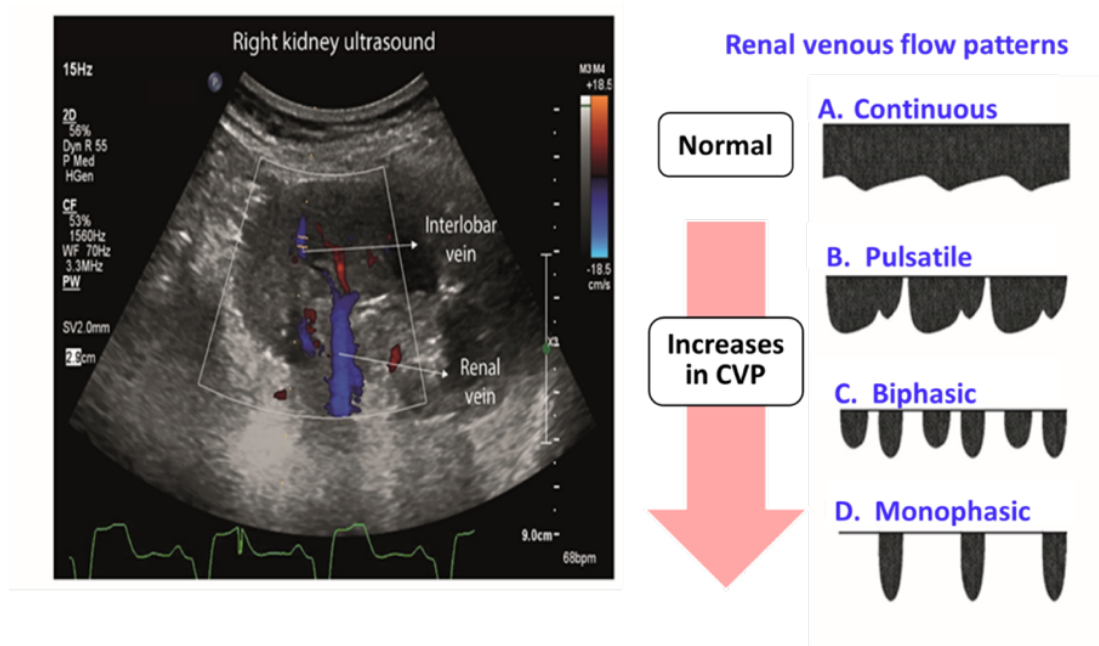


### **2.3.3. Renal Venous Doppler**

Recently, an additional parameter has been reported, which could greatly expand our understanding of congestion profiles. Renal venous ultrasound may need to be integrated in this congestion profiling since it provides unique information about renal congestion through the assessment of venous renal blood flow<sup>172-175</sup>. Renal venous flow (RVF) appears to reflect the changes in central venous pressure<sup>177, 178</sup>. In normal conditions, RVF is continuous with a small varying amplitude during the cardiac cycle<sup>177</sup> whereas it becomes pulsatile<sup>178</sup> with a biphasic and monophasic pattern when pressure rise. Identification of the RVF pattern thus allows a semi-quantitative assessment of the impact of CVP on renal hemodynamics (**Figure 3**). In hospitalized patients with HF (N=217), this RVF pattern

is associated (but not redundant) with high right atrial pressure and is very strongly associated with a poor prognosis<sup>172</sup>. In addition, another study including 50 patients with stable HF showed that RVF is an earlier marker of congestion development than the inferior vena cava and central venous pressure, and that patients with a lower RVF (namely, less renal congestion) had a better diuretic response<sup>173</sup>.

**Figure 3. Renal Venous Doppler**



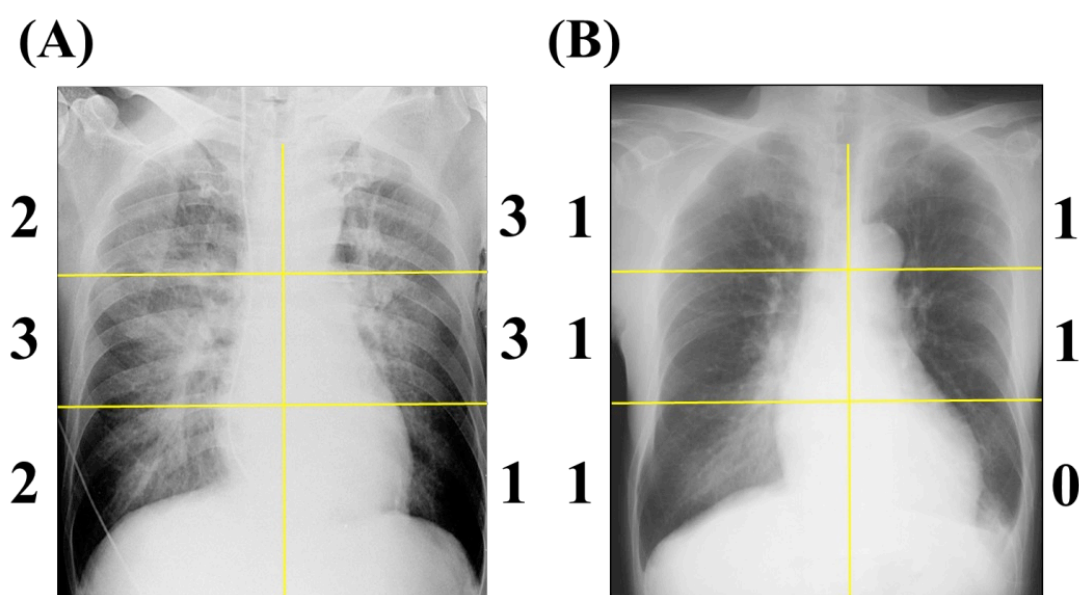
### 2.3.4. Chest radiography

Chest radiography (CXR) is a fast, inexpensive and widely available method to detect pulmonary congestion<sup>81, 88, 124-126</sup>. Limited diagnostic value of CXR was repeatedly reported using a single or combination of typical radiographic signs (i.e. cephalization, peri-bronchial cuffing and alveolar edema) of congestion<sup>125, 127-130</sup>. However, recently published data showed that radiographic pulmonary congestion can be quantified using a congestion score index (CSI, 0 to 3, with higher scores indicating more severe pulmonary congestion) (**Figure 4**)<sup>131</sup>. Using this technique, the lung fields on chest radiography is divided into six topographical zones, and each area is assessed as follows: Score 0, no congestion sign; Score 1, cephalization (superior area), perihilar haze or perivascular/peribronchial cuffing or Kerley's A lines (middle area), Kerley's B or C lines (inferior area); Score 2, interstitial or localized/mild alveolar pulmonary edema; Score 3, intense alveolar pulmonary edema. Lung areas are not scored when more than one third of the divided lung fields are occupied by pleural effusion



(including vanishing tumor), atelectasis or cardiac silhouette. Radiographic CSI was calculated as the sum of the scores in each zone divided by the number of available zones. Some data suggested the clinical importance of pulmonary congestion quantification on CXR to predict the development of overt HF during hospital stay in patients admitted for myocardial infarction and its association with poor outcome in patients with CHF<sup>130, 131</sup>.

**Figure 4. Radiographic congestion score index**



	1	2			3
Superior	Cephalization	Interstitial pulmonary edema	Alveolar pulmonary edema		
Middle	Peribronchial cuffing		Localized edema	Confluent mild edema*	Confluent intense edema*
	Perivascular cuffing				
	Kerley A line				
Inferior	Kerley B line				
	Kerley C line				
No congestive sign; Vanishing tumor / Costophrenic angle					

\*Confluent edema was regarded as intense edema, when the density in an area of the divided lung field was visually similar to that of cardiac silhouette.

## **2.4. Other congestion markers**

### **2.4.1. Directly measured plasma volume**

Nuclear medicine techniques can assess PV status along with red blood cell and total blood volume taking advantage of the accurate measurement of a radioisotope tracer concentration in fluid samples <sup>132</sup>. Normalized hematocrit determined using this technique provides a direct assessment that consequently take into account red blood cell abnormalities (non-hemodilutional anemia or polycythemia) <sup>75, 133</sup>. There are several validated and standardized available techniques for directly measuring PV (e.g., <sup>131</sup>I-labeled albumin, <sup>125</sup>I-HSA and <sup>99m</sup>Tc-HSA methods <sup>75, 90, 133, 134</sup>). Previously published data showed that measured PV may provide more accurate information about volume profile post-diuretic therapy and subsequent prognosis in patients hospitalized for HF <sup>38, 133, 135</sup>. However, the radioisotope assays require specialized equipment with relatively high cost, which needs frequent venous blood sampling, processing delays and high logistical issues to implement <sup>90</sup>. Thus, this measurement is unavailable to a majority of clinicians.

### **2.4.2. Right heart catheterisation and pulmonary artery pressure monitoring**

Right heart catheterization is the gold standard assessment of intracardiac pressures and cardiac output. However, a report of ESCAPE trial showed that, in 433 patients hospitalized with severe symptomatic and recurrent HF, right heart catheterisation failed to show a clinical benefit of hemodynamic-guided management as compared with usual care, although the safety of this invasive management was ascertain <sup>136</sup>. Therefore, in the current clinical practice guidelines, the use of invasive monitoring is usually limited to patients with severe HF amended for heart transplantation or mechanical circulatory support <sup>50</sup>. Importantly, increases in intracardiac/pulmonary artery pressures are apparent several days to weeks before the onset of symptomatic congestion and urgent HF hospitalization <sup>137, 138</sup>, suggesting a benefit for earlier detection of hemodynamic congestion. The CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients (CHAMPION) trial showed the important benefit of HF management based on pulmonary pressure monitoring using wireless devices on HF re-hospitalization in 550 ambulatory patients with HF <sup>139</sup>. During a mean follow-up of 15 months, the intervention group (n=270) experienced a 37% reduction in

the risk for hospitalization for HF compared with the control group (n=280) (HR, 95%CI=0.63, 0.52-0.77;  $p<0.0001$ ). These results highlight that the frequent titration of diuretic doses based on pulmonary pressure data significantly reduced intracardiac pressure and subsequently improved HF-related outcomes<sup>139</sup>. However, this invasive assessment of congestion may not be available in all patients with HF, especially in the context of elderly, high comorbidity burden and economic concerns.

### **3. Integrative approach to systemic and pulmonary congestion.**

#### **3.1. Systemic congestion in right-sided heart failure**

Right-sided HF is caused by right ventricular dysfunction, aggravated tricuspid regurgitation and possibly subsequent deteriorations by left-sided HF<sup>2, 3</sup>. Systemic congestion is characterized by clinical congestion signs (i.e., leg edema, jugular venous distention and hepatjugular reflex), echocardiographic parameters (i.e., inferior vena cava and tricuspid valvular regurgitation) and other measurements (i.e., RAP and liver stiffness). Presence/aggravation of systemic congestion does not always require urgent hospitalization but is associated with poor patient outcomes. Ambulatory quantification or monitoring of systemic congestion may be of clinical importance to detect patients at a high risk and optimize congestion status, especially in the context of patients with other underlying causes of fluid accumulation (i.e., renal impairment and malnutrition).

#### **3.2. Pulmonary congestion in left-sided heart failure**

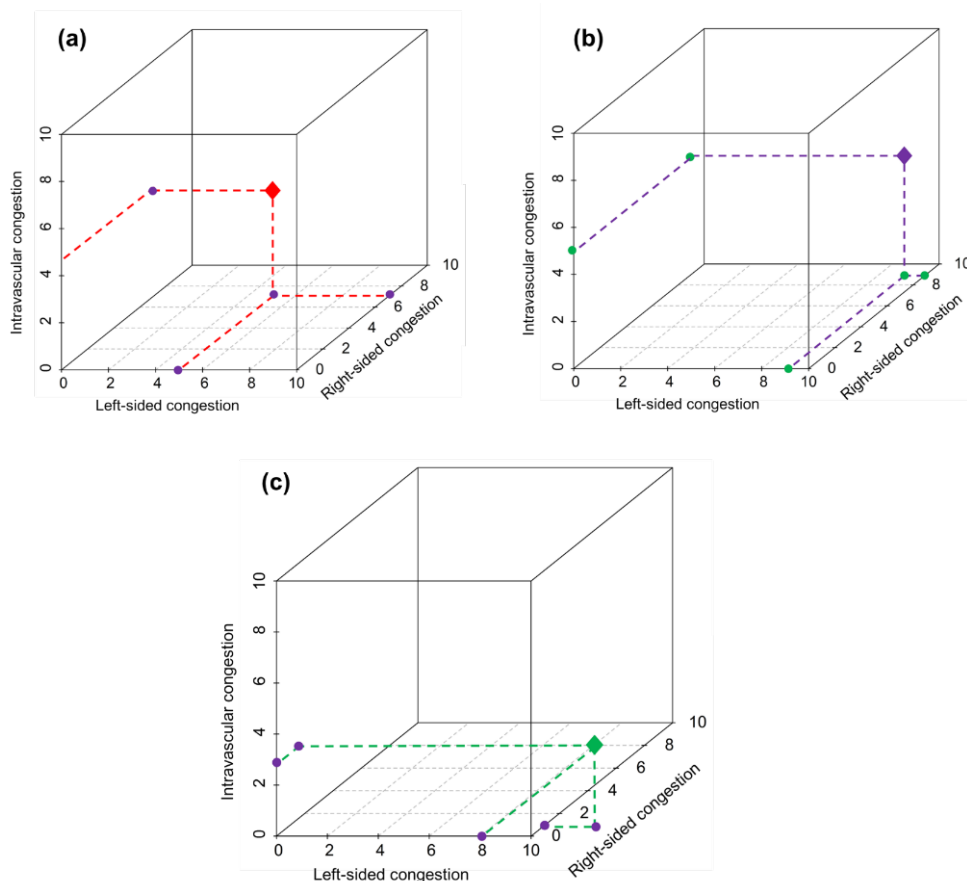
Development of pulmonary congestion is mainly due to increases in left ventricular filling pressure and/or central venous pressure (given with decreased ability of lymphatic drainage)<sup>140-142</sup>. Patients with advanced HF are usually perceived as being less likely to have signs of pulmonary congestion such as rales and/or pulmonary edema on CXR, even in patients with severe hemodynamic congestion. Therefore, patients experiencing pulmonary congestion need to be closer management during their hospital stay and may require aggressive diuretic approaches. In patients hospitalized for worsening HF, acute ischemic attack and/or arrhythmia are the main underlying causes of the rapid development of pulmonary congestion. In addition, isolated pulmonary congestion especially in the context of extreme hypertension is a well-known phenotype of acute HF with a lower risk of mid-term

outcomes<sup>27, 143, 144</sup>. Detection of mild pulmonary congestion may be challenging in ambulatory patients or hospitalized patients at discharge. In this setting, lung ultrasound can detect a low level of pulmonary congestion with high sensitivity and specificity, and may provide additional patient risk-stratification.

### 3.3. Conceptualized figure of congestion profile

Signs and symptoms of congestion is generally classified into right-sided (systemic) and left-sided (pulmonary) congestion, whereas intravascular congestion is perceived as being the preclinical form of congestion. Congestion often accompanies with the underlying complex interactions of these components. Therefore, we propose that congestion profile in each patient may be determined according to three components (namely, intravascular congestion, left-sided and right-sided congestion) in a three-dimensional space. This multidimensional approach may help clinicians assess congestion profiles (**Figure 5**). Each congestion profile could possibly link to a different mechanism of congestion and require different treatment approach (i.e. diuretics and vasodilator).

**Figure 5. Scheme of different congestion profiles on acutely decompensated heart failure**



For example, patients in group “a” expressed right-sided rather than left-sided congestion, whereas patients in group “b” had both severe right-sided and left-sided congestion despite similar extent of intravascular congestion than group “a”. Furthermore, patients in group “c” had predominantly (almost isolated) left-sided congestion. Such patients often present with acute onset of high blood pressure, leading to elevations in pulmonary and cardiac filling pressure, and need to take a vasodilator to alleviate these elevated pressures without a reduction in fluid volume. By contrast, patients expressing more severe right-sided congestion are perceived as being mainly due to a gradual increase in cardiac filling pressures accompanied with slowly progressive peripheral, abdominal and peripheral edema. These patients are more likely to take advantage of loop diuretics to reduce their accumulated fluid volume and thereby reduce intravascular congestion. We believe that a better evaluation on a multimodal approach could help an appropriate intensification of a personalized treatment approach in the field of HF.

## 4. Hypothesis and objectives

Congestion can be classified into systemic and pulmonary congestion, and is an important feature for the diagnosis of AHF in patients with acute dyspnea. A better assessment of congestion might improve inpatient management and help discharge timing decision-making in patients admitted for worsening HF<sup>1, 4, 10, 139, 145, 146</sup>. There is a large body of evidence regarding the assessment of congestion using various clinical, biological and echocardiographic parameters. However, data from clinical trials showed the limited utilities of these congestion parameters (i.e., natriuretic peptide and hemodynamic monitoring) as compared with standardized care alone<sup>136, 147-149</sup>. In addition, the availability or the ability to monitor these parameters is usually limited in routine practice. More routinely used exams could help evaluate congestion repeatedly in routine practice. Specifically, congestion variables derived from chest radiography and hemoglobin/hematocrit may provide additional diagnostic and prognostic performance on top of routine clinical evaluation and possibly other more refined congestion measurements.

### 4.1. Objectives

To investigate the diagnostic and prognostic value of congestion evaluation tools easily available in routine practice, namely the radiographic congestion score index and the plasma volume status estimated from hemoglobin/hematocrit, as well as their combination, in patients with HF.

### 4.2. Hypothesis

We hypothesized that;

- Radiographic CSI evaluated from CXR might improve diagnostic value of AHF in acute dyspneic patients in the emergency department.
- Radiographic CSI evaluated from CXR might identify patients admitted for worsening HF who were at a higher risk of post-discharge outcomes.
- PV estimated from hemoglobin and hematocrit might have prognostic value in patients with ADHF or those with HF and a preserved ejection fraction (HFpEF).
- The combined assessment of CSI and PV estimated from hemoglobin and hematocrit might be more efficient than an isolated assessment of one congestion parameter in patients with ADHF.

## 5. Articles in thesis

*During the course of this PhD, I first-authored 7 manuscripts related to this thesis 5 of which are already published.*

The first part of our research was focused on **radiographic congestion scoring using CSI**. First, we assessed its diagnostic value for AHF in acute dyspneic patients in the emergency department in the PRADISE cohort study (**1<sup>st</sup> paper under-review**). Our results showed that CSI provided excellent diagnostic accuracy, which was of similar magnitude that the diagnostic accuracy of BNP, and this diagnostic performance was consistent across various patients' subgroup (e.g. older age, overweight and concomitant lung diseases). Second, we investigated the prognostic value of CSI on admission, at discharge as well as the change in CSI from admission to discharge in patients hospitalized for worsening HF in the Tokyo cohort study, showing that high CSI at discharge increased the risk of post-discharge outcomes (**2<sup>nd</sup> paper published** in the *International Journal of Cardiology*).

The second focus of our research was **estimated PV**. Third, we investigated the association of Duarte-derived ePVS with clinical, biological and hemodynamic congestion markers in dyspneic patients (**3<sup>rd</sup> paper published** in *Clin Res Cardiol*). These results highlighted that Duarte-derived ePVS is more closely related to left-sided congestion markers such as E/e', natriuretic peptide and invasive LV filling pressure. In our fourth and fifth research paper, we respectively assessed the prognostic value of Duarte-derived ePVS in patients hospitalized for worsening HF and those with HFpEF. In both papers, our findings showed that ePVS improved risk-stratification (**4<sup>th</sup> paper published** and **5<sup>th</sup> paper published** both in *Clin Res Cardiol*). Then, we provided an in-depth review of available evidence, including the papers published during the course of this PhD, to promote the use of PV estimated from hemoglobin and hematocrit in routine practice (**6<sup>th</sup> paper under-review – transferred from EJHF to ESC-HF**).

In the last part of our research, we explored the prognostic value of the **combination of CSI and ePVS** on admission in patients hospitalized for worsening HF. Our results showed that the combination of CSI and ePVS may identify patients at high-risk for post-discharge outcome (**7<sup>th</sup> paper published** in *International Journal of Cardiology*).

## 5.1. Radiographic congestion score index

### 5.1.1. Congestion Score Index Evaluated from Chest Radiography for Diagnosing Acute Heart Failure in the Emergency Department: insights from the PARADISE cohort (1<sup>st</sup> paper)

Chest radiography is one of the most often used exam in patients with acute dyspnea in the emergency department<sup>8, 11, 12</sup>, but its diagnostic accuracy for AHF has been reported to be relatively low<sup>125, 128, 150</sup>. However, previous reports explored the diagnostic value of Chest radiography using a single or combination of typical radiographic signs of congestion in overall lung fields<sup>125, 127-130</sup>. Systematic and quantified assessment of radiographic pulmonary congestion may improve its diagnostic accuracy<sup>130, 131</sup>. In this first paper, we studied the diagnostic value of radiographic CSI for AHF in acute dyspneic patients from the Pathway of dyspneic patients in Emergency (PARADISE) cohort study.

We studied 1,333 acute dyspneic patients to assess diagnostic value for AHF using quantified pulmonary congestion on CXR. The diagnostic value of CSI was externally validated in an independent cohort (N=224). Briefly, half of the patients were men, mean age was 72±19 years and mean BMI was 26±6 kg/m<sup>2</sup>. Patients with a higher CSI had more cardiovascular risk factors, comorbidities, more severe congestion, inflammation status, higher BNP and poorer renal function.

The diagnostic accuracy of CSI for acute HF was excellent, whether alone (C-index=0.84, 0.82-0.86) or in addition to clinical model (0.87, 0.85-0.90). CSI improved diagnostic accuracy on top of clinical variables (NRI=94.9%) and clinical variables plus BNP (NRI=55.0%). In patients with available BNP (N=496), the accuracy of CSI combined with clinical variables was similar to the accuracy of BNP combined with clinical variables (delta C-index=-0.01, p=0.43). Good diagnostic accuracy was observed in the validation cohort (C-index=0.75, 0.68-0.82).

Our findings suggest that a semi-quantified (in contrast with most of available literature, focused on qualitative interpretation of Chest radiography) assessment of radiographic pulmonary congestion can improve the diagnostic approach for acute HF, and that its diagnostic accuracy was similar magnitude to that of BNP. Chest radiography is a fast, inexpensive, readily and widely available to assess the severity of pulmonary congestion. Systematic assessment of pulmonary congestion may improve diagnostic performance, shorten the delay of initial treatment approach and subsequently lead to favorable prognosis. This manuscript could change the perception of clinicians regarding the usefulness of Chest radiography for the diagnostic of AHF.



## PLOS Medicine

# Diagnostic Performance of Congestion Score Index Evaluated from Chest Radiography for Acute Heart Failure in the Emergency Department

--Manuscript Draft--

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<b>Abstract:</b>	<p><b>Background</b></p> <p>Congestion score index (CSI), a semi-quantitative evaluation of congestion on chest radiography, is associated with outcome in patients with heart failure (HF). However, its diagnostic value in patients admitted for acute dyspnea has yet to be evaluated.</p> <p><b>Methods</b></p> <p>The diagnostic value of CSI for acute HF (adjudicated from patients' discharge files) was studied in the PARADISE cohort (Pathway of dyspneic patients in Emergency). CSI was evaluated using a semi-quantitative method on chest radiography in consecutive patients admitted for acute dyspnea in the emergency department.</p>

	<p>Results were validated in an independent cohort (N=224).</p> <p>Findings</p> <p>Among 1,333 included patients (mean age 72.0±18.5 years, male 51.5%), mean CSI was 1.42±0.79. Patients with a higher CSI had more cardiovascular comorbidities, more severe congestion, higher b-type natriuretic peptide (BNP), poorer renal function and more respiratory acidosis at admission. Acute HF was diagnosed in 289 (21.7%) patients at discharge. CSI was significantly associated with acute HF diagnosis (adjusted-OR for 0.1-unit CSI increase=1.19, 1.16-1.22, p&lt;0.001). The diagnostic accuracy of CSI for acute HF was excellent, whether alone [area under ROC curve (AUROC)=0.84, 0.82-0.86] or in addition to clinical model (0.87, 0.85-0.90). CSI improved diagnostic accuracy on top of clinical variables [Net reclassification improvement (NRI)=94.9%] and clinical variables plus BNP (NRI=55.0%). In patients with available BNP (N=496), the accuracy of CSI combined with clinical variables was similar to the accuracy of BNP combined with clinical variables (delta AUROC=-0.01, p=0.43). Good diagnostic accuracy was observed in the validation cohort (AUROC=0.75, 0.68-0.82).</p> <p>Conclusions</p> <p>A systematic semi-quantified assessment of pulmonary congestion on chest radiography provides excellent diagnostic value for acute HF in dyspneic patients, which is similar magnitude to that of BNP. Better use of chest radiography may provide a cheap, widely and readily available method for acute heart failure triage in the emergency department.</p>
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<p><b>Financial Disclosure</b></p> <p>Enter a financial disclosure statement that describes the sources of funding for the work included in this submission. Review the <a href="#">submission guidelines</a> for detailed requirements. View published research articles from <a href="#">PLOS Medicine</a> for specific examples.</p> <p>This statement is required for submission and <b>will appear in the published article</b> if the submission is accepted. Please make sure it is accurate.</p>	<p>MK is granted by the RHU Fight-HF, a public grant overseen by the French National Research Agency (ANR) as part of the second "Investissements d'Avenir" program (ANR-15-RHUS-0004).</p> <p>MK, PR, KD, NG, and FZ are supported by the RHU Fight-HF, a public grant overseen by the French National Research Agency (ANR) as part of the second "Investissements d'Avenir" program (ANR-15-RHUS-0004) and by the FrenchPIA project "Lorraine Université d'Excellence" (ANR-15-IDEX-04-LUE).</p>

## **Diagnostic Performance of Congestion Score Index Evaluated from Chest Radiography for Acute Heart Failure in the Emergency Department**

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**Running title:** Diagnostic Value of Radiographic Congestion Scoring for Acute Heart Failure

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## Abstract

**Background:** Congestion score index (CSI), a semi-quantitative evaluation of congestion on chest radiography, is associated with outcome in patients with heart failure (HF). However, its diagnostic value in patients admitted for acute dyspnea has yet to be evaluated.

**Methods:** The diagnostic value of CSI for acute HF (adjudicated from patients' discharge files) was studied in the PARADISE cohort (Pathway of dyspneic patients in Emergency). CSI was evaluated using a semi-quantitative method on chest radiography in consecutive patients admitted for acute dyspnea in the emergency department. Results were validated in an independent cohort (N=224).

**Findings:** Among 1,333 included patients (mean age  $72.0 \pm 18.5$  years, male 51.5%), mean CSI was  $1.42 \pm 0.79$ . Patients with a higher CSI had more cardiovascular comorbidities, more severe congestion, higher b-type natriuretic peptide (BNP), poorer renal function and more respiratory acidosis at admission. Acute HF was diagnosed in 289 (21.7%) patients at discharge. CSI was significantly associated with acute HF diagnosis (adjusted-OR for 0.1-unit CSI increase=1.19, 1.16-1.22,  $p < 0.001$ ). The diagnostic accuracy of CSI for acute HF was excellent, whether alone [area under ROC curve (AUROC)=0.84, 0.82-0.86] or in addition to clinical model (0.87, 0.85-0.90). CSI improved diagnostic accuracy on top of clinical variables [Net reclassification improvement (NRI)=94.9%] and clinical variables plus BNP (NRI=55.0%). In patients with available BNP (N=496), the accuracy of CSI combined with clinical variables was similar to the accuracy of BNP combined with clinical variables (delta AUROC=-0.01,  $p=0.43$ ). Good diagnostic accuracy was observed in the validation cohort (AUROC=0.75, 0.68-0.82).

**Conclusions:** A systematic semi-quantified assessment of pulmonary congestion on chest radiography provides excellent diagnostic value for acute HF in dyspneic patients, which is similar magnitude to that of BNP. Better use of chest radiography may provide a cheap, widely and readily available method for acute heart failure triage in the emergency department.

**Keywords:** Chest radiography; Heart failure; Pulmonary congestion; Respiratory Insufficiency, Acute dyspnea; Cardiac Edema; Emergency department; Diagnosis.



## Introduction

Acute heart failure (HF) is one of the leading causes of acute dyspnea in the emergency department (ED) <sup>1</sup> and is associated with a higher risk of morbidity and mortality <sup>2, 3</sup>. In-hospital mortality is reported to be greater than 10% <sup>6</sup> and has remained stable in the last 30 years. As prognosis is related to initiation time of specific therapies <sup>5</sup>, current guidelines emphasize the importance of early diagnosis and treatment initiation to improve clinical outcomes <sup>4, 5</sup>. However, a minority of patients with acute HF receive treatment within one hour of admission,<sup>5</sup> in contradiction with current recommendations <sup>4</sup>. In addition, a third of acute HF diagnosis are missed in the ED <sup>1</sup>, further delaying access to care. An increasing number of better diagnostic tools for acute HF (AHF) are available in the ED <sup>6-8</sup>. However, there is likely room for improving the diagnostic approach to AHF from widely available routine tools including chest radiography (CXR).

Chest radiography is a fast and inexpensive method performed systematically in the ED in patients with acute dyspnea <sup>9-11</sup>. It is the first-line diagnostic imaging modality advocated in current guidelines <sup>12</sup>. However, its diagnostic accuracy for HF has been reported to be relatively low <sup>13-15</sup>. In particular, diagnosing HF in patients with concomitant lung diseases such as chronic obstructive pulmonary disease (COPD) and pneumonia still remains a challenge <sup>16</sup>.

A new semi-quantitative approach to pulmonary congestion has recently emerged in the field of HF. Congestion score index (CSI) is a semi-quantitative approach to pulmonary congestion based on a 6-zone evaluation of CXR, scoring each zone from 0 (no congestion) to 3 (intense alveolar pulmonary edema). CSI is a strong risk-stratifier in patients with stable or worsening HF <sup>17-19</sup>. However, there are very little available data regarding its diagnostic value for AHF.

The aims of the present study are to investigate the diagnostic value of pulmonary congestion assessed with CSI for AHF in patients admitted for acute dyspnea in the ED and to assess its discriminative value comparatively to and on top of currently used clinical diagnostic models and natriuretic peptide measurements.

## Methods

### Study population

The Pathway of dyspneic patients in Emergency (PARADISE) cohort is a retrospective cohort study including patients 18 years or older admitted in the ED of the Nancy University Hospital (France) between January 1, 2015 and December 31, 2015 as detailed previously<sup>20, 21</sup>. The hospital's electronic charts (Resurgences®) were systematically reviewed by investigators to search for the records of all patients admitted for acute dyspnea in the ED. All patients with signs or symptoms of dyspnea, or requiring oxygen treatment during their ED stay were included. Patients with shock or cardiac arrest were excluded from this analysis as dyspnea was not the primary condition triggering ED admission. In the current study, a total of 1,333 dyspneic patients with available information on CXR at the emergency department were analyzed (**Supplementary figure 1**). Demographic parameters, medical history, physical examination, laboratory findings and treatment received in the ED were retrieved from the patients' electronic records. The PARADISE cohort was approved by the Commission d'Informatique et Libertés (CIL) (Number R2016-08) and registered on "clinicaltrials.gov" (NCT02800122).

External validation was performed on the merged dataset from the HF disease management program entitled "Insuffisance Cardiaque en LORraine (ICALOR)"<sup>22, 23</sup> (included at a different time-period than the data from Nancy University Hospital used in the derivation set) and data from Epinal Hospital (a secondary care hospital located at 70 km from Nancy University Hospital) within the PURPLE multi-centre cohort (NCT03194243). Briefly, we used the data from the previously described<sup>18</sup> 117 patients included in the ICALOR disease management cohort during an hospitalization for acutely decompensated HF in the Cardiology Department, of the Nancy University Hospital (France). We also used the data of 107 consecutive patients admitted for acute dyspnea with available CXR data and discharge diagnosis in the Emergency department of the Epinal hospital. This external validation set allowed us to test CSI in a significantly different setting (mixing cardiology department from a tertiary care hospital and an ED of a secondary care hospital) than our derivation set.

### Diagnosis of Heart Failure

HF was diagnosed according to ESC guidelines<sup>24</sup>. Diagnosis of AHF was coded independently by 2 medical physicians (GG and TH) according to ESC guidelines<sup>24</sup>. Each physician had access to all ED medical charts as well as additional hospital admission test results and records (*e.g.*, echocardiography, natriuretic peptide level and patient response to diuretic/broncholytic therapy), but were blinded to CSI quantification on CXR. Homogenous coding was ensured by a trained senior physician (TC).

### Radiographic Congestion Score Index

Radiographic CSI was used to quantify the severity of pulmonary congestion in CXR as previously published<sup>17, 18</sup>. After dividing the lung field into six topographical zones, each area was assessed as follows: Score 0, no congestion sign; Score 1, cephalization (superior area), perihilar haze or perivascular/peribronchial cuffing or Kerley's A lines (middle area), Kerley's B or C lines (inferior area); Score 2, interstitial or localized/mild alveolar pulmonary edema; Score 3, intense alveolar pulmonary edema (**Figure 1**). To enhance the reproducibility of the severity of confluent edema, a portion of the divided lung fields which was visually similar to the cardiac silhouette was regarded as an intense zone, whereas the field with weaker density was regarded as a mildly intense zone. Lung areas were not scored when more than one third of the divided lung fields were occupied by pleural effusion (including vanishing tumor), atelectasis or cardiac silhouette. CSI was calculated as the sum of the scores in each zone divided by the number of available zones. An examiner also assessed the presence of pneumonia, pleural effusion, cardiomegaly by cardiothoracic ratio (>50%) and the difficulty in assessing CSI.

CXR was analyzed by a single emergency physician (AD), blinded to clinical data and discharge diagnosis, with no previous training in congestion quantification on CXR prior to that in the present study. After a short training (~3 hours) using a 20-patient sample with a radiographic CSI expert (MK), intra-observer and inter-observer agreement (with MK) was tested on 30 randomly selected patients, while blinded to clinical status and diagnosis. Intra-class correlation coefficients showed good

reproducibility [0.85 (0.71–0.93) and 0.81 (0.64–0.90) for intra and inter-observer reproducibility, respectively].

### **Brest Score**

The Brest score was calculated for every patient based on the patients' medical charts. This diagnostic score for AHF in dyspneic patients is based on age, comorbidities (*i.e.* prior history of heart failure, myocardial infarction and COPD), pattern of dyspnea, ST segment abnormalities and signs/symptoms of congestion (*i.e.* rales and leg edema)<sup>25, 26</sup>.

### **Statistical analysis**

Categorical variables are expressed as frequencies (percentages) and continuous variables as means  $\pm$  standard deviation or median (25th and 75th percentiles) according to the distribution of the variables. Comparisons of demographic, clinical and biological parameters among quartiles of radiographic CSI were analyzed using  $\chi^2$  tests for categorical variables and ANOVA or Kruskal-Wallis test for continuous variables.

Inter-observer and intra-observer agreements of CSI were assessed with the intraclass correlation coefficient.

A logistic regression model was used to assess the association of CSI with diagnosis of AHF. Multivariable analyses included clinically relevant confounders: model 1: age, sex, body mass index (BMI), presence of hypertension, diabetes mellitus, coronary artery disease, atrial fibrillation, prior HF admission, use of angiotensin converting enzyme inhibitor/angiotensin receptor blocker, beta-blocker, diuretics, leg edema, jugular venous distension, hemoglobin, white blood cell count, estimated glomerular filtration rate (eGFR, as calculated by the Chronic Kidney Disease Epidemiology Collaboration formula<sup>27</sup>) at admission; model 2: Brest Score. Receiver operating characteristics (ROC) curve was used to determine the diagnostic value of CSI in AHF.



The increase in discriminative value of the addition of CSI on top of the aforementioned potential covariates were assessed using continuous net reclassification improvement (NRI) <sup>28</sup>. In addition, in 498 (37.4%) patients who had available brain natriuretic peptide (BNP) measurements, the added value of CSI on the top of the Brest Score and BNP was assessed.

All analyses were performed using R version 3.4.0 (R Development Core Team, Vienna, Austria). A two-sided p-value <0.05 was considered statistically significant.

## Results

### Baseline Characteristics

Less than 10% of the population had no available data on CXR (**Supplementary table 1**). These patients were markedly younger and had less comorbidities than patients who underwent CXR.

In a total of 1,333 patients included in this study, a half were men, mean age was 72.0±18.5 years, mean BMI was 25.5±5.5 kg/m<sup>2</sup> and less than 10% had a prior admission for HF (7.1%) (**Table 1**). CXR was considered as difficult to interpret during CXR reviewing in 502 patients (37.7%). Mean CSI was 1.42±0.79. Patients with a higher CSI had more cardiovascular risk factors, comorbidities, more frequent prior HF admission, more severe congestion, inflammation status, higher BNP, poorer renal function and more respiratory acidosis at admission (**Table 1**).

### Association of Congestion Score Index with Adjudicated Discharge Diagnosis of Acute Heart Failure

In this study, 289 (21.7%) patients were diagnosed with AHF at discharge. Higher CSI was significantly associated with AHF [OR (95%CI) for a 0.1-unit increase in CSI=1.22 (1.19-1.25), p<0.001] even after adjustment for potential confounders [adjusted OR CSI=1.18 (1.15-1.22), p<0.001] (**Table 2**). Association with AHF gradually rose across CSI quartiles [adjusted OR=3.05 (1.27-8.49), p=0.03 in Q2, OR=8.32 (3.69-22.40), p<0.001 in Q3 and OR=28.89 (12.69-78.36), p<0.001 in Q4 versus Q1]. (**Table 2**). Similar results were observed after adjustment for the Brest Score (**Table 2**).

### Diagnostic value of the Congestion Score Index

In the whole population, CSI exhibited high discrimination for AHF as reflected by an area under the curve (AUC) of 0.84 (0.82 to 0.86) (**Figure 2 & Central illustration**). Similarly, high AUC were observed across subgroups of age, sex and comorbidities (obesity, COPD) or associated diagnosis (pneumonia and pleural effusion) (**Figure 2**). In contrast, subgroups without cardiomegaly assessed by CXR had higher AUC compared to those with cardiomegaly [AUC (95%CI)=0.85 (0.81-0.89) vs. 0.75 (0.70-0.79) respectively]. In addition, the diagnostic value of CSI was influenced by the patient's position [AUC (95%CI)=0.83 (0.80-0.89) in sitting position and 0.79 (0.73-0.84) in supine position] as well as the difficulty in assessing CSI [AUC (95%CI)=0.92 (0.86-0.97) for easy, 0.84 (0.80-0.88) for moderate and 0.80 (0.75-0.84) for difficult assessments].

AUC for the Brest score was 0.78 (0.75-0.81). The combination of CSI and Brest score yielded a high AUC for AHF [AUC (95%CI)=0.87 (0.85-0.90)].

### Improvement in Reclassification Associated with Acute Heart Failure Diagnosis

The addition of CSI on top of the Brest score significantly improved reclassification [NRI (95%CI)=94.9 (83.5-106.2),  $p<0.001$  for continuous CSI and 88.4 (76.3-100.5),  $p<0.001$  for the highest quartile of CSI] (**Figure 3**).

Furthermore, in patients with available BNP data (N=496), CSI still significantly improved reclassification on top of BNP and the Brest score [NRI (95%CI)=55.0 (38.0-72.0),  $p<0.001$ , delta AUC (95%CI)=2.9 (0.6-5.2,  $p=0.015$ ] (**Figure 3 & 4**). The diagnostic value of the joint use of the Brest score and CSI was not significantly different that the joint use of the Brest score and BNP [NRI (95%CI)=4.4 (-13.3-22.1),  $p=0.63$ , delta AUC (95%CI)=-1.4 (-5.0-2.1,  $p=0.42$ ]. In this subgroup, the Brest score had a moderate accuracy [AUC (95%CI)=0.72 (0.75-0.81)], but the combination of CSI, BNP and Brest score resulted in high diagnostic value for AHF [AUC (95%CI)=0.85 (0.82-0.89)] (**Figure 4**).

### **Validation in an external cohort**

In the validation cohort (N=224), more than a half of the patients (56.7%) were men, mean age was  $75.8 \pm 13.9$  years, mean CSI was  $1.85 \pm 0.87$ , and 72.7% had a diagnosis of AHF at discharge. The diagnostic performance of CSI was good [AUC (95%CI)=0.75 (0.68-0.82)].

### **Discussion**

Our results show that pulmonary congestion quantified by a simple standardized CXR scoring can efficiently identify patients with AHF in the ED, consistently across the various subgroups (e.g., elderly, overweight, COPD and pneumonia). Furthermore, CSI significantly improved the reclassification of patients on top of the recognized clinical diagnostic markers of AHF and natriuretic peptides. Our findings suggest that a semi-quantified assessment of congestion on CXR could represent a readily available and clinically useful diagnostic tool for AHF in acute dyspneic patients in the emergency department.

### **Radiographic Congestion Score Index as a Diagnostic Tool for Acute Heart Failure**

CXR exhibited a higher diagnostic performance in diagnosing HF than usually reported in the literature<sup>13-15</sup>. Of note, previous reports assessed the diagnostic value of CXR using a single or combination of typical radiographic signs of congestion using a global evaluation of the lungs<sup>14, 15, 29-31</sup> rather than a systematic approach, with lung segmentation as used in the CSI method. Our group recently showed that more severe pulmonary congestion, quantified by either CSI or lung ultrasound at admission, was associated with higher pulmonary artery systolic pressure<sup>18, 32</sup>. This association of CSI with hemodynamic data emphasizes the mechanistic plausibility of our results.

Recent registry data have shown that approximately 20% of patients hospitalized for AHF had concomitant lung diseases such as pneumonia and COPD<sup>33-35</sup>, and these patients generally excluded in previous reports assessing the diagnostic value of CXR<sup>15, 16, 36, 37</sup>. However, our subgroup analysis provided a remarkably homogenous diagnostic performance of CSI across various subgroups (i.e., elderly, body mass index, COPD and pneumonia). The only factor appearing to decrease the diagnostic

value of CSI was cardiomegaly, possibly as a result of the overlapping of relevant information of the lung fields with cardiac silhouette in these patients.

### **Radiographic Congestion Score Index and Other Diagnostic Measurements: Clinical Parameters and Natriuretic Peptide**

In keeping with previous literature data<sup>18, 38</sup>, our results showed that patients with more severe pulmonary congestion were predominantly elderly, had higher BMI, more cardiovascular risk factors and comorbidities, severe congestion, poorer renal function and higher inflammatory markers. Those comorbid conditions may have weakened the value of natriuretic peptides<sup>39-43</sup>, *i.e.*, BNP in our study, leading to diagnostic uncertainty in a sizeable proportion of dyspneic patients<sup>6</sup>. The Brest score, based on clinical parameters, has also recently been shown to have good diagnostic accuracy for diagnosing HF in the ED<sup>26</sup>. However, as in the case of natriuretic peptides, almost half of the patients with dyspnea in the ED have intermediate scores<sup>25</sup>. The unmet need in clinical practice, even when using the Brest score and natriuretic peptides, thus remains high.

In the current study, CSI was found to improve reclassification on top of the Brest score and BNP. In addition, the combination of CSI and the Brest score improved the diagnostic value (AUC 0.81) to a similar degree of the combination of BNP and the Brest score (AUC 0.82, *p* for delta AUC 0.42). CSI also significantly improved diagnostic accuracy on top of the Brest Score and BNP, and the combined use of these 3 parameters resulted in an AUC of 0.85. Taken together, these findings further strengthen that CSI may play a complementary role to the clinical model and natriuretic peptides in diagnosing AHF.

### **Clinical Implications**

An early accurate diagnosis and consequently a prompt appropriate management improve outcomes in AHF patients admitted to the ED<sup>44 5, 45</sup>. Our results show that a standardized evaluation of CXR, using CSI, improves diagnosis performance and potentially the ability to swiftly manage AHF in the ED. This approach could moreover be easily scalable since training for this assessment is fairly simple; the operator (AD) who evaluated all CXRs of this cohort efficiently acquired the technique in

the context of this study in a matter of a few hours. Alternatively, an automated assessment of pulmonary congestion based on CSI could be developed and subsequently implemented in current radiography software. In any event, based on the promising results herein, we propose that multi-center trials assessing the impact of the implementation of CSI in the ED on the outcome of patients with acute dyspnea are worth undertaking.

### **Limitations and strengths**

The main limitation of our derivation cohort is its single-center and retrospective nature. However, the large-sized population sample, the relatively homogenous management of dyspneic patients and adjudication of AHF diagnosis, along with the external validation of our results would appear to support the validity and generalizability of our results. In the present study, left ventricular ejection fraction was not recorded, which may influence diagnostic accuracy of CSI. This parameter, however, is not a major determinant of decision-making for acute dyspneic management in the emergent department.

In the derivation cohort, we had no data on CSI in 138 (9.4%) patients who did not undergo CXR or had no available lung field to assess CSI. These patients, however, had better clinical status (i.e., younger age and less severe congestion), and only 8% of these patients (N=11) were diagnosed of AHF (**Supplementary table 1**). In addition, all CSI readings were performed blinded for other parameters and diagnoses, suggesting that this limitation is unlikely to have major influence on our findings.

CSI is a semi-quantitative tool with some subjectivity. However, in our experience, a short training period of approximately 3 hours is sufficient to achieve accurate and reproducible scoring.

Lastly, 502 (37.7%) of patients in the current study were assessed with difficulty, although persisting diagnostic value in these patients (AUC=0.80, 0.75-0.84) was provided.

## **Conclusions**

A semi-quantified assessment of radiographic pulmonary congestion provides excellent diagnostic value for AHF in dyspneic patients, which is similar magnitude to that of BNP. Implementing radiographic CSI in the diagnostic approach to AHF in addition to clinical parameters and BNP measurement could be rewarding. Better use of chest radiography may provide a cheap, widely and readily available method for acute heart failure triage in the emergency department.

## **Conflict of interest:**

NG received honoraria from Novartis and Boehringer. NG, FZ and PR are supported by the French National Research Agency Fighting Heart Failure (ANR-15-RHU-0004), by the French PIA project Lorraine Université d'Excellence GEENAGE (ANR-15-IDEX-04-LUE) programs, and the Contrat de Plan Etat Région Lorraine and FEDER IT2MP. FZ and PR are the cofounders of CardioRenal, a startup focused on HF management based on repeated biomarker evaluation. Dr. Rossignol reports grants and personal fees from AstraZeneca, Bayer, CVRx, Fresenius, and Novartis, personal fees from Grunenthal, Servier, Stealth Peptides, Vifor Fresenius Medical Care Renal Pharma, Idorsia, NovoNordisk, Ablative Solutions, G3P, Corvidia, Relypsa.

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**Figure 1. Radiographic Congestion Score Index**

The scoring is performed in six lung fields. Panels A and B provide examples of grades 0 to 3.

\*Confluent edema was regarded as intense edema, when the density in an area of the divided lung field was visually similar to that of cardiac silhouette

**Figure 2. Diagnostic Value of Radiographic Congestion Score Index for Discharge Diagnosis of Acute Heart Failure**

\*Pneumonia was diagnosed at discharge.

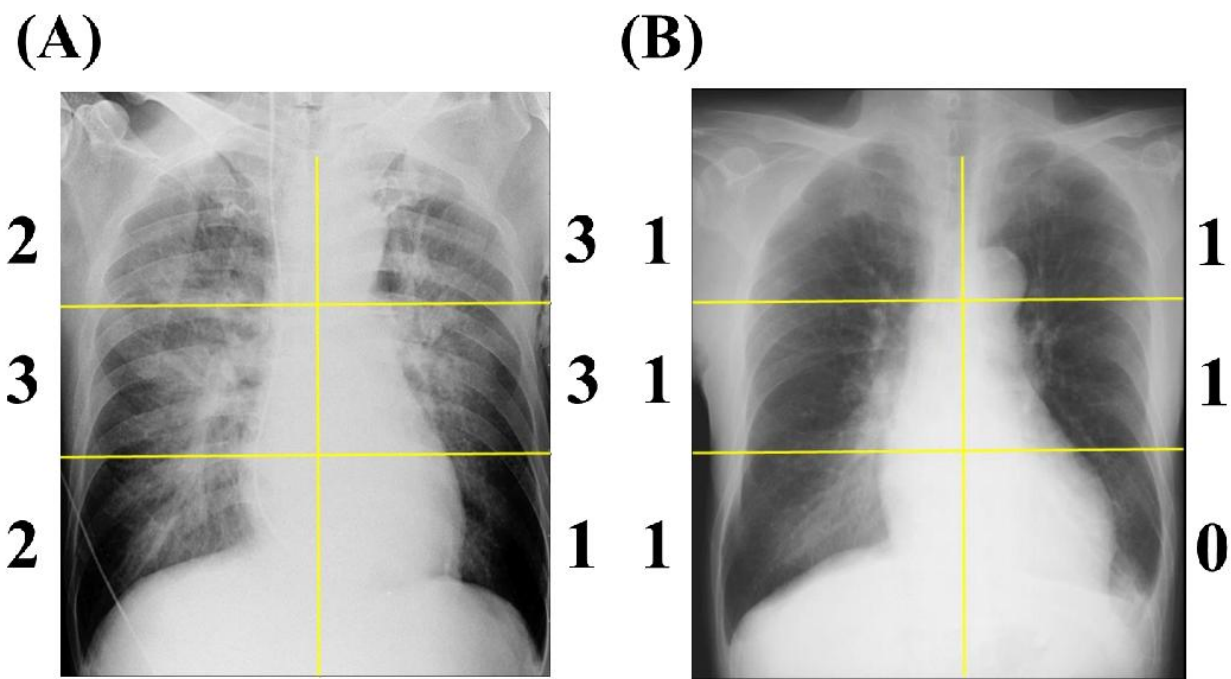
**Figure 3. Central Illustration**

CSI, congestion score index; AHF, acute heart failure; BNP, b-type natriuretic peptide; AUC, area under the curve; NRI, net classification improvement.

**Figure 4. Added values of CSI and BNP for the Diagnosis of Acute Heart Failure on Top of the BREST score in Patients with Available BNP (N=496)**

CSI, congestion score index; BNP, b-type natriuretic peptide; AUC, area under the curve; NRI, net classification improvement.

Figure 1. Radiographic Congestion Score Index



	1	2			3
Superior	Cephalization	Interstitial pulmonary edema	Alveolar pulmonary edema		
Middle	Peribronchial cuffing		Localized edema	Confluent mild edema*	Confluent intense edema*
	Perivascular cuffing				
Inferior	Kerley A line				
	Kerley B line				
	Kerley C line				
No congestive sign; Vanishing tumor / Costophrenic angle					

**Figure 2. Diagnostic Value of Radiographic Congestion Score Index for Discharge Diagnosis of Acute Heart Failure**

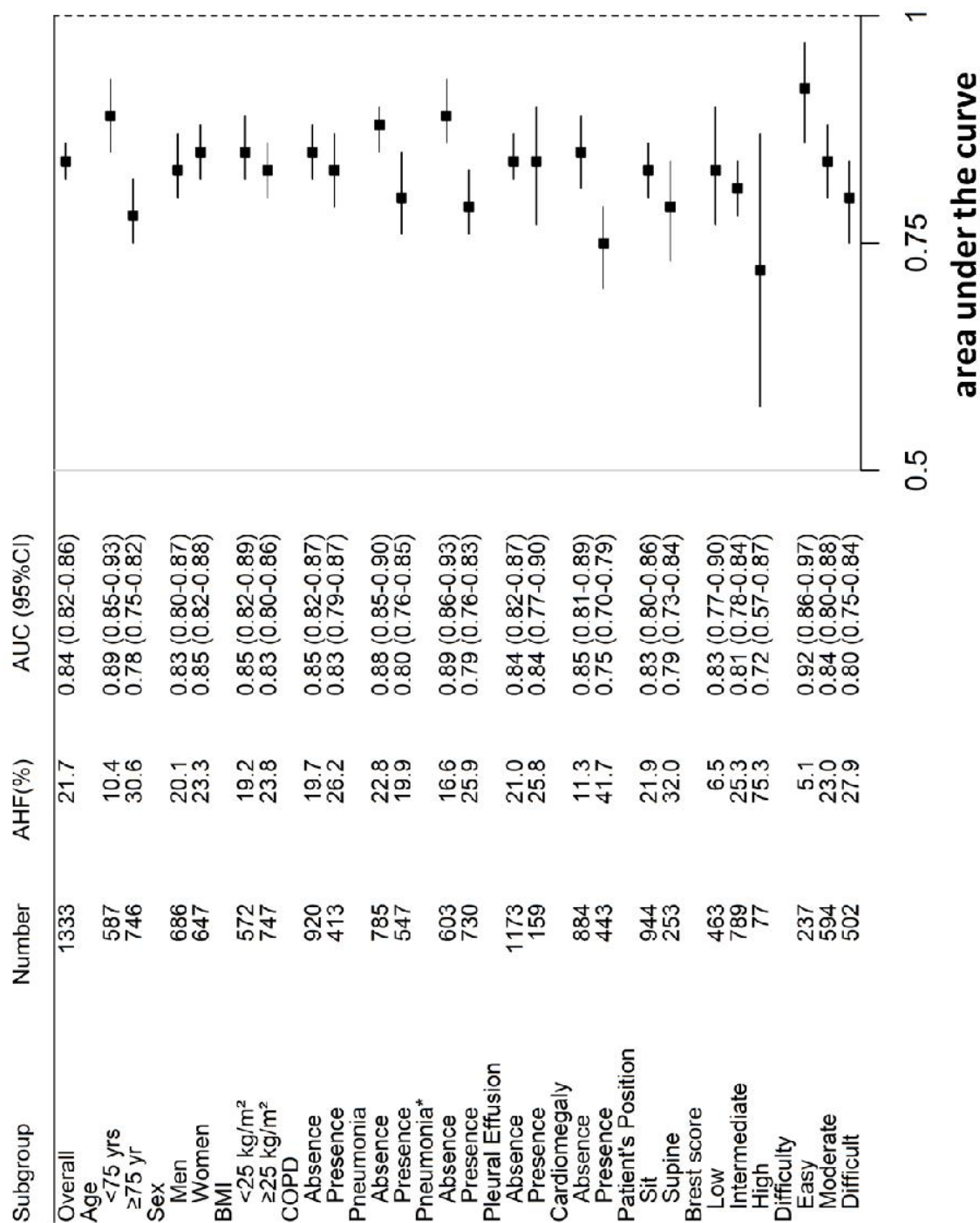
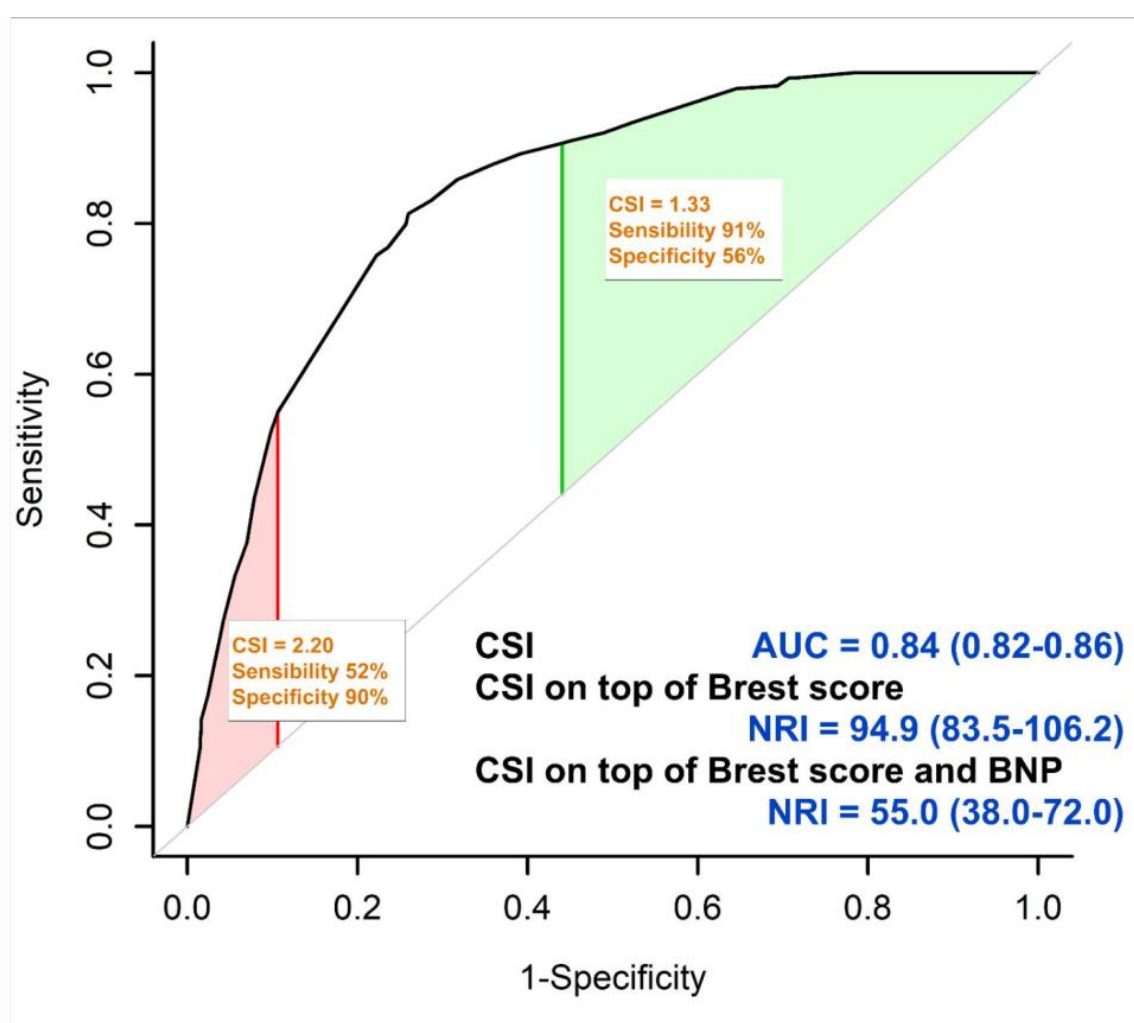
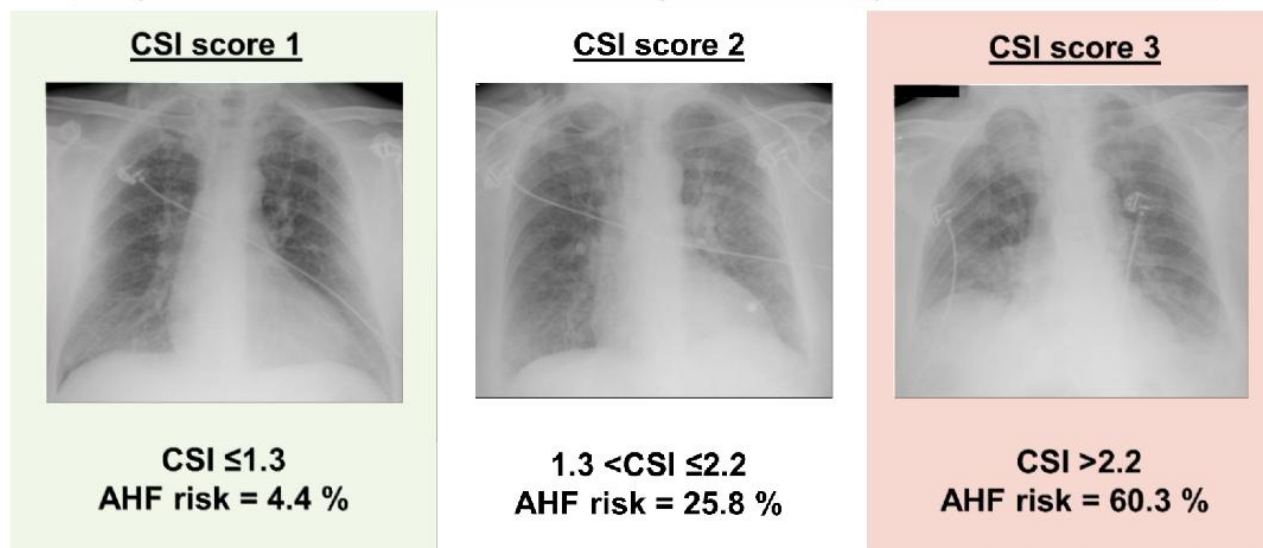
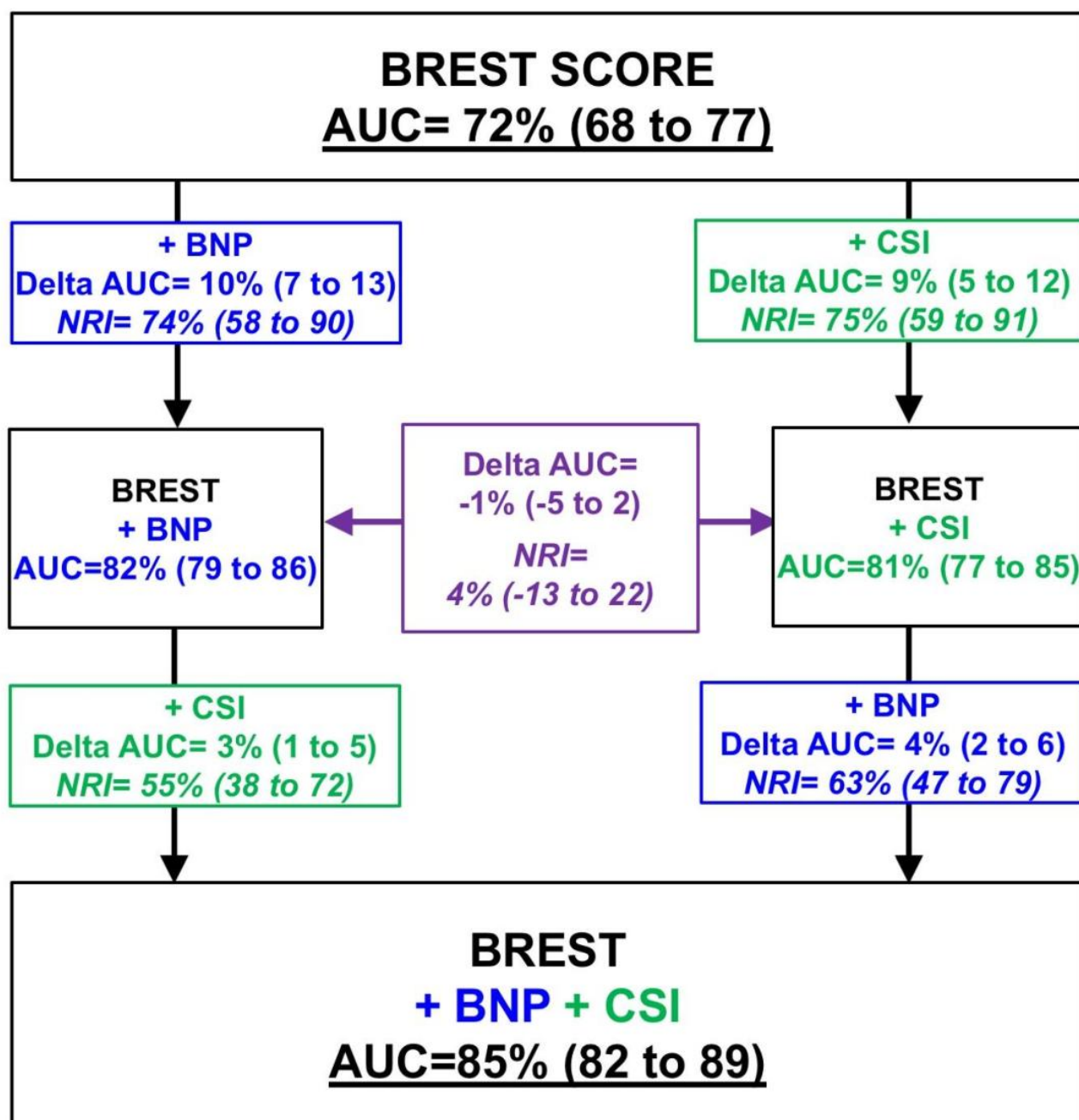


Figure 3. Central Illustration

**Diagnostic performance of Radiographic Congestion Score Index**



**Figure 4. Added values of CSI and BNP for the Diagnosis of Acute Heart Failure on Top of the BREST score in Patients with Available BNP (N=496)**





**Table 1. Baseline Characteristics according to the Radiographic Congestion Score Index (Quartiles)**

Values are Mean  $\pm$ SD, n (%) or median (25th to 75th percentile)

\* p-value adjusted for age and body mass index at admission.

HF, heart failure; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide; PaO<sub>2</sub>, partial pressure of oxygen; PaCO<sub>2</sub>, partial pressure of carbon dioxide

**Table 2. Association of Radiographic Congestion Score Index with Discharge Diagnosis of Acute Heart Failure**

OR, odds ratio; CI, confidence interval.

Multivariable model 1; adjusted for age, sex, body mass index, presence of hypertension, diabetes mellitus, coronary artery disease, atrial fibrillation, prior admission for heart failure, prescription of either angiotensin converting enzyme inhibitor or angiotensin receptor blocker, prescription of beta-blockers, diuretics, leg edema, jugular venous distension, hemoglobin, white blood cell count, estimated glomerular filtration rate at admission.

Multivariable model 2; adjusted for Brest Score.

Table 1. Baseline Characteristics according to the Radiographic Congestion Score Index (Quartiles)

	CSI quartiles					Adjusted p-value*
	Global (N=1333)	Quartile I, <0.84 (N=376)	Quartile II, 0.84-1.40 (N=328)	Quartile III, 1.40-2.00 (N=359)	Quartile IV, ≥2.00 (N=270)	
Age, yrs	72.0 ± 18.5	57.4 ± 20.9	73.4 ± 15.4	79.3 ± 12.6	80.9 ± 11.8	<0.001
Men, N (%)	686 (51.5 %)	212 (56.4 %)	168 (51.2 %)	166 (46.2 %)	140 (51.9 %)	0.06
Body mass index, kg/m <sup>2</sup>	25.5 ± 5.5	24.7 ± 4.8	25.3 ± 5.0	25.5 ± 5.8	26.8 ± 6.4	<0.001
Medical history, N (%)						
Hypertension	729 (54.7 %)	111 (29.5 %)	194 (59.1 %)	236 (65.7 %)	188 (69.6 %)	<0.001
Diabetes mellitus	302 (22.7 %)	50 (13.3 %)	62 (18.9 %)	94 (26.2 %)	96 (35.6 %)	<0.001
Dyslipidemia	280 (21.0 %)	51 (13.6 %)	79 (24.1 %)	82 (22.8 %)	68 (25.2 %)	<0.001
Coronary artery disease	162 (12.2 %)	16 (4.3 %)	36 (11.0 %)	63 (17.5 %)	47 (17.4 %)	<0.001
Atrial fibrillation	313 (23.5 %)	33 (8.8 %)	70 (21.3 %)	107 (29.8 %)	103 (38.1 %)	<0.001
Prior HF admission, N (%)	95 (7.1 %)	6 (1.6 %)	15 (4.6 %)	28 (7.8 %)	46 (17.0 %)	<0.001
Medication, N (%)						
ACEi/ARB	444 (34.7 %)	67 (18.3 %)	112 (36.5 %)	142 (40.8 %)	123 (47.7 %)	<0.001
Beta-blocker	306 (23.9 %)	45 (12.3 %)	70 (22.8 %)	103 (29.6 %)	88 (34.1 %)	<0.001
Spirinolactone	64 (5.0 %)	16 (4.4 %)	13 (4.2 %)	19 (5.5 %)	16 (6.2 %)	0.65
Diuretics	368 (28.8 %)	40 (10.9 %)	81 (26.4 %)	127 (36.5 %)	120 (46.5 %)	<0.001
Calcium channel blocker	258 (20.2 %)	24 (6.6 %)	67 (21.8 %)	82 (23.6 %)	85 (32.9 %)	<0.001
Statin	300 (23.5 %)	58 (15.8 %)	81 (26.4 %)	87 (25.0 %)	74 (28.7 %)	<0.001
O2 flow, L/min	4.0 (2.0 - 9.0)	3.0 (2.0 - 9.0)	3.0 (2.0 - 9.0)	3.0 (2.0 - 9.0)	5.0 (3.0 - 9.0)	0.005
Physical examination, N (%)						
Leg edema	334 (25.1 %)	28 (7.4 %)	65 (19.8 %)	117 (32.6 %)	124 (45.9 %)	<0.001
Jugular venous distension	43 (3.3 %)	4 (1.1 %)	8 (2.4 %)	12 (3.4 %)	19 (7.3 %)	<0.001
Rales	454 (35.2 %)	63 (17.3 %)	104 (32.3 %)	148 (42.8 %)	139 (54.5 %)	<0.001
Systolic BP, mmHg	132.1 ± 26.0	129.6 ± 22.7	132.3 ± 26.0	132.9 ± 26.8	134.5 ± 28.9	0.13
Diastolic BP, mmHg	73.5 ± 17.6	77.2 ± 16.3	72.4 ± 17.8	71.6 ± 18.1	72.4 ± 18.0	<0.001
Heart rate, bpm	95.7 ± 20.7	98.1 ± 19.0	94.7 ± 20.2	94.2 ± 20.1	95.5 ± 23.8	0.02
Respiratory rate, /min	26.3 ± 7.9	24.5 ± 7.6	26.5 ± 7.5	26.8 ± 8.0	27.5 ± 8.4	<0.001
Congestion score index	1.4 ± 0.8	0.5 ± 0.3	1.2 ± 0.2	1.8 ± 0.2	2.5 ± 0.3	<0.001
Laboratory findings						
Hemoglobin, g/dl	12.8 ± 2.0	13.5 ± 1.9	12.8 ± 2.0	12.6 ± 2.0	12.2 ± 2.0	<0.001
White blood count	11300 (8300 - 15400)	10765 (8420 - 14100)	10900 (7700 - 15100)	11575 (7800 - 15600)	12600 (8900 - 16700)	0.006
C-reactive protein, mg/dl	6.6 (1.8 - 14.0)	3.9 (0.8 - 10.5)	7.7 (2.3 - 14.8)	7.7 (2.3 - 14.5)	7.1 (2.1 - 15.4)	<0.001
Sodium, mmol/l	136.9 ± 5.3	137.1 ± 4.9	136.3 ± 5.4	137.0 ± 5.7	137.2 ± 5.0	0.17

Potassium, mmol/l	4.1 ± 0.6	4.0 ± 0.5	4.1 ± 0.6	4.2 ± 0.6	4.3 ± 0.7	5.6	<0.001	<0.001
Blood glucose, mmol/l	7.7 ± 3.5	6.8 ± 2.6	7.4 ± 3.0	7.8 ± 3.4	9.3 ± 4.5	3.0	<0.001	<0.001
BUN, mg/dl	25.3 ± 18.0	19.3 ± 15.5	23.5 ± 15.9	27.7 ± 17.5	32.6 ± 20.8	2.9	<0.001	<0.001
eGFR, ml/min/1.73m <sup>2</sup>	82.6 ± 55.4	96.2 ± 38.4	85.0 ± 42.2	79.8 ± 83.1	65.4 ± 34.4	3.5	<0.001	0.03
BNP, pg/ml	274	65	155	280	480	62.6	<0.001	<0.001
Blood gas								
PH	7.41	7.43	7.42	7.41	7.36	18.8	<0.001	<0.001
	(7.34 - 7.45)	(7.39 - 7.46)	(7.37 - 7.46)	(7.34 - 7.45)	(7.28 - 7.42)			
PaO <sub>2</sub> , mmHg	65.0	64.0	64.5	64.0	66.0	19.0	0.68	0.57
	(56.0 - 79.0)	(58.0 - 78.0)	(56.0 - 79.5)	(53.0 - 79.0)	(57.0 - 79.0)			
PaCO <sub>2</sub> , mmHg	40.4	39.0	41.0	41.0	42.0	18.8	<0.001	<0.001
	(35.0 - 48.0)	(34.0 - 44.0)	(35.0 - 47.0)	(35.2 - 51.0)	(36.0 - 52.0)			
Lactate, mmol/L	1.10	1.00	1.00	1.10	1.10	19.5	0.008	<0.001
	(0.80 - 1.60)	(0.70 - 1.50)	(0.80 - 1.40)	(0.80 - 1.70)	(0.80 - 1.90)			

Table 2. Association of Radiographic Congestion Score Index with Discharge Diagnosis of Acute Heart Failure

	Number	AHF, N (%)	univariable			Multivariable 1			Multivariable 2		
			OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
Continuous (per 0.1)	1333	289 (27.7 %)	1.22	1.19 - 1.25	<0.001	1.18	1.15 - 1.22	<0.001	1.19	1.16 - 1.22	<0.001
Quartiles	Q1	376		(reference)			(reference)			(reference)	
	Q2	328	5.98	2.62 - 16.13	<0.001	3.05	1.27 - 8.49	0.03	4.46	1.93 - 12.16	0.001
	Q3	359	22.19	10.41 - 57.55	<0.001	8.32	3.69 - 22.40	<0.001	13.36	6.16 - 35.01	<0.001
	Q4	270	88.33	41.37 - 229.54	<0.001	28.89	12.69 - 78.36	<0.001	43.77	20.11 - 115.07	<0.001

### **5.1.2. Mid-term prognostic impact of residual pulmonary congestion assessed by radiographic scoring in patients admitted for worsening heart failure (2<sup>nd</sup> paper)**

As shown in our first paper, a systematic quantitative assessment of radiographic pulmonary congestion can improve diagnostic accuracy in the emergency department. However, questions remain about the application of this quantitative approach of pulmonary congestion for the risk-stratification of worsening HF, as well as the relative importance of admission to discharge congestion clinical relevance. The aim of the present study is to assess prognostic value of CSI on admission, at discharge and change from admission to discharge in patients hospitalized for worsening HF.

We retrospectively studied patients hospitalized for acutely decompensated HF to assess the prognostic value of radiographic CSI evaluated from on CXR on admission and at discharge. Primary outcome was a composite of death and/or hospitalization for HF.

In a total of 292 patients with acutely decompensated HF (mean age of  $71 \pm 14$  years; 64.4% male; mean LVEF of  $39 \pm 17\%$ ), we showed that higher CSI at discharge (adjusted-HR for 1-point increase = 1.83 [1.02 to 3.27]  $p=0.04$ ) and higher discharge BNP were significantly associated with a higher risk of the composite outcome, whereas neither admission CSI nor conventional clinical congestion variables (i.e., NYHA, leg edema, rales and echocardiography) were significant multivariable predictors of outcome. Furthermore, CSI at discharge, but not BNP, improved significantly reclassification on top of clinical prognostic model (NRI=19.6% [4.0 to 30.0]  $p=0.03$  and IDI=2.2% [0.0 to 7.6]  $p=0.046$ ).

Our results suggested that residual pulmonary congestion on CXR is a prognostic factor independent of clinical congestion markers and improves patient risk-stratification over clinical-based risk model. Furthermore, the improvement of congestion scoring during hospital stay was associated with subsequent prognosis. The use of chest radiography is not recommended in the non-acute setting despite several typical congestion signs exist<sup>50</sup>. However, in our study, 71.9% of patients had residual pulmonary congestion even when clinicians believed that HF was compensated. Our research suggested that radiographic pulmonary congestion is useful as a risk-stratifier at discharge of HF hospitalization and its quantification might be an important factor determining decision-making at the timing of discharge. **This paper was published in the International Journal of Cardiology.**



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## Mid-term prognostic impact of residual pulmonary congestion assessed by radiographic scoring in patients admitted for worsening heart failure

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### ABSTRACT

**Aims:** Pulmonary congestion is associated with poor prognosis following hospitalization for worsening heart failure (HF), although its quantification and optimal timing during HF hospitalization remains challenging. The aim of this study was to assess the prognostic value of radiographic pulmonary congestion at admission and discharge in patients with worsening HF.

**Methods and results:** Clinical, echocardiographic, laboratory and chest X-ray data of 292 acute decompensated HF patients were retrospectively studied (follow-up 1 year). Lung congestion was blindly scored on chest X-ray performed at admission and discharge using a systematic 6-zone approach. Primary clinical outcome was a composite outcome of re-hospitalization for worsening HF or all cause death.

Patients were stratified according to the median of congestion score index (CSI) at both admission (median CSI (A) = 1.33) and discharge (median CSI(D) = 0.33). BNP levels, LVEF and eGFR did not differ between CSI categories. In multivariable Cox regression analysis, discharge CSI (HR for 1-point increase = 1.83 [1.02 to 3.27]  $p = 0.04$ ) and discharge BNP were significantly associated with the composite outcome whereas NYHA class, physical signs, admission CSI and echocardiographic data were not. Furthermore, discharge CSI significantly increased reclassification on top of clinical covariates (continuous NRI = 19.6% [4.0 to 30.0]  $p = 0.03$  and IDI = 2.2% [0.0 to 7.6]  $p = 0.046$ ) while discharge BNP did not significantly improve risk reclassification.

**Conclusions:** Residual pulmonary congestion assessed by radiographic scoring predicts poor prognosis beyond physical assessment, echocardiographic parameters and BNP. These findings further support the capital prognostic value of radiographic pulmonary congestion in patients hospitalized for worsening HF.

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### 1. Introduction

Signs and symptoms of congestion are the most important contributors of heart failure (HF) hospitalization and readmission [1,2] to a significantly greater degree than low cardiac output [3,4]. Thus, decongestive therapy has been a major goal of acute heart failure management during hospitalization [5]. Discharge congestion variables such as brain natriuretic peptide (BNP) [6,7], physical assessments [8] and lung congestion assessed by lung ultrasound (LUS) [9–11] have been shown to be strongly associated with post-discharge morbidity and mortality [12].

Nevertheless, no standardized evaluation of congestion and subsequent tailored therapeutic management are currently recommended by the latest clinical guidelines [5,13]. In addition, there is evidence that clinical signs and symptoms of congestion on admission are associated with adverse outcome following a hospitalization for worsening HF [14,15]. Consequently, it remains unclear whether the interplay between residual congestion and higher values of admission congestion predicts outcome or whether the change in congestion during hospital stay or achieved discharge decongestion per-se are the best predictors of outcome.

Chest X-ray is a fast, simple and classic method to assess pulmonary congestion, with good specificity and moderate sensitivity in diagnosing HF [16,17]. Representative signs of pulmonary congestion, such as cephalization, peribronchial cuffing and Kerley lines, are widely known in clinical practice [18,19]. Assessment of lung congestion by a composite radiological score is useful to predict the development of overt HF during

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hospital stay in patients admitted for myocardial infarction [20] and is associated with outcome in patients with chronic HF [21]. However, there is lack of data regarding prognostic values of radiographic congestion in the setting of patients hospitalized for worsening HF. In the present study, we sought to evaluate the prognostic value of lung congestion assessed by chest X-ray scoring at admission and discharge (including changes from admission to discharge) in patients with worsening HF.

## 2. Methods

### 2.1. Study participants

This retrospective analysis included a total of 292 patients admitted for acute decompensated HF (ADHF) at the Tokyo Medical University from August 2009 to September 2015. ADHF was defined according to clinical and radiographic evidence of congestion [12] by treating cardiologists. Exclusion criteria were: acute coronary syndrome, infective endocarditis, acute pericarditis and myocarditis, cardiac device implantation, percutaneous coronary intervention during hospital stay and planned cardiac surgery. Other non-cardiac exclusion criteria were: pneumonitis, lung cancer/metastases, pneumothorax, post lung surgery, severe chronic obstructive pulmonary disease, severe obesity, transcutaneous pacing on admission, maintenance for hemodialysis, admission creatinine  $\geq 3$  mg/dl or greater and infectious diseases (including C-reactive protein  $\geq 10$  mg/dl or greater). The study was conducted with the approval of the Ethics Guidelines Committee of the Tokyo Medical University.

### 2.2. Measurements

Medical charts of all patients in the present cohort were carefully reviewed and coded within an electronic database. The following information was collected: age, gender, comorbidities, medications (at discharge), laboratory findings, blood pressure, heart rate, physical signs and symptoms (at admission and discharge). In addition, as part of routine care management, all patients underwent standard echocardiography (within 72 h of admission) and chest X-ray (at admission and a few days before discharge when the treating physician perceived patients as regaining a compensated status (2.0 [1.0–4.0] days).

### 2.3. Radiographic congestion scoring

The severity of lung congestion was quantified by a single physician-cardiologist blinded to the clinical data and to the timing of the assessment, namely admission or prior to discharge. Lung congestion was quantified by chest X-ray (antero-posterior view at admission and postero-anterior view prior to discharge) using a previously validated method [21]. To enhance the reproducibility of this scoring with regard to the degree of confluent edema, a part of the divided lung field which visually occupied a density similar to cardiac silhouette was regarded as an intense area whereas the field with weaker density was considered to be a mild area. The grades of congestion in each of the six areas were defined as follows: 0 = normal; 1 = cephalization, perihilar haze, peribronchial cuffing, or Kerley lines (A, B, C); 2 = interstitial pulmonary edema and localized or confluent mild edema; and 3 = confluent intense edema (Fig. 1). These values were summed into a congestion score ranging from 0 to 18. Segments covered with pleural effusion, atelectasis or cardiac silhouette were not scored, and the congestion score index (CSI) was calculated as the congestion score divided by number of available lung segments. In terms of reproducibility of CSI, two experienced clinical physicians (M.K. and M.B.) blinded to each other, to the clinical parameters and to the timing of the chest X-ray, performed a separate complete analysis of 20 randomly selected subjects. CSI demonstrated good test-retest reproducibility (intra-observer agreement was 0.96 (0.91–0.98) and inter-observer agreement was 0.83 (0.62–0.93).

In addition, CSI drop was defined as the change from admission to discharge in CSI:

$$\text{CSI drop} = \text{CSI admission} - \text{CSI prior to discharge}$$

### 2.4. Outcomes

All patients were followed 1 year from discharge. Follow-up data were extracted from medical records in a blinded manner. The primary outcome of this analysis was a composite outcome of re-hospitalization for worsening HF or all-cause mortality whichever occurred first.

### 2.5. Statistical analysis

Continuous variables are reported as mean  $\pm$  standard deviation or median (25th–75th percentiles), as appropriate. Patients with ADHF were divided into four groups according to median CSI at admission [CSI(A)] (1.33) and median CSI prior to discharge [CSI(D)] (0.33), namely 'LowCSI(A)/LowCSI(D)', 'HighCSI(A)/LowCSI(D)', 'LowCSI(A)/HighCSI(D)' and 'HighCSI(A)/HighCSI(D)'. Reduced left ventricular ejection fraction (LVEF) was defined as ejection fraction of  $<40\%$ . Continuous variables and categorical variables were compared using the Kruskal-Wallis test and  $\chi^2$  test respectively.

Interobserver and intraobserver agreements of CSI were assessed with the intraclass correlation coefficient (ICC).

A linear regression model was used to examine the correlations of lung congestion, at both admission and discharge; significant univariable predictors and other variables a priori considered as being relevant (reduced LVEF, estimated glomerular filtration rate (eGFR), total protein, BNP and diuretic therapy at discharge) were entered into multivariable analysis.

Kaplan-Meier analysis was used to estimate survival probabilities. Cox proportional-hazards models were used to obtain unadjusted and covariate adjusted hazard ratios, which were chosen from all variables with  $p < 0.05$  by univariable analysis. The increase in discriminative value to predict a 1-year composite outcome following the additional of discharge variables (CSI and BNP) in survival model on a baseline set of covariates including age, a previous history of HF hospitalization, reduced LVEF, hemoglobin and eGFR at discharge were evaluated using continuous NRI and IDI [22].

Descriptive analyses, associations with CSI and Cox hazard models were performed using SPSS package version 24.0 (SPSS Inc., Chicago, IL, USA). R statistical software (3.1.3) was used for ICC, continuous NRI and IDI (ICC and survIDINRI packages).

## 3. Results

### 3.1. Patient characteristics

The admission and discharge data of the 292 included ADHF patients are reported in Table 1. The majority of patients were male with a mean age of  $71 \pm 14$  years and LVEF of  $39 \pm 17\%$ . Approximately 40% of patients had a history of HF hospitalization, and were in New York Heart Association (NYHA) class IV at admission. Median BNP at admission and discharge was 560 pg/ml (327–1089) and 274 pg/ml (134–499), respectively. Mean CSI dropped significantly between admission and discharge (respectively  $1.49 \pm 0.51$  and  $0.44 \pm 0.40$ ,  $p < 0.001$ ).

Among patients with higher admission CSI (172/292, 59%), two-thirds still had a higher prior to discharge CSI (124/172, 72%). Compared with other groups, patients with HighCSI(A)/HighCSI(D) were more frequently in NYHA class IV and had more congestive HF symptoms (orthopnea and rales) at admission and ankle edema at discharge but similar laboratory findings as well as echocardiographic parameters. Patients with higher admission CSI had a higher dosage of furosemide at discharge regardless of prior to discharge CSI.

### 3.2. Predictors of chest radiographic scoring at admission and prior to discharge

In multivariable analysis, SBP, NYHA class IV and rales were independently associated with higher admission CSI whereas BNP was not (Supplementary table 1).

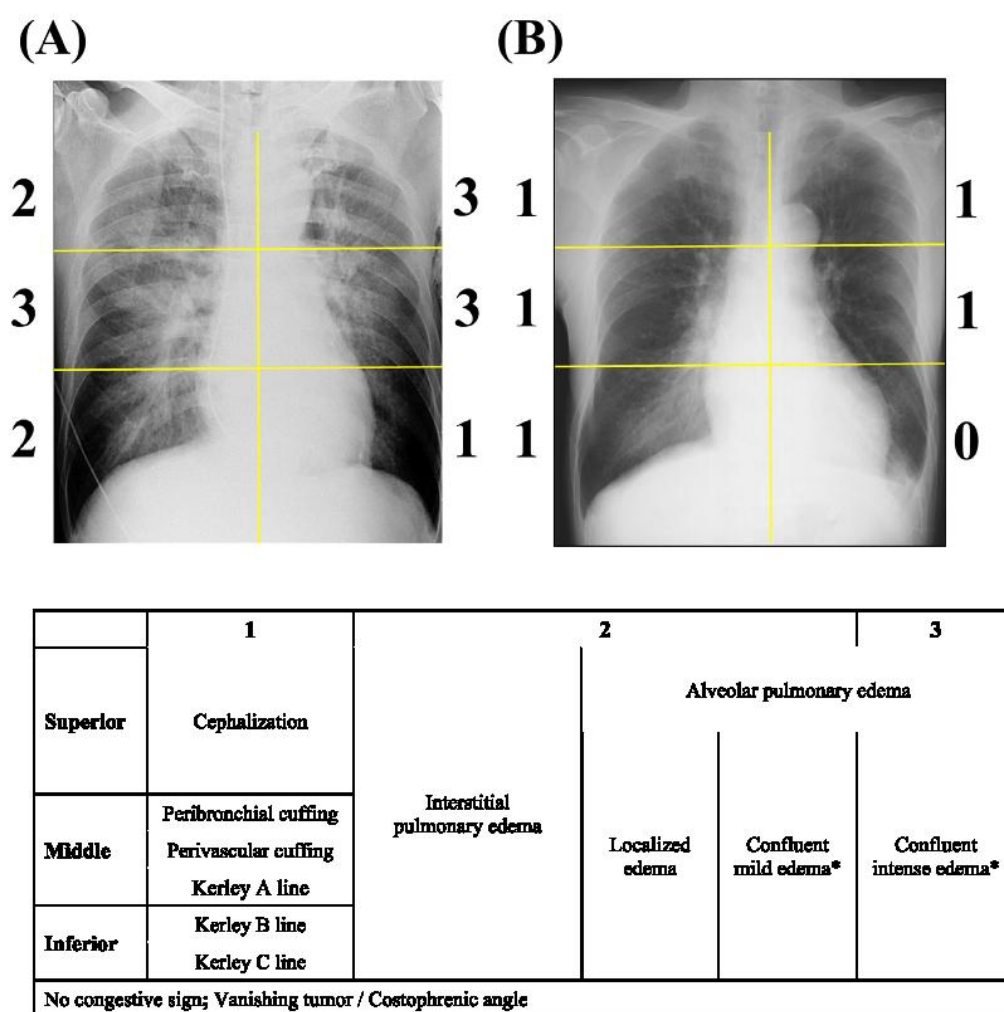
When considering prior to discharge CSI as outcome, the only independent predictor of higher prior to discharge CSI was ankle edema at discharge. When considering variables measured at both admission and discharge, ankle edema at discharge remained the only independent predictor of higher prior to discharge CSI (Supplementary table 1), although the association was weak, with ankle edema being associated with a 0.16 higher prior to discharge CSI ( $\beta = 0.16$ ,  $p = 0.04$ ).

### 3.3. Association between admission and prior to discharge radiological pulmonary congestion and post-discharge outcome

During the first year after discharge, a total of 71 patients experienced one of the components of the composite events (67 HF re-hospitalizations and 7 all-cause deaths). The unadjusted Kaplan-Meier curves showed that the risk of composite outcome was higher in patients with HighCSI (A)/HighCSI(D) (log rank = 10.8,  $p = 0.013$ ) (Fig. 2).

In univariable Cox analysis, unit increase in prior to discharge CSI was significantly associated with a 1.9-fold higher risk of the composite endpoints [HR (95% CI) = 1.85 (1.05–3.28),  $p = 0.03$ ] whereas admission CSI was not significantly associated with outcome. In multivariable analysis using variable selection procedures, prior to discharge CSI was retained as a significant predictor for the composite endpoint [HR for a 1-unit increase in CSI (95% CI) = 1.83 (1.02–3.27),  $p = 0.04$ ], along with discharge BNP [HR for a 100 pg/ml increase in BNP (95% CI) = 1.09 (1.04–1.14),  $p < 0.001$ ] and furosemide dose (Table 2).





**Fig. 1.** Radiographic congestion scoring. The scoring is performed in six lung fields. Examples A and B provide examples of grades 0 to 3. \*With regard to confluent edema, when the density in a part of divided lung field was visually similar to that of cardiac silhouette, the field was regarded as intense edema.

HighCSI(A)/HighCSI(D) was significantly associated with a higher risk for the composite outcomes after adjustment for discharge BNP and furosemide dose [HR (95% CI) = 2.34 (1.09–5.01),  $p = 0.03$ ] compared with LowCSI(A)/LowCSI(D). Importantly, there was no significant interaction between admission and prior to discharge CSI either used as continuous variables ( $p = 0.49$ ) or dichotomous variables ( $p = 0.65$ ), thus suggesting that the predictive value of prior to discharge CSI was not dependent on admission CSI.

#### 3.4. Association between changes in radiological pulmonary congestion during hospital stay and post-discharge outcome

The drop in CSI adjusted for admission CSI was significantly associated with better outcome in crude analysis [HR for a 1-unit drop (95% CI) = 0.55 (0.31–0.97),  $p = 0.04$ ]. When adjusting for furosemide dose, discharge BNP and admission CSI [HR (95% CI) = 1.94 (0.96–3.92),  $p = 0.07$ ], the drop in CSI remained significantly associated with better outcome [HR for a 1-unit drop (95% CI) = 0.55 (0.31–0.99),  $p = 0.048$ ].

#### 3.5. Improvement in reclassification associated with prior to discharge CSI

The increase in discriminative value to predict 1-year composite outcomes following the addition of prior to discharge CSI and BNP in survival models on top of age, previous HF hospitalization, reduced LVEF, hemoglobin and eGFR at discharge, were evaluated using continuous NRI and IDI

(Supplementary figure 1). The addition of high prior to discharge CSI ( $\geq 0.33$ ) significantly improved reclassification [NRI (95% CI) = 19.6 (4.0–30.0),  $p = 0.03$  and IDI (95% CI) = 2.2 (0–7.6),  $p = 0.046$ ], whereas high discharge BNP did not improve the risk classification on the aforementioned clinical covariates (Supplementary figure 1). Furthermore, after including high BNP in the baseline model, high prior to discharge CSI still significantly improved reclassification [NRI (95% CI) = 19.6 (4.1–30.9),  $p = 0.02$  and IDI (95% CI) = 2.2 (0.1–7.0),  $p = 0.04$ ].

## 4. Discussion

The principal findings of the present study are that residual pulmonary congestion (rather than admission pulmonary congestion) as assessed by chest X-ray scoring is a prognostic factor over and above BNP and other clinical markers of congestion, and that the drop in pulmonary congestion is a key predictor of outcome in patients admitted for ADHF. In addition, prior to discharge CSI was associated with a significant reclassification on clinical risk stratification variables (whereas discharge BNP was not in this cohort), thus suggesting a relevant improvement in risk assessment at discharge following ADHF.

#### 4.1. Radiographic congestion scoring

As demonstrated by our team [9,23] and others [10,11], residual pulmonary congestion, assessed by LUS at discharge, is a key prognostic



Table 1

Patient characteristics according to the levels of pulmonary radiologic congestion at admission and discharge.

	Overall ADHF patients (N = 292)	Low CSI (A) Low CSI (D) (N = 57)	Low CSI (A) High CSI (D) (N = 63)	High CSI (A) Low CSI (D) (N = 48)	High CSI (A) High CSI (D) (N = 124)	p-Value
Age, years	71.1 ± 13.6	69.1 ± 13.5	71.5 ± 13.5	70.3 ± 12.6	72.1 ± 14.2	0.37
Male, n (%)	188 (64.4%)	38 (66.7%)	44 (69.8%)	31 (64.6%)	75 (60.5%)	0.62
Body weight, kg	61.0 ± 15.9	60.2 ± 12.9	63.4 ± 13.5	58.1 ± 18.7	61.2 ± 17.1	0.12
Clinic characteristics, n (%)						
Previous HF hospitalization	123 (42.1%)	21 (36.8%)	25 (39.7%)	19 (39.6%)	58 (46.8%)	0.57
Coronary artery disease	62 (21.2%)	6 (10.5%)	11 (17.5%)	10 (20.8%)	35 (28.2%)	<b>0.045</b>
Atrial fibrillation	143 (49.0%)	24 (42.1%)	38 (60.3%)	29 (60.4%)	52 (41.9%)	<b>0.03</b>
Hypertension	210 (71.9%)	36 (63.2%)	42 (66.7%)	32 (66.7%)	100 (80.6%)	<b>0.04</b>
Diabetes mellitus	100 (34.2%)	14 (24.6%)	22 (34.9%)	14 (29.2%)	50 (40.3%)	0.17
Physical examinations at admission						
NYHA IV, n (%)	118 (40.4%)	10 (17.5%)	21 (33.3%)	27 (56.2%)	60 (48.4%)	<b>&lt;0.001</b>
Orthopnea, n (%)	105 (36.1%)	10 (17.5%)	13 (20.6%)	26 (54.2%)	56 (45.2%)	<b>&lt;0.001</b>
Rales, n (%)	154 (52.7%)	20 (35.1%)	29 (46.0%)	31 (64.6%)	74 (59.7%)	<b>0.004</b>
Ill sound, n (%)	151 (51.7%)	24 (42.1%)	30 (47.6%)	31 (64.6%)	66 (53.2%)	0.12
Ankle edema, n (%)	190 (65.1%)	37 (64.9%)	41 (65.1%)	30 (62.5%)	82 (66.1%)	0.98
Systolic blood pressure, mm Hg	141.9 ± 32.4	129.5 ± 23.3	130.0 ± 34.2	144.6 ± 36.1	152.6 ± 29.8	<b>&lt;0.001</b>
Heart rate, bpm	96.3 ± 27.2	92.9 ± 26.2	92.9 ± 27.3	99.6 ± 23.3	98.3 ± 28.9	0.30
Laboratory findings at admission						
WBC, 10 <sup>3</sup> /μl	7.2 ± 2.9	6.6 ± 2.2	7.2 ± 3.9	7.7 ± 3.4	7.3 ± 2.4	0.15
Lymphocyte, %	22.2 ± 10.7	23. ± 9.8	21.0 ± 8.6	25.0 ± 12.4	20.9 ± 11.2	0.07
Hemoglobin, g/dl	12.6 ± 2.5	13.0 ± 2.4	12.8 ± 2.6	13.0 ± 2.3	12.2 ± 2.5	
C-reactive peptide, mg/dl	1.0 ± 1.1	0.8 ± 1.0	1.0 ± 1.0	1.2 ± 1.2	1.1 ± 1.2	<b>0.01</b>
Total-bilirubin, mg/dl	1.2 ± 0.8	1.1 ± 0.6	1.4 ± 1.1	1.1 ± 0.6	1.1 ± 0.7	0.47
Serum sodium, mEq/l	141.2 ± 3.7	141.4 ± 3.5	140.9 ± 3.2	141.0 ± 4.6	141.3 ± 3.7	0.61
Blood urea nitrogen, mg/dl	23.6 ± 12.4	22.5 ± 9.9	24.2 ± 13.6	22.0 ± 10.2	24.4 ± 13.5	0.72
eGFR, ml/min/1.73 m <sup>2</sup>	55.1 ± 23.0	56.2 ± 18.5	57.0 ± 25.0	56.3 ± 20.1	53.3 ± 24.9	0.36
BNP, pg/ml	560 (327–1089)	593 (332–997)	574 (254–1160)	524 (320–1100)	555 (365–1112)	0.80
Physical examinations at discharge						
Rales, n (%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	0.72
Ankle edema, n (%)	33 (11.3%)	5 (8.8%)	13 (20.6%)	2 (4.2%)	13 (10.5%)	<b>0.04</b>
Systolic blood pressure, mm Hg	112.9 ± 18.5	109.6 ± 18.6	110.5 ± 18.6	117.3 ± 20.7	113.9 ± 17.2	0.11
Heart rate, bpm	68.3 ± 12.2	66.2 ± 12.6	70.5 ± 12.9	66.8 ± 10.0	68.8 ± 12.3	0.15
Laboratory findings at discharge						
Hemoglobin, g/dl	12.9 ± 2.5	13.4 ± 2.4	13.1 ± 2.5	13.1 ± 2.3	12.4 ± 2.5	0.08
Serum sodium, mEq/l	139.8 ± 3.1	140.3 ± 2.6	140.2 ± 3.1	140.0 ± 2.8	139.3 ± 3.5	0.14
Blood urea nitrogen, mg/dl	24.9 ± 14.4	22.6 ± 10.7	23.1 ± 14.1	23.8 ± 13.7	27.3 ± 16.1	0.07
eGFR, ml/min/1.73 m <sup>2</sup>	53.2 ± 21.8	53.6 ± 18.6	56.8 ± 21.2	52.7 ± 18.3	51.4 ± 24.5	0.26
BNP, pg/ml	274 (134–499)	239 (158–437)	280 (90–601)	284 (146–453)	288 (140–470)	0.83
Echocardiography at admission (within 72 h)						
LVDD, mm	56.0 ± 9.5	57.6 ± 8.1	54.1 ± 10.1	57.1 ± 10.1	55.8 ± 9.5	0.15
LVEF, %	39.4 ± 17.4	36.2 ± 17.4	43.7 ± 18.7	37.4 ± 16.0	39.5 ± 17.0	0.12
LVEF < 40%, n	163 (55.8%)	41 (71.9%)	28 (44.4%)	26 (54.2%)	68 (54.8%)	<b>0.03</b>
MR (≥ moderate), n (%)	162 (56.4%)	33 (58.9%)	33 (52.4%)	23 (48.9%)	73 (60.3%)	0.50
PASP, mm Hg	40.9 ± 17.8	41.2 ± 15.6	42.9 ± 17.4	35.5 ± 16.7	41.9 ± 19.1	0.19
IVC diameter, mm	18.3 ± 5.2	19.0 ± 4.9	18.2 ± 5.4	17.4 ± 5.2	18.5 ± 5.1	0.52
Congestion score index						
CSI admission	1.5 ± 0.5	1.0 ± 0.2	1.1 ± 0.1	1.9 ± 0.5	1.8 ± 0.4	<b>&lt;0.001</b>
CSI prior to discharge	0.4 ± 0.4	0.0 ± 0.1	0.7 ± 0.3	0.1 ± 0.1	0.7 ± 0.3	<b>&lt;0.001</b>
CSI drop	1.0 ± 0.6	1.0 ± 0.2	0.4 ± 0.3	1.8 ± 0.5	1.1 ± 0.5	<b>&lt;0.001</b>
Pleural effusion, n (%)						
PE admission	168 (57.5%)	31 (54.4%)	37 (58.7%)	30 (62.5%)	70 (56.5%)	0.78
PE admission (bilateral)	109 (37.3%)	17 (29.8%)	26 (41.3%)	17 (35.4%)	49 (39.5%)	0.55
PE discharge	51 (17.5%)	7 (12.3%)	12 (19.0%)	7 (14.6%)	25 (20.2%)	0.56
PE discharge (bilateral)	21 (7.2%)	1 (1.8%)	4 (6.3%)	3 (6.3%)	13 (10.5%)	0.20
Medications at discharge						
ACE-I/ARB, n (%)	228 (78.1%)	48 (84.2%)	41 (65.1%)	40 (83.3%)	99 (79.8%)	<b>0.04</b>
Beta-blockers, n (%)	245 (83.9%)	51 (89.5%)	50 (79.4%)	43 (89.6%)	101 (81.5%)	0.26
Aldosterone antagonist, n (%)	228 (78.1%)	48 (84.2%)	49 (77.8%)	37 (77.1%)	94 (75.8%)	0.65
Diuretics, n (%)	234 (80.1%)	42 (73.7%)	46 (73.0%)	39 (81.2%)	107 (86.3%)	0.09
Furosemide, mg/day	20.0 (0.0–20.0)	10.0 (0.0–20.0)	20.0 (0.0–20.0)	20.0 (2.5–20.0)	20.0 (10.0–40.0)	<b>0.04</b>
Digitalis, n (%)	47 (16.1%)	8 (14.0%)	13 (20.6%)	9 (18.8%)	17 (13.7%)	0.59

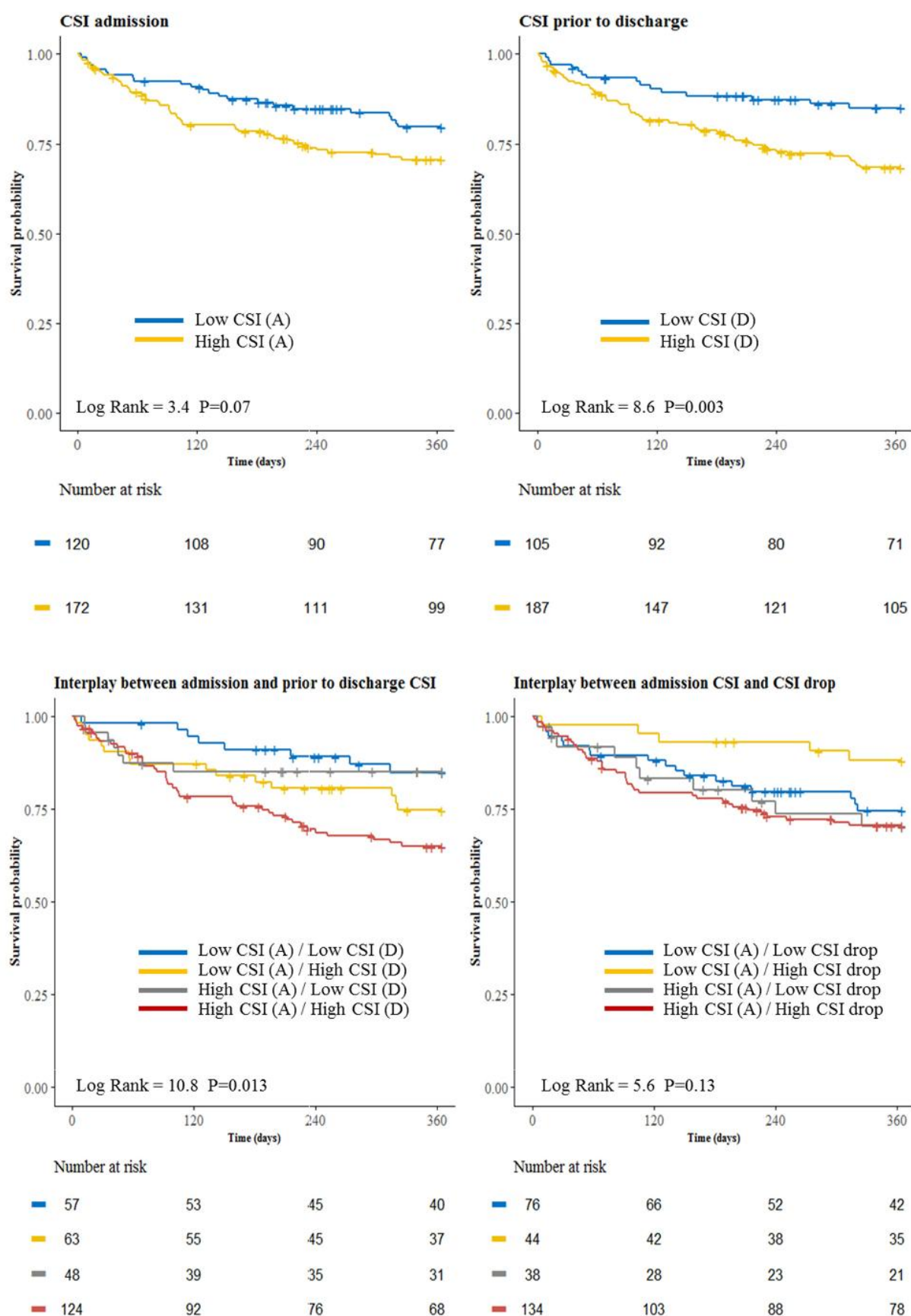
Values are mean ± SD for all continuous variables, except BNP and furosemide (interquartile range); values for categorical variables are expressed as number of cases (%). Bold values statistically significance at P-value < 0.05.

ADHF, acute decompensated heart failure; CSI, congestion score index; HF, heart failure; NYHA, New York Heart Association; WBC, white blood cells; eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide; LVDD, left ventricular diastolic diameter; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; PASP, pulmonary artery systolic pressure; IVC, inferior vena cava; PE, pleural effusion; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

marker in patients hospitalized for worsening HF [9,10,24]. Specifically, we previously demonstrated that pulmonary congestion assessed by LUS was more strongly associated with outcome than echocardiographic, clinical and laboratory (namely BNP) measurements of congestion. While there is increasing evidence for the value of LUS, the

utilization of this novel tool is dependent on portable ultrasound device availability and operator expertise [25,26].

Chest X-ray is usually considered to be poorly sensitive for excluding pulmonary congestion despite being a useful tool in clinical practice [12,16,17,27]. There are large differences in pulmonary congestion



**Fig. 2.** Survival curves for the composite of all-cause death and heart failure re-hospitalization according to admission CSI, discharge CSI and the interplay among admission CSI, discharge CSI and CSI drop. Congestion score index was dichotomized using median values of 1.33 (admission), 0.33 (prior to discharge) and 1.0 (drop from admission and discharge), respectively. CSI; congestion score index.



Table 2

Univariable and multivariable Cox model analysis for the composite of heart failure re-hospitalization or all cause death.

	Univariable			Multivariable model with continuous CSI			Multivariable model with admission and discharge CSI interplay categories			Multivariable model with continuous drop CSI		
	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
Continuous CSI variables												
CSI admission	1.16	0.75–1.79	0.51	/	/	/	/	/	/	1.94	0.96–3.92	0.07
CSI prior to discharge	1.85	1.05–3.28	<b>0.03</b>	1.83	1.02–3.27	<b>0.04</b>	/	/	/	/	/	/
CSI drop	0.85	0.57–1.26	0.42	/	/	/	/	/	/	0.55	0.31–0.99	<b>0.048</b>
Categorical CSI variables												
Low CSI (A)/Low CSI (D)	/	(Reference)	/	/	/	/	/	(Reference)	/	/	/	/
Low CSI (A)/High CSI (D)	1.85	0.78–4.35	0.16	/	/	/	1.59	0.67–3.80	0.30	/	/	/
High CSI (A)/Low CSI (D)	1.13	0.41–3.11	0.82	/	/	/	0.85	0.30–2.38	0.75	/	/	/
High CSI (A)/High CSI (D)	2.73	1.28–5.83	<b>0.01</b>	/	/	/	2.34	1.09–5.01	<b>0.03</b>	/	/	/
Adjustment variables												
Hypertension	1.41	0.81–2.46	0.23	/	/	/	/	/	/	/	/	/
SBP admission, mm Hg (per 10 mm Hg)	1.00	0.93–1.08	0.97	/	/	/	/	/	/	/	/	/
NYHA IV admission	1.20	0.75–1.91	0.46	/	/	/	/	/	/	/	/	/
Orthopnea admission	0.95	0.58–1.56	0.84	/	/	/	/	/	/	/	/	/
Rale admission	1.08	0.68–1.72	0.76	/	/	/	/	/	/	/	/	/
Ankle edema discharge	1.26	0.65–2.46	0.50	/	/	/	/	/	/	/	/	/
Sodium discharge, mEq/l	0.97	0.90–1.05	0.43	/	/	/	/	/	/	/	/	/
Baseline IVC, mm	1.00	0.96–1.05	0.91	/	/	/	/	/	/	/	/	/
Baseline PASP, mm Hg (per 10 mm Hg)	1.04	0.91–1.19	0.57	/	/	/	/	/	/	/	/	/
BNP admission, pg/ml (per 100 pg/ml)	1.01	0.99–1.04	0.30	/	/	/	/	/	/	/	/	/
BNP discharge, pg/ml (per 100 pg/ml)	1.10	1.05–1.15	<b>&lt;0.001</b>	1.09	1.04–1.14	<b>&lt;0.001</b>	1.10	1.05–1.15	<b>&lt;0.001</b>	1.09	1.04–1.14	<b>&lt;0.001</b>
Furosemide, mg/day (per 10 mg)	1.02	1.01–1.03	<b>&lt;0.001</b>	1.18	1.08–1.29	<b>&lt;0.001</b>	1.17	1.07–1.29	<b>0.001</b>	1.17	1.07–1.29	<b>&lt;0.001</b>

CSI, congestion score index; HR, hazard ratio; CI, confidence interval; SBP, systolic blood pressure; NYHA, New York Heart Association; IVC, inferior vena cava; PASP, pulmonary artery systolic pressure; BNP, brain natriuretic peptide. Bold values statistically significance at P-value < 0.05.

prevalence reported among trials [28–30], likely due to the inconsistent definition of X-ray-based pulmonary congestion and large inter-observer variability. A simple and standardized evaluation of congestion on chest X-ray (such as performed herein) could overcome this limitation and increase its diagnostic and prognostic value. Ware et al. reported that systematic radiographic congestion scoring was closely correlated with actual lung weights in 84 brain dead organ donors [31], which strongly supports the value of X-ray scoring in quantifying extravascular lung water. In addition, Melenovsky et al. reported that CSI was significantly associated with clinical outcome independently of pulmonary artery wedge pressure and natriuretic peptides in patients with chronic HF [21]. In this study, we demonstrated that radiographic pulmonary congestion using CSI was also a strong predictor of clinical outcome in patients with worsening HF, more so than other clinical and biological markers of congestion (including natriuretic peptides). Taken together, these data suggest a strong prognostic value of pulmonary congestion as assessed by a simple standardized chest X-ray scoring. In addition, higher prior to discharge CSI was found to improve reclassification on traditional clinical covariates (e.g. age, previous history of HF hospitalization, systolic function and renal function) whereas BNP did not increase discrimination. These findings further strengthen the prognostic value of congestion scoring using CSI in patients with worsening HF.

#### 4.2. Congestion trajectories and clinical outcome

Most previous studies have focused on congestion assessment at either admission [14,32,33] or discharge [8,9,34] but only few have focused on the change from admission to discharge [35,36]. It is essential to determine the optimal period for predicting long-term outcomes, in order to guide the most clinically useful congestion assessment strategy. With regard to LUS, our group recently demonstrated that different cut-offs at admission and discharge (B-lines  $\geq 45$  and B-lines  $\geq 30$ , respectively) were able to predict short-term adverse prognosis although both timings had good prognostic ability. In contrast, Kociol et al. who reported that discharge BNP was the most important predictor of post-discharge outcome at 1 year compared with BNP evaluated at other timings (including admission BNP and change from admission to discharge BNP) [35].

However, in addition to prognostic value at discharge, we identified that change in CSI from admission to discharge was strongly associated with better outcome when adjusting for baseline CSI (HR for 10% decrease), which is in keeping with the neutral prognosis of patients with HighCSI (A)/LowCSI(D); HR (95% CI) = 0.85 (0.30–2.38)  $p = 0.75$ ). Importantly, it is likely that admission congestion variables are associated with worse mid-term outcome solely because a higher level of admission congestion increases the risk of residual congestion (due to the fact that a higher change in congestion status is needed to achieve decongestion). More importantly, our results provide evidence that pulmonary congestion using CSI could represent a valuable actionable target in clinical routine. Eventually, clinical trials should evaluate whether this standardized assessment of pulmonary congestion could help optimizing decongestive therapy and identifying the most appropriate timing of discharge.

#### 4.3. Limitations

This retrospective single-center cohort study has several limitations. First, the moderate size of our study cohort limits the statistical power of our analysis. In addition, the proportion of NYHA IV was rather low at admission and our results may consequently not apply to the sickest population of ADHF patients. In addition, different approaches in performing the chest X-ray exam (i.e. antero-posterior view at admission and postero-anterior view at discharge) could have impacted the results: antero-posterior chest radiograms may detect the extent of congestion with a lower sensitivity.) Additionally, discharge chest X-rays were not necessarily performed at discharge but on the day when patients were considered to have reached a compensated status by the treating cardiologists, which might not be reproducible across physicians and countries. Patients with coronary artery disease or pneumonia were excluded in the present study in order to better assess the predictive value of congestion; this methodological point could limit the generalizability of our results. Certain important variables (e.g., jugular vein distention, abdominal-jugular reflux and intravenous diuretic administration) were not available and consequently could not be adjusted for. All patients with ADHF underwent echocardiography within 72 h of admission, which may partly explain the absence of strong association of echocardiographic parameters with admission CSI. In addition, we did



not have information regarding discharge echocardiography, which was not performed in most patients. As a result, we cannot assess the added value of CSI on top of discharge echocardiographic data in patients with ADHF.

## 5. Conclusions

In worsening HF patients, radiographic pulmonary congestion assessed by CSI was the best predictor of post-discharge outcome. This result should promote performing congestion assessment during the latter portion of the hospital stay for worsening HF, and possibly targeting decongestion based on clinical, laboratory and imaging parameters, such as echocardiographic (LUS) or radiological parameters (CSI).

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## Conflict of interests

F.Z. has received consulting fees from Actelion, Amgen, AstraZeneca, Bayer, Boehringer, Boston Science, CEVA, CVRx, Vifor-Fresenius, GE Healthcare, J&J, KBP BioSciences, Livanova, Novartis, NovoNordisk, Pfizer, Quantum Genomics, Relypsa, Resmed, Roche, Takeda and ZS pharma. P.R. has received fees from Honoraria, research grants and/or travel grants from AstraZeneca, Bayer, BG Medicine, BMS, CVRx, Daichii-Sankyo, Fresenius, Gambro, HAC-Pharma, Novartis, Relypsa, Roche, Sanofi, Servier, Stealth Peptides, CTMA and Vifor Fresenius Medical Care Renal Pharma. PR and FZ are CardioRenal cofounders. N.G. has received Board and consulting Fees (Honoraria) for Novartis and consulting fees (Honoraria) for Servier. MW has received consulting fees from Medtronic and Philips and YI has received consulting fees from Medtronic.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcard.2019.01.091>.

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## 5.2. Estimated plasma volume status

### 5.2.1. Association of Estimated Plasma Volume Status with Hemodynamic and Echocardiographic Parameters (3<sup>rd</sup> paper)

Patients with HF often expand PV, which eventually contributes to the development of clinical congestion. Accumulating evidence shows that PV may be estimated from routine clinical parameters (i.e., hemoglobin and body mass index). Although the estimates of PV were validated with PV measured using radioisotope assay, clinical implications of ePVS remains unclear. In addition, this association may be influenced by sex given underlying differences in hematopoiesis<sup>151</sup> and myocardial structure and/or function<sup>152, 153</sup>.

We studied patients with significant dyspnea (NYHA II) who underwent echocardiography and LUS within four hours prior to cardiac catheterization in the Rennes cohort study to explore the association of Duarte-derived ePVS with clinical, biological, echocardiographic and hemodynamic parameters.

Among a total of 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 higher Duarte-derived ePVS had more frequent HF, higher NT-proBNP, E/e', larger LAV index and lower RV isovolumic acceleration.

By multivariable analysis, higher E/e' and lower diastolic BP 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). In contrast, Hakim-derived ePVS was not associated with echocardiographic, biologic and invasive congestion markers.

Our results suggested that Duarte-derived ePVS rather than Hakim-derived ePVS may be an easily accessible surrogate of left-sided hemodynamic congestion. Further research may be needed to explore clinical utilities of ePVS in guiding congestion in patients with HF.





# Association of estimated plasma volume status with hemodynamic and echocardiographic parameters

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## 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 4 h 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;  $p_{interaction}=0.08$ ).

**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.

**Electronic supplementary material** The online version of this article (<https://doi.org/10.1007/s00392-020-01599-9>) contains supplementary material, which is available to authorized users.

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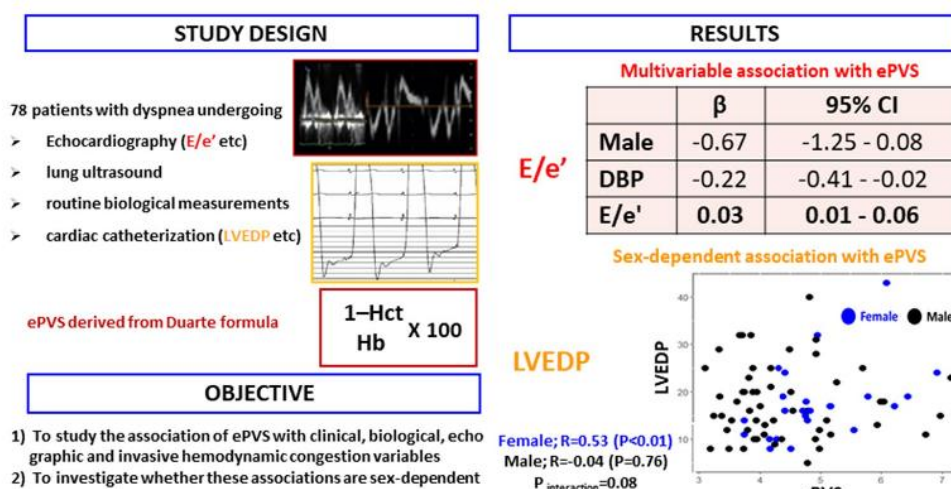
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## Graphical abstract



**Keywords** Plasma volume · Congestion · Left-ventricular filling pressure · Sex difference

## Introduction

Plasma volume is a marker of volume overload, and is linked to the regulation between interstitial and intravascular spaces [1, 2]. 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) [3–6]. Previous reports showed only a moderate association between ePVS using various equations and radiotracer-based quantitative plasma volume measurements [4, 7, 8]. 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,  $p < 0.01$ ) [9]. There are only sparse data, however, regarding the association of ePVS with clinical, biological, and echocardiographic congestion as well as with invasive hemodynamic parameters [5, 6, 10–12]. 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 [13], and myocardial structure and function [14, 15]. 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 (NYHA  $\geq$  II) who underwent a coronary angiography with left heart catheterization (LHC) between May 2016 and July 2017 [16]. 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 [17]. Estimated glomerular filtration rate (eGFR) was calculated by the Chronic Kidney Disease Epidemiology Collaboration formula [18]. 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 [19]. 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 [19]. Pulmonary arterial systolic pressure was estimated using tricuspid velocity and inferior vena cava compliance and diameter [19]. Right-ventricular (RV) function was assessed according to recent guidelines [19].

### Hemodynamic data and lung ultrasonography

LHC was performed within 4 h 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 five 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 four consecutive heart cycles.

Lung ultrasound was performed immediately before echocardiography with patients in supine or near-to-supine position, as previously described [20]. 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 (eight-zone method). An excellent reproducibility of measurements, performed by experienced cardiologists, has previously been reported in this population [16].

### Estimated plasma volume status

ePVS was calculated from the Strauss-derived Duarte formula using hematocrit and hemoglobin values [3] as follows:

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

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

Actual plasma volume

$$= (1 - \text{hematocrit}) \times (a + b \times \text{body weight in kg}).$$

Ideal plasma volume =  $c \times \text{body weight in kg}$ .

(males :  $a = 1530, b = 41.0, c = 39$ ;

females;  $a = 864, b = 47.9, c = 40$ ).

$$\text{ePVS} = [(\text{actual plasma volume} - \text{ideal plasma volume}) / \text{ideal plasma volume}] \times 100.$$

### 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-square 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  $\geq 30$  kg/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



**Table 1** Patient characteristics according to sex-specific tertiles of estimated plasma volume status

	Global ( <i>N</i> = 78)	Low <i>M</i> , < 3.8 mL/g; <i>F</i> , < 4.4 mL/g ( <i>N</i> = 26)	Intermediate <i>M</i> , 3.8–4.5 mL/g; <i>F</i> , 4.4–5.0 mL/g ( <i>N</i> = 26)	High <i>M</i> , > 4.5 mL/g; <i>F</i> , > 5.0 mL/g ( <i>N</i> = 26)	<i>p</i> value vs. 3	<i>p</i> value 1 vs. 3	<i>p</i> value 2 vs. 3
Age, years	74.5 (67.0 to 80.0)	73.5 (64.0 to 78.0)	71.5 (67.0 to 78.0)	77.5 (70.0 to 82.0)	0.15	0.11	0.08
Males, <i>N</i> (%)	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 to 29.5)	27.9 (24.7 to 32.6)	25.9 (23.3 to 28.9)	23.6 (20.7 to 26.7)	< <b>0.01</b>	< <b>0.01</b>	0.12
Medical history, <i>N</i> (%)							
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, <i>N</i> (%)							
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, <i>N</i> (%)	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 to 148.0)	139.0 (130.0 to 144.0)	133.0 (119.0 to 148.0)	130.0 (110.0 to 147.0)	0.48	0.27	0.64
Diastolic BP, mmHg	72.5 (65.0 to 84.0)	76.0 (68.0 to 90.0)	75.0 (67.0 to 81.0)	67.0 (65.0 to 80.0)	0.17	0.06	0.20
Heart rate, bpm	70.5 (61.0 to 83.0)	70.0 (61.0 to 86.0)	76.5 (59.0 to 83.0)	67.0 (62.0 to 75.0)	0.69	0.82	0.35
Laboratory measurements							
Hemoglobin, g/dl	13.6 (12.5 to 14.7)	15.0 (14.3 to 15.4)	13.9 (13.3 to 14.3)	11.9 (10.9 to 12.5)	< <b>0.01</b>	< <b>0.01</b>	< <b>0.01</b>
Sodium, mmol/l	140.0 (137.0 to 141.0)	140.0 (138.0 to 141.0)	140.0 (138.0 to 142.0)	138.0 (137.0 to 141.0)	0.22	0.18	0.12
eGFR, ml/min/1.73m <sup>2</sup>	70.0 (53.0 to 85.0)	67.1 (57.2 to 88.0)	75.3 (48.0 to 85.0)	71.0 (49.0 to 81.0)	0.66	0.44	0.53
NT-proBNP, pg/ml	1025 (283 to 2384)	668 (112 to 2168)	576 (172 to 1472)	2327 (1025 to 5752)	<b>0.03</b>	<b>0.04</b>	<b>0.01</b>
ePVS, mL/g	4.4 (3.8 to 5.0)	3.7 (3.5 to 3.8)	4.2 (4.0 to 4.5)	5.4 (5.0 to 6.1)	< <b>0.01</b>	< <b>0.01</b>	< <b>0.01</b>
LV function							
LVS index, ml/m <sup>2</sup>	31.4 (19.3 to 50.6)	29.6 (18.3 to 42.7)	34.8 (23.2 to 59.1)	42.7 (20.9 to 69.2)	0.18	0.08	0.99
LAV index, ml/m <sup>2</sup>	47.7 (33.4 to 62.3)	47.3 (31.8 to 58.9)	41.9 (33.3 to 52.3)	55.4 (44.4 to 65.5)	<b>0.046</b>	0.06	<b>0.02</b>
LVEF, %	52.0 (33.0 to 62.0)	54.0 (43.0 to 63.0)	50.5 (31.0 to 58.0)	50.4 (31.0 to 62.0)	0.25	0.25	0.76

Table 1 (continued)

	Global (N=78)	Low <i>M</i> , <3.8 mL/g; <i>F</i> , <4.4 mL/g (N=26)	Intermediate <i>M</i> , 3.8–4.5 mL/g; <i>F</i> , 4.4–5.0 mL/g (N=26)	High <i>M</i> , >4.5 mL/g; <i>F</i> , >5.0 mL/g (N=26)	<i>p</i> value vs. 3	<i>p</i> value 1 vs. 3	<i>p</i> value 2 vs. 3
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 to −8.6)	−15.2 (−19.0 to −10.0)	−13.2 (−19.4 to −8.6)	−10.2 (−16.9 to −7.4)	0.24	0.08	0.40
E/A ratio (N=61)	0.9 (0.7 to 1.6)	0.9 (0.6 to 1.6)	0.9 (0.7 to 1.5)	1.1 (0.7 to 1.8)	0.58	0.49	0.90
<i>e'</i> mean, cm/s	6.5 (4.5 to 8.5)	6.8 (5.5 to 10.0)	6.5 (5.0 to 9.0)	6.0 (3.5 to 7.0)	0.11	<b>0.04</b>	0.14
<i>E/e'</i> mean	12.5 (9.3 to 18.3)	10.9 (8.5 to 15.0)	11.7 (8.6 to 15.6)	16.3 (11.6 to 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 to 34.4)	29.4 (19.4 to 44.8)	22.8 (19.5 to 28.8)	26.3 (19.5 to 34.4)	0.27	0.29	0.52
TAPSE, mm	22.8 (18.0 to 25.3)	23.0 (19.0 to 26.0)	24.0 (20.0 to 30.0)	20.5 (18.0 to 24.0)	0.12	0.16	<b>0.047</b>
RV IVA, m/sec	1.4 (0.9 to 2.1)	1.3 (0.9 to 1.6)	1.9 (1.4 to 2.3)	1.1 (0.8 to 1.9)	<b>0.03</b>	0.71	<b>0.03</b>
IVC dimension, mm	13.0 (8.0 to 16.7)	13.0 (6.0 to 16.0)	12.0 (7.5 to 16.0)	13.5 (10.0 to 20.5)	0.29	0.20	0.15
Estimated PAPS, mmHg	34.0 (26.0 to 45.0)	34.0 (26.0 to 38.0)	30.0 (25.0 to 42.0)	35.0 (26.0 to 50.0)	0.38	0.21	0.28
Other parameters							
LVEDP, mmHg	16.0 (12.0 to 22.0)	15.5 (11.0 to 20.0)	16.0 (13.0 to 21.0)	17.0 (12.0 to 23.0)	0.77	0.52	0.79
LV-PreA, mmHg (N=61)	10.0 (7.0 to 16.0)	10.0 (5.0 to 12.0)	10.0 (6.5 to 16.0)	12.0 (8.0 to 16.0)	0.33	0.15	0.54
Total B lines	3.0 (0.0 to 12.0)	2.5 (0.0 to 12.0)	1.0 (0.0 to 9.0)	4.0 (0.0 to 19.0)	0.52	0.46	0.29

*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, *LVS* 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

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

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

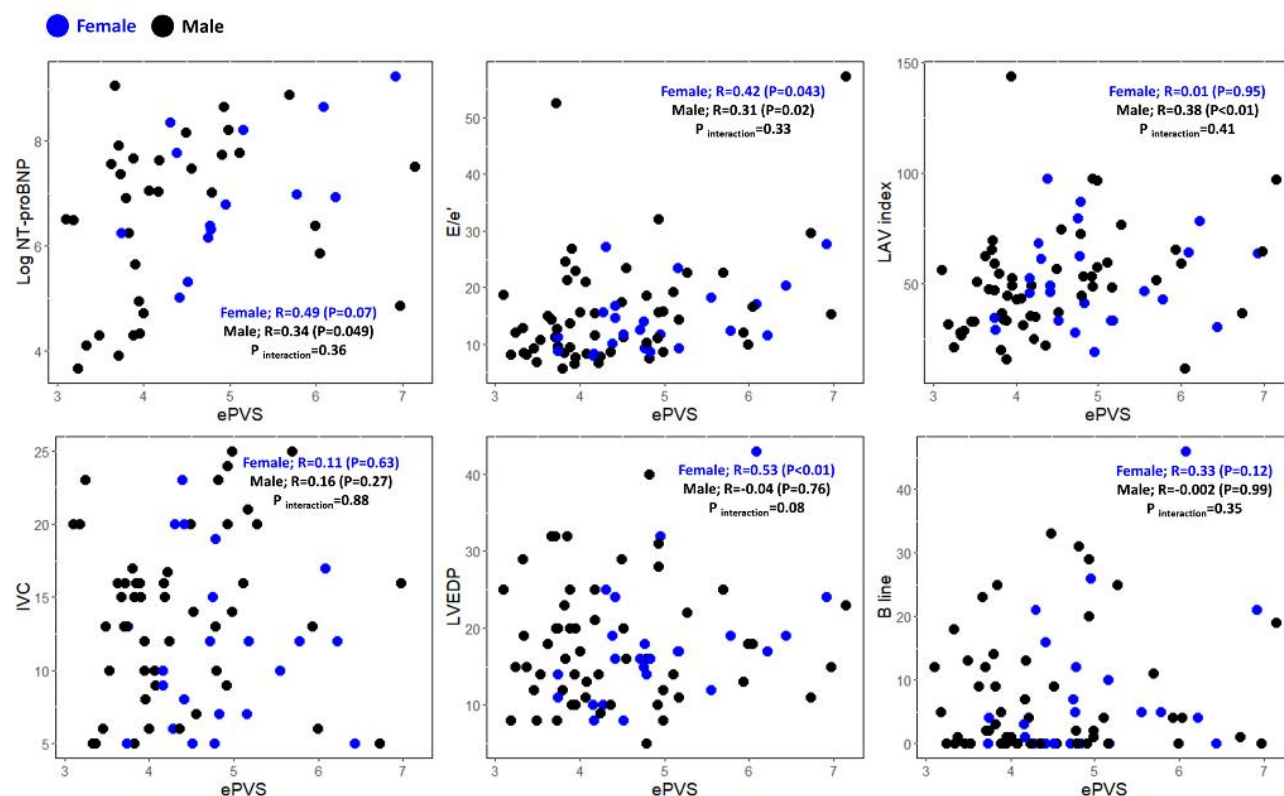
NYHA New York Heart Association, BP diastolic blood pressure, eGFR estimated glomerular filtration rate, NT-proBNP N-terminal prohormone brain natriuretic peptide, LVS left-ventricular stroke volume, LAV left atrial volume, E/A ratio of peak early and late diastolic velocities, E/e' ratio of early mitral 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

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;  $p_{\text{interaction}} = 0.08$ ) (Fig. 1). Of note, LVEDP was not associated with higher ePVS in either univariable or multivariable analysis (Table 2).



**Fig. 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

### 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

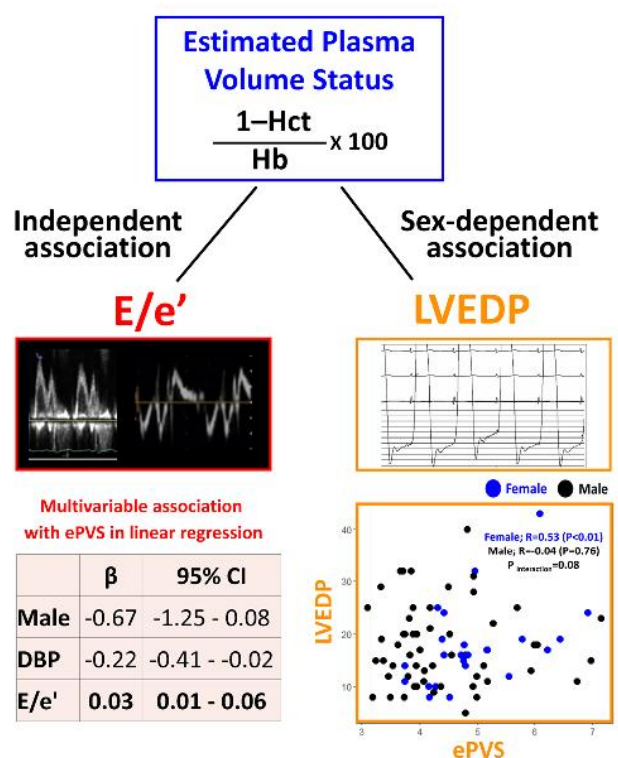
The current study is the first to assess the association of ePVS with clinical, biological, echocardiographic, and invasive hemodynamic congestion markers. Our main findings are that: (1) higher ePVS derived from the Duarte formula

was significantly associated with higher *E/e'* in multivariable analysis; (2) LVEDP was correlated with ePVS using the Duarte formula in females, while was 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 [16, 22]. In contrast, a recent meta-analysis emphasized the lack of diagnostic value of *E/e'* ratio in predicting LV filling pressure [23]. This being said, *E/e'* is, nevertheless, a recognized





**Fig. 2** Central illustration. Association between congestion markers and estimated plasma volume status

congestion marker shown to be associated with clinical outcome in population-based or HF cohorts [24–26]. 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 [27, 28]. This result is also in keeping with previous reports in patients with HF and reduced or preserved LVEF [3, 4, 29, 30]. 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 [19].

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 [31]. 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 [1]. 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 [14, 32]. 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 [33, 34]. 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 dependence [35–37], 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 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 [38, 39]. 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 (Fig. 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 [28]. 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 micro-manometer-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.

Finally, 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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## Compliance with ethical standards

**Conflict of interest** N.G. reports honoraria from Novartis and Boehringer. P.R. reports grants and personal fees from AstraZeneca, grants and personal fees from Bayer, grants and personal fees from

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### 5.2.2. Prognostic value of estimated plasma volume in acute heart failure in three cohort studies (4<sup>th</sup> paper)

Duarte-derived ePVS is associated with left-sided congestion markers (i.e., E/e' and natriuretic peptide)<sup>154</sup> and outcomes in patients with stable CHF and HF following acute myocardial infarction<sup>81</sup>. However, little information is available regarding the prognostic value of Duarte-derived ePVS in patients hospitalized for worsening HF. We hypothesized that this congestion marker might provide additional patient risk-stratification in such decompensated HF patients.

Three independent cohort studies involving patients with ADHF were analyzed stemming from different patient populations, namely a Cardiology department in Japan and France and an Emergency department in Portugal. We assessed the associations of ePVS on admission and at discharge as well as its change thereof using the Duarte/Strauss formulas. The primary outcome is the composite of mortality and/or hospitalization for HF.

This merged study included a total of 712 patients derived from 383 patients (mean age, 71±14yrs; male, 65%; mean LVEF, 40±17%) in the Tokyo cohort, 165 patients (mean age 76±10 yrs; male 51%; mean LVEF, 44±11%) in the ICALOR cohort, and 164 patients (mean age 72±15 yrs; male 56%; mean LVEF, 40±17%) in the Porto cohort.

Higher ePVS was consistently associated with a higher risk of the composite outcome across three studies [adjusted HR(95%CI)=1.21(1.01-1.44), p=0.04 in the Tokyo cohort; adjusted HR(95%CI)=1.45(1.16-1.81), p<0.01 in the ICALOR cohort; adjusted HR(95%CI)=1.45(1.16-1.81), p<0.01, in the Porto cohort, respectively]. Furthermore, a pooled-analysis provided significant association of discharge ePVS with improved reclassification (NRI=13.6%, 5.9-22.7, p=0.004).

In the current study, these findings, concordant in three independent cohorts, emphasize the prognostic importance of residual congestion assessed by Duarte-derived ePVS beyond routine clinical assessments in patients with acutely decompensated HF. PV estimated from hemoglobin and hematocrit enables to be assessed sequentially during hospital index. Even if clinicians know that residual congestion is associated with poor prognosis, this study shows that ePVS might be a useful tool to monitor and manage congestion in patients admitted for worsening HF.





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

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## Abstract

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

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

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

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

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

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## Introduction

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

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

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

## Methods

### Studied population

Three independent cohort studies were used for the present analysis:

*The Tokyo cohort* included patients with ADHF admitted to critical care units or cardiac units of the Tokyo Medical University Hospital, Japan, from August 2009 to December 2015. Comorbidities, medications (at discharge), physical assessment, biological findings including

brain natriuretic peptide (BNP) and chest X-ray at both admission and discharge and echocardiographic data from the physical exam performed during the hospitalization were collected retrospectively.

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

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

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

### Outcomes

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

### Estimated plasma volume status

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

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

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



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

## Statistical analysis

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

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

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

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

## Results

### Patient characteristics

In the Tokyo and Porto cohorts and ICALOR study, a total of 383, 165 and 164 patients were, respectively,

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

### Factors associated with estimated plasma volume at discharge

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

### Associations between ePVS variables and clinical outcomes

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

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

**Table 1** Overall patient characteristics in the three cohort studies

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

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

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

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

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

### Improvement in reclassification associated with ePVS variables

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



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

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

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

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

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

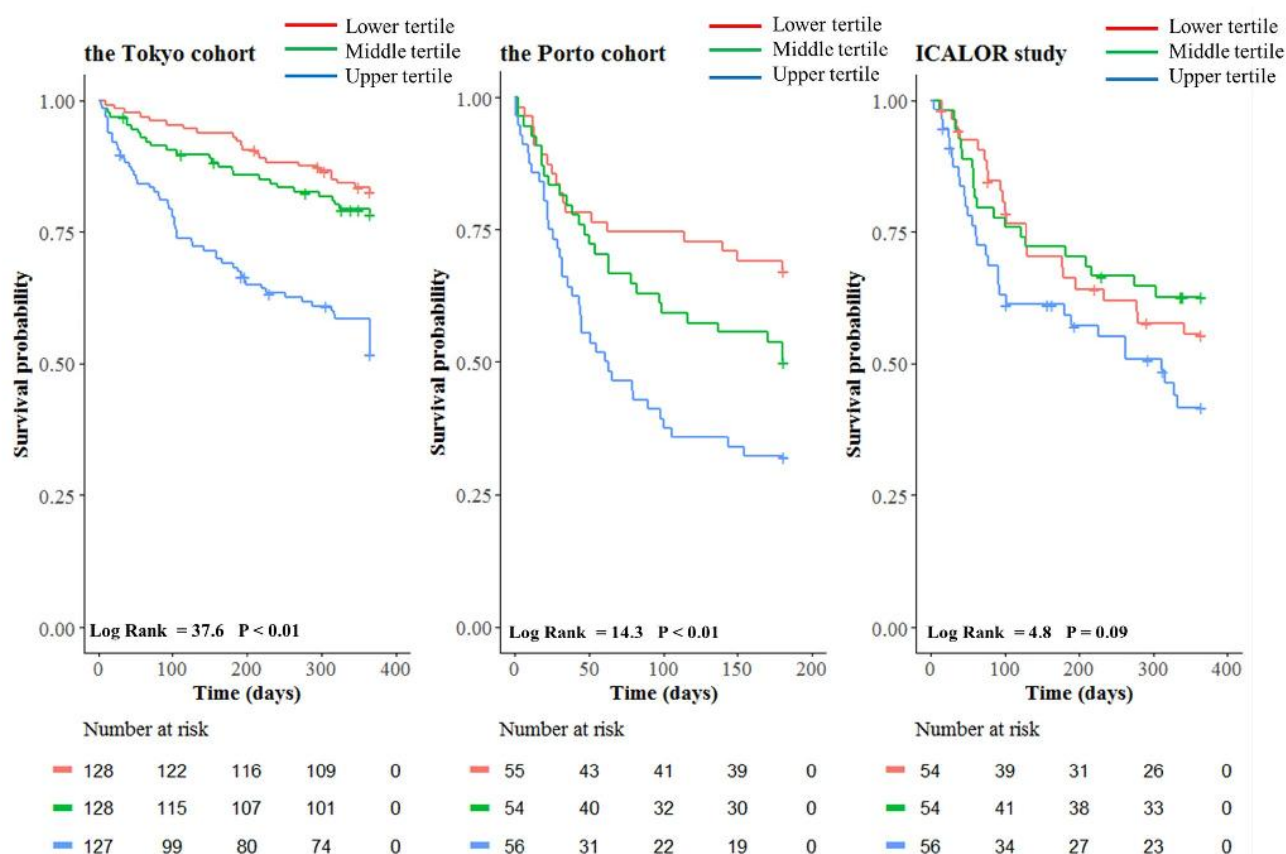
**Table 3** Association between clinical characteristics and discharge-estimated plasma volume in the three cohort studies in logistic regression analysis

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

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

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

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



**Fig. 1** Survival curves for the composite outcome of all-cause mortality and heart failure re-hospitalization according to estimated plasma volume discharge tertile in the three cohort studies. Estimated plasma volume status (ePVS): (Tokyo cohort) lower tertile:

≤ 4.23 dl/g; middle tertile: 4.23–5.67 dl/g; upper tertile: > 5.67 dl/g (porto cohort), lower tertile: ≤ 4.82 dl/g; middle tertile: 4.82–6.10 dl/g; upper tertile: > 6.10 dl/g (ICALOR study). Lower tertile: ≤ 4.48 dl/g; middle tertile: 4.48–5.78 dl/g; upper tertile: > 5.78 dl/g

## Discussion

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

### ePVS as a prognostic factor in ADHF patients

The present study provides evidence for the strong association between ePVS and post-discharge outcome in ADHF, in concordance with prior publications which focused on patients with chronic or de novo HF. Our group had notably

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

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

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

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

(Tokyo cohort) Upper tertile (admission):  $\geq 5.82$  dl/g; Upper tertile (discharge)  $\geq 5.67$  dl/g; Lower tertile  
(change)  $\leq -0.30$  dl/g

(Porto cohort), Upper tertile (admission):  $\geq 5.71$  dl/g; Upper tertile (discharge)  $\geq 6.10$  dl/g; Lower tertile  
(change)  $\leq -1.37$  dl/g

(ICALOR study) Upper tertile (admission):  $\geq 5.85$  dl/g; Upper tertile (discharge)  $\geq 5.78$  dl/g; Lower tertile  
(change)  $\leq -0.80$  dl/g

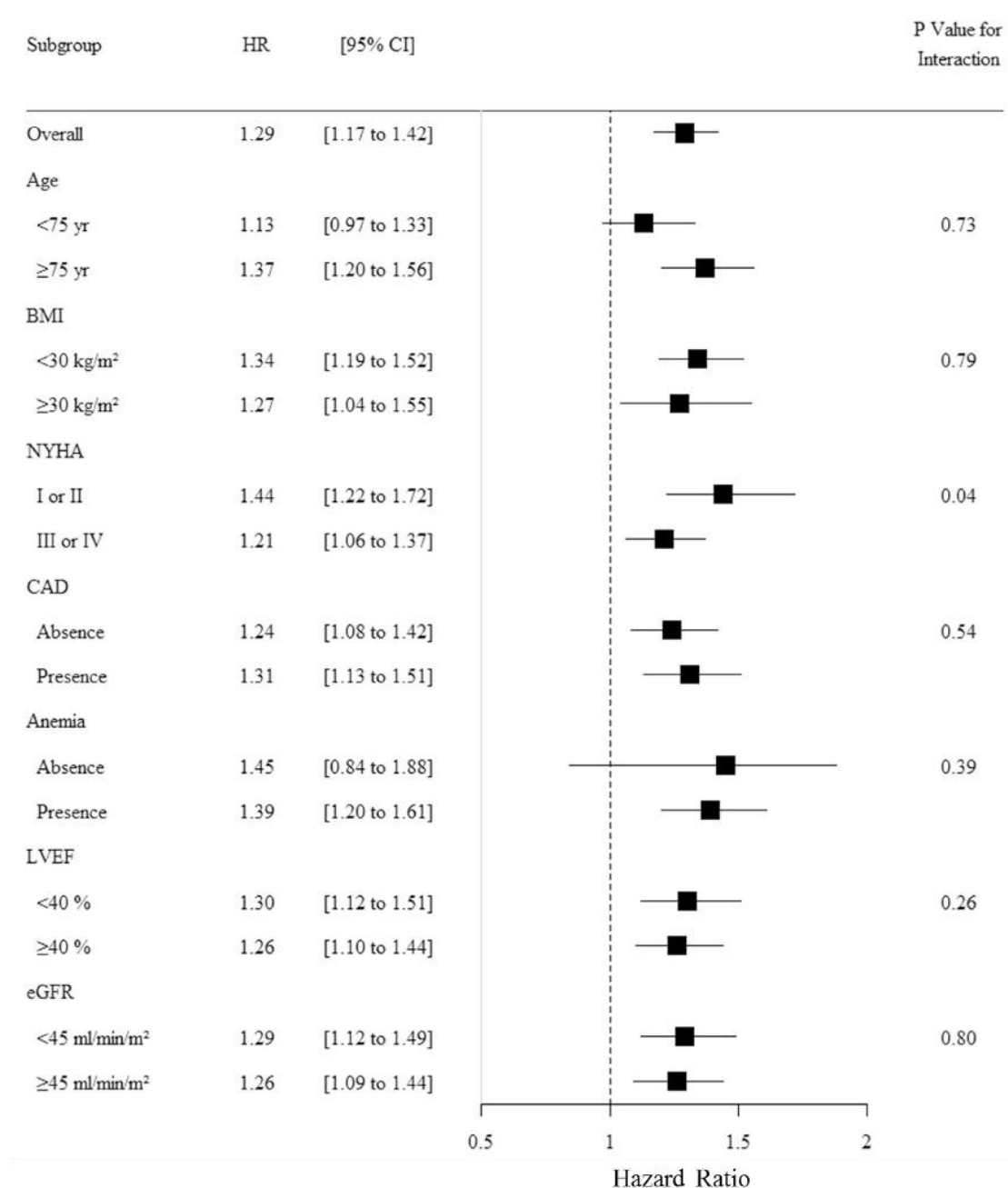
Values in bold represent significant values ( $p < 0.05$ )

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

at the end of hospitalization, as patients can have residual systemic congestion (i.e., have yet to reach their dry weight) [23]. Therefore, in the present analysis, we used the Duarte and Strauss formulas without dry weight for their respective calculation and found that ePVS, which is a simple and non-invasive plasma volume estimation using hemoglobin

and hematocrit, was a strong predictor of post-discharge clinical outcomes, on top of traditional clinical assessments (e.g., LVEF, eGFR and natriuretic peptide). Interestingly, in the subgroup analyses, discharge ePVS did not interact with anemia although it did interact with NYHA functional class in patients with ADHF. This finding strengthens the





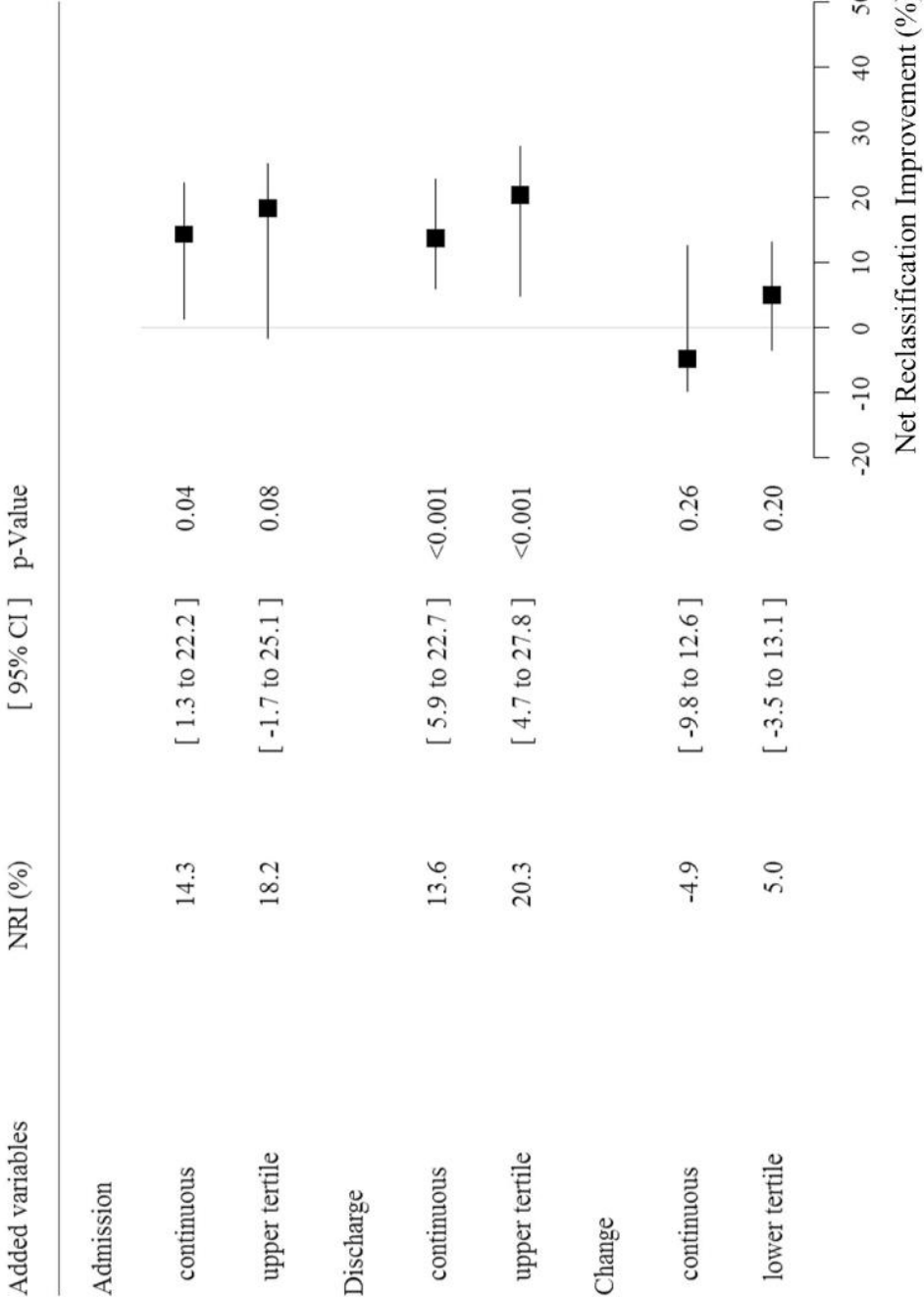
**Fig. 2** Subgroup analyses for associations between estimated plasma volume status at discharge and the composite outcome of all-cause mortality and heart failure re-hospitalization from the pooled data of the three cohort studies. Discharge ePVS was analyzed as a continuous variable. Cox proportional hazards model stratified according to subgroups were performed after adjusting for age, sex, the presence of CAD and LVEF, BUN, eGFR and natriuretic peptides (BNP in

the Tokyo and ICALOR cohort studies and NT-pro BNP in the Porto study) at discharge. *ePVS* estimated plasma volume status, *HR* hazard ratio, *CI* confidential interval, *CAD* coronary artery disease, *LVEF* left ventricular ejection fraction, *BUN* blood urea nitrogen, *eGFR* estimated glomerular filtration rate, *BNP* brain natriuretic peptide, *NT-proBNP* N-terminal pro-brain natriuretic peptide

notion that ePVS could provide prognostic implication without influence of anemic status as well as reflect the severity of congestion. Indeed, patients with NYHA class III/IV are

intrinsically at high risk mostly because of residual congestion and ePVS has less prognostic power in this more homogeneously congested subgroup.

Baseline variables Clinical covariates



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

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

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

To the best of our knowledge, this is the first study to compare the prognostic performance of ePVS at different time points of hospital stay in patients with ADHF, thus enabling the determination of the relative contribution of each variable in clinical outcome. Importantly, in the three cohorts, only discharge ePVS was found to be associated with a composite outcome. Conversely, admission ePVS was significantly associated with outcome only in the Porto cohort and not in the Tokyo cohort and ICALOR study. One possible explanation for the discrepancy of prognostic information may be differences in clinical characteristics; patients from the Porto cohort were more likely to have obesity, compared to those in the Tokyo cohort and ICALOR study (51.8% vs. 8.0% vs. 26.6%, respectively) and coronary artery disease (56.6% vs. 24.3% vs. 33.3%), and also had mild HF symptoms at admission (NYHA class III or greater, 29.7% vs. 80.2% vs. 89.4%). Furthermore, change ePVS was not significantly associated with outcome in univariable analysis in either of the three cohorts. This result is in contrast to previous studies which reported a fair prognostic value of short-term changes in hemoglobin [28] and hematocrit [29] during ADHF hospitalization. Because the prognostic value of hemoconcentration/decongestion can be time-dependent [30], the longer length of hospital stay in our cohorts may have affected the prognostic value of change ePVS; indeed, previous studies [median length of hospital stay, 8.0 days (4.0–11.0) in the EVEREST trial and 8.0 days (6.0–14.0) in the PROTECT trial] [31, 32] investigated shorter-term changes in ePVS than in the present cohort [median length

of hospital stay 18.0 days (13.0–25.0) in the Tokyo cohort, 11.0 days (7.0–15.0) in the Porto cohort and 10.0 days (7.0–15.0) in the ICALOR study]. In addition, the majority of patients enrolled in the aforementioned trials had LVEF of less than 40%, whereas our study included a population irrespective of LVEF. While there are similarities in the clinical course of decongestion [33], management of HF differs [34, 35] across the LVEF strata. LVEF may influence prognostic implication of hemoconcentration/ePVS due to differing pathophysiological mechanisms [36]. Of note, patients with preserved LVEF have been reported to be particularly susceptible to intravascular volume depletion, which could modify the prognostic value of change ePVS [37].

## Limitations

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

## Clinical perspectives

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



## Conclusions

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

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## Compliance with ethical standards

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### **5.2.3. Prognostic Impact of Plasma Volume Estimated from Hemoglobin and Hematocrit in Heart Failure with Preserved Ejection Fraction (5<sup>th</sup> paper)**

Duarte-derived ePVS has been associated with poor prognosis in patients with HF. However, previously published data showed that HFpEF was associated with a greater extravascular volume compared with HFrEF<sup>135, 155</sup>, leading possibly to a lesser impact of ePVS in this HF phenotype. Therefore, it remained unclear whether ePVS guided management could be envisaged in HFpEF because of a similar risk-stratification performance than in HFrEF<sup>87, 156</sup>.

From the dataset of Patients from North and South America enrolled in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist trial (TOPCAT), we explored clinical and prognostic implications of Duarte-derived ePVS, and compared the discriminative prognostic values of Duarte- and Hakim-derived ePVS on top of the clinical model.

In a total of 1,747 patients (mean age 72±10years; males 50%; mean LVEF 58±8%), patients with higher Duarte-derived ePVS had more frequent prior HF admission, diabetes, more severe congestion, poorer renal function, higher levels of natriuretic peptide and E/e'.

Highest Duarte-derived ePVS was associated with an increased rate of the primary outcome compared to the lowest of ePVS [highest vs. lowest ePVS quartile: adjusted-HR (95%CI)=1.79 (1.28-2.50), p<0.001]. Importantly, Duarte-derived ePVS improved prognostic performance on top of clinical and routine variables (including natriuretic peptides) (NRI=11, P<0.001), whereas Hakim-derived ePVS did not (P=0.59).

This study suggests that PV estimated from hemoglobin and hematocrit may be a useful surrogate expressing the severity of congestion, and that this marker could help clinicians in the management of congestion and subsequently tailoring treatment in patients with HFpEF. However, a recent report showed that obese patients with HF had more frequently severe (not mild or moderate) volume expansion. Indeed, in the current study, >60% of patients were obesity (BMI>30kg/m<sup>2</sup>), leading to less applicability of our results in other phenotypes of HFpEF. Further research may be warranted to determine whether this prognostic value is actually dependent on the HFpEF phenotype.



# Prognostic impact of plasma volume estimated from hemoglobin and hematocrit in heart failure with preserved ejection fraction

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## Abstract

**Background** Plasma volume (PV) estimated from Duarte's formula (based on hemoglobin/hematocrit) has been associated with poor prognosis in patients with heart failure (HF). There are, however, limited data regarding the association of estimated PV status (ePVS) derived from hemoglobin/hematocrit with clinical profiles and study outcomes in patients with HF and preserved ejection fraction (HFpEF).

**Methods and results** Patients from North and South America enrolled in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist trial (TOPCAT) with available hemoglobin/hematocrit data were studied. The association between ePVS (Duarte formula and Hakim formula) and the composite of cardiovascular mortality, HF hospitalization, or aborted cardiac arrest was assessed. Among 1747 patients (age 71.6 years; males 50.1%), mean ePVS derived from Duarte formula was  $4.9 \pm 1.0$  mL/g. Higher Duarte-derived ePVS was associated with prior HF admission, diabetes, more severe congestion, poor renal function, higher natriuretic peptide level, and E/e'. After adjustment for potential covariates including natriuretic peptide, higher Duarte-derived ePVS was associated with an increased rate of the primary outcome [highest vs. lowest ePVS quartile: adjusted-HR (95%CI) = 1.79 (1.28–2.50),  $p < 0.001$ ]. Duarte-derived ePVS improved prognostic performance on top of clinical and routine variables (including natriuretic peptides) (NRI = 11,  $p < 0.001$ ), whereas Hakim-derived ePVS did not ( $p = 0.59$ ). The prognostic value of Duarte-derived ePVS was not modified by renal function ( $P$  interaction  $> 0.10$  for all outcomes).

**Conclusion** ePVS from Duarte's formula was associated with congestion status and improved risk stratification regardless of renal function. Our findings suggest that Duarte-derived ePVS is a useful congestion variable in patients with HFpEF.

Masatake Kobayashi and Nicolas Girerd contributed equally to this work.

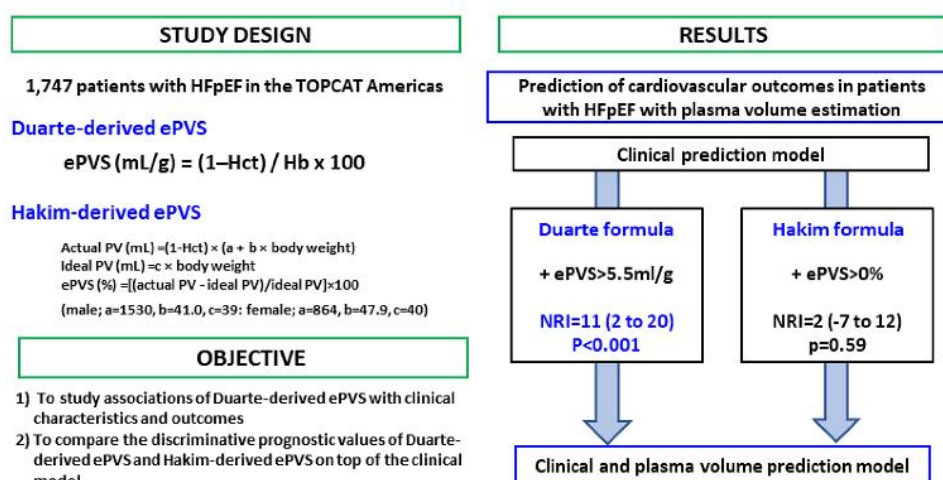
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## Graphic abstract



**Keywords** Plasma volume · Hemoglobin · Hematocrit · Congestion · Heart failure with preserved ejection fraction

## Introduction

Patients with heart failure (HF) often present signs and symptoms of congestion, which is one of the main causes of hospitalization. Hospitalization for worsening HF has been associated with a higher risk of cardiovascular death [1, 2]. There is a large body of literature regarding the clinical importance of assessing and monitoring congestion repeatedly before its progression to decompensation or during decongestion therapy [1, 3–6]. However, there is little consensus among clinicians with regard to the strategy for the quantification and monitoring of congestion. A readily available and inexpensive monitoring tool to assess patients' congestion status may represent a valuable avenue of investigation.

Plasma volume (PV) is a marker of volume overload [7, 8], and patients with decompensated HF exhibit a 40% increase in PV compared with healthy controls [9]. PV may be estimated from the Duarte formula (based on hemoglobin and hematocrit) or from the Hakim formula (based on hematocrit and dry body weight), both of which have been reported to be associated with clinical outcomes in patients with acute HF and HF with reduced ejection fraction (HFrEF) [10–16]. However, despite the published data on the different fluid distributions between HFrEF and preserved ejection fraction (HFpEF) [17, 18], whether estimated plasma volume status (ePVS) contributes to poor clinical outcome in patients with HFpEF has not been sufficiently investigated [19, 20]. Recent data showed that the Duarte formula rather than Hakim formula was associated with left-sided hemodynamic marker of congestion [21].

It is, however, unclear which ePVS formula, between the Duarte formula and Hakim formula, has better risk stratification in this setting. Furthermore, previous studies have shown a significant association between ePVS and renal function [12, 13, 16, 20, 22], although whether the prognostic value of ePVS may be influenced by renal function is yet to be studied in HFpEF.

The main objectives of the present study were to: (1) determine the association between clinical characteristics and other congestion variables using Duarte-derived ePVS; (2) study the association between Duarte-derived ePVS and study outcomes; (3) compare the discriminative prognostic values of Duarte-derived ePVS and Hakim-derived ePVS on top of the clinical model; (4) assess whether the prognostic value of Duarte-derived ePVS is modified by renal function, i.e., the presence of chronic kidney disease as defined by an estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73m<sup>2</sup>.

## Methods

### Study population

The present study consists of a post hoc analysis of data obtained in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial [23]. Inclusion criteria were age 50 years or older, > 1 sign and at least one symptom of HF, left-ventricular ejection fraction (LVEF) ≥ 45%, controlled systolic blood pressure, and serum potassium < 5.0 mmol/L. Additional criteria were either a history of HF hospitalization within the prior



12 months, or B-type natriuretic peptide (BNP)  $\geq 100$  pg/mL or N-terminal proBNP (NT-proBNP)  $\geq 360$  pg/mL within 60 days prior to randomization. Due to previously published regional differences in patient characteristics, outcomes, and response to spironolactone between patients enrolled in Russia/Georgia and the Americas [24], the current study was analyzed in patients who had available hemoglobin/hematocrit data in the Americas (United States, Canada, Brazil, and Argentina). Each site approved the protocols and all patients signed informed consent prior to randomization. This study complies with the Declaration of Helsinki and the local Institutional Review Board has approved this research.

### Estimated plasma volume status

ePVS was calculated from the Strauss-derived Duarte formula using hematocrit and hemoglobin [10, 25] as follows:

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

The Hakim formula was also used for calculating PV estimation derived from hematocrit and dry body weight using the following equations [26]:

Actual plasma volume =  $(1 - \text{Hematocrit}) \times (a + b \times \text{Body weight in kg})$

Ideal plasma volume =  $c \times \text{body weight in kg}$

(Males :  $a = 1530$ ,  $b = 41.0$ ,  $c = 39$ ; Females;  $a = 864$ ,  $b = 47.9$ ,  $c = 40$ ),

$\text{ePVS} = [(\text{Actual plasma volume} - \text{ideal plasma volume}) / \text{ideal plasma volume}] \times 100$ .

### Study outcomes

The primary outcome of TOPCAT was the composite of cardiovascular mortality, HF hospitalization, or aborted cardiac arrest. The current analysis also included all-cause mortality, cardiovascular mortality, and HF hospitalization as previously published [23]. Cardiovascular mortality was defined by any death from myocardial infarction, pump failure, sudden death, stroke, pulmonary embolism, or others. Patients hospitalized for worsening HF needed to meet at least one symptom, two signs of congestion, and requiring decongestion treatment.

### Statistical analysis

Categorical variables are expressed as frequencies (percentages) and continuous variables as means  $\pm$  standard deviation or median (25th and 75th percentiles) according to the distribution of the variables. Comparisons of demographic, clinical, biological, and echocardiographic parameters among ePVS quartiles were analyzed using Chi-square tests for categorical variables and ANOVA or Kruskal–Wallis test for continuous variables. Patients were also divided into four groups according to the categories of ePVS and

eGFR calculated by the Modification of Diet in Renal Disease formula [27].

Linear regression analyses were performed to assess the associations of clinical, biological, and echocardiographic variables with ePVS. Variables were entered into the multi-variable model with backward selection. Covariates considered to be of potential predictive impact comprised 34 baseline patient characteristics (Supplementary Table 1). These variables had a small proportion of missing values ( $< 10\%$ ), and no multiple imputation was performed. Internal validation of the model was performed by bootstrapping ( $\times 200$ ).

Time-to-event comparisons were analyzed using log-rank test and Cox proportional hazard models. Survival probabilities were estimated using the Kaplan–Meier method and plotted as survival curves with ePVS quartiles and ePVS/eGFR categories, respectively. Cox proportional hazard models were then used to obtain unadjusted and covariate adjusted hazard ratios (HRs). Time-to-event analysis for HF hospitalization was conducted using a competing risk model as described by Fine and Gray [28], with HF hospitalization as the outcome and all-cause mortality as the competing risk. The covariates used for adjustment included

age, sex, BMI, previous myocardial infarction, NYHA III or IV, LVEF, potassium, and eGFR at baseline. An additional adjustment consisting of the aforementioned covariates plus log-transformed standardized ( $z$  score) natriuretic peptide (*i.e.*, BNP or NT-proBNP) was also performed. Interactions between ePVS and eGFR on clinical outcomes were assessed using both continuous and categorical variables.

Continuous net reclassification improvement (NRI) and integrated diagnostic improvement (IDI) were calculated to estimate an improvement in risk prediction of the primary outcome by the addition of ePVS on top of the aforementioned variables [29].

All analyses were performed using R (R Development Core Team, Vienna, Austria). A two-sided  $p$  value  $< 0.05$  was considered statistically significant.

## Results

### Baseline characteristics

Among the 1,747 patients included in this study, half of the patients ( $N = 875$ ) were male, mean age was  $71.6 \pm 9.7$  years,



mean BMI was  $33.8 \pm 8.1$  kg/m<sup>2</sup>, and over half had a prior admission for HF (58.8%) (Table 1).

Mean ePVS was  $4.9 \pm 1.0$  mL/g. Patients with higher ePVS were more likely to have atrial fibrillation, prior HF admission, more severe congestion, poorer renal function, higher natriuretic peptide level, E/e', and a more impaired quality of life (Table 1).

### Clinical determinants of estimated plasma volume status

In the linear regression models, poorer renal function, prior HF admission, congestion signs/symptoms (i.e., NYHA, orthopnea, jugular venous distention, and leg edema), female sex, diabetes, and use of beta-blocker remained significantly associated with higher ePVS levels (Table 2). Similar results were obtained in considering the highest ePVS quartiles as outcome (Supplementary Table 2).

### Survival analysis

During a median follow-up of 2.5 years, 29.6%, 22.0%, and 22.7% of patients met the primary outcome, all-cause mortality, and HF hospitalization, respectively. The primary outcome occurred more frequently in patients with higher ePVS (Fig. 1). Compared with the lowest quartile, the highest ePVS quartile ( $> 5.5$  mL/g) was associated with a doubling of the rates of the primary outcome [adjusted-HR (95%CI) = 2.00 (1.55–2.59),  $p < 0.001$ ] (Table 3). After further adjustment for covariates including natriuretic peptide, the highest ePVS quartiles remained significantly associated with the primary outcome [adjusted-HR (95%CI) = 1.79 (1.28–2.50),  $p < 0.001$ ]. Similarly, the highest ePVS level was associated with increased HF hospitalization rates (Supplementary Table 3).

In univariable model, when compared with patients with low ePVS ( $< 5.5$  mL/g) and high eGFR ( $> 60$  mL/min/1.73m<sup>2</sup>), patients with high ePVS ( $> 5.5$  mL/g) with either lower eGFR ( $< 60$  mL/min/1.73m<sup>2</sup>) or higher eGFR ( $> 60$  mL/min/1.73m<sup>2</sup>) had a significantly higher risk of the primary outcome [respectively, HR (95%CI) = 2.65 (2.08–3.37),  $p < 0.001$ ; HR (95%CI) = 1.90 (1.41–2.55),  $p < 0.001$ ]. After adjusting for potential confounders including natriuretic peptide, patients with high ePVS expressed an increased risk of similar magnitude for the primary outcome in patients with lower and higher eGFR (Table 3). Concordantly, patients with higher ePVS were associated with a higher risk of other clinical outcomes irrespective of eGFR level (Supplementary Table 3).

There was no significant interaction between ePVS and eGFR on study outcomes (all- $P_{\text{interaction}} > 0.1$ ). In addition, no interaction was found between ePVS and spironolactone (all- $P_{\text{interaction}} > 0.1$ ).

### Estimated plasma volume status on top of the clinical models

In the current analysis, patients in the highest quartile of Duarte-derived ePVS ( $> 5.5$  mL/g) had a worse prognosis. The addition of Duarte-derived ePVS ( $> 5.5$  mL/g) significantly improved reclassification [NRI (95%CI) = 10.1 (3.2–16.5),  $p = 0.004$  and IDI (95%CI) = 1.3 (0.4–2.7),  $p < 0.001$ ] on the aforementioned potential covariates, whereas the addition of higher Hakim-derived ePVS ( $> 0\%$ ) did not (Fig. 2, Supplementary Table 4). Furthermore, Duarte-derived ePVS still significantly improved reclassification [NRI (95%CI) = 10.3 (2.9–18.5),  $p < 0.001$  and IDI (95%CI) = 0.80 (0.01–2.10),  $p = 0.04$ ] on top of a model containing the Hakim-derived ePVS and baseline clinical variables.

### Discussion

The present study investigated the clinical and prognostic impact of Duarte-derived ePVS in patients with HFpEF. Our main findings were: (1) higher Duarte-derived ePVS was associated with a more severe congestion status; (2) higher Duarte-derived ePVS was independently associated with a higher risk of study outcomes; (3) the Duarte-derived ePVS prognosis value persisted irrespective of renal function; (4) Duarte-derived ePVS significantly improved risk stratification on top of clinical and routine biological variables (including natriuretic peptides), whereas the Hakim-derived ePVS did not. Our findings suggest that PV estimated from the Duarte formula may provide better patient risk stratification than the Hakim formula in patients with HFpEF.

### Duarte-derived estimated plasma volume status as a better prognostic marker

In the present analysis, median Duarte-derived ePVS was  $4.9 \pm 1.0$  mL/g, which is in line with the previous reports [10, 12, 19]. Our results, furthermore, showed that Duarte-derived ePVS was associated with the primary outcome. In a previous post hoc analysis of TOPCAT, ePVS values were calculated based on the Hakim formula in 3414 patients with CHF and LVEF  $> 45\%$  [20]. Within 5 years (during which 19.2% of patients met the primary outcome), higher ePVS ( $> 0\%$ ) was significantly associated with a higher incidence of the primary outcome. However, given the well-known regional differences in the TOPCAT trial [24], analyzing the individuals enrolled in the Americas has proven to be more informative. In this latter subset, and contrary to the results herein using the Duarte-derived formula, higher ePVS was not significantly associated with study outcomes in multivariable Cox models adjusted for natriuretic peptide [e.g.,

**Table 1** Baseline characteristics according to quartiles of Duarte-derived estimated plasma volume status

	ePVS quartiles				<i>p</i> value	Adjusted <i>P</i> value*
	Quartile 1, <4.15, ( <i>N</i> =438)	Quartile 2, 4.15–4.79 ( <i>N</i> =437)	Quartile 3, 4.79–5.50 ( <i>N</i> =437)	Quartile 4, >5.50 ( <i>N</i> =435)		
Age, years	70.2±9.5	71.9±9.7	72.3±9.5	72.0±9.8	<b>0.005</b>	—
Female gender, <i>N</i> (%)	145 (33.1%)	219 (50.1%)	238 (54.5%)	270 (62.1%)	<b>&lt;0.0001</b>	—
Body mass index, kg/m <sup>2</sup>	33.8±7.5	33.1±7.4	33.9±8.8	34.2±8.6	0.24	0.14
Obesity, <i>N</i> (%)	283 (65.1%)	278 (63.8%)	276 (63.2%)	284 (65.7%)	0.85	0.87
Medical history, <i>N</i> (%)						
Hypertension	389 (88.8%)	391 (89.5%)	393 (90.1%)	399 (91.7%)	0.52	0.64
Diabetes	142 (32.4%)	181 (41.4%)	208 (47.7%)	248 (57.0%)	<b>&lt;0.0001</b>	<b>&lt;0.0001</b>
Atrial fibrillation	206 (47.0%)	185 (42.3%)	190 (43.6%)	156 (35.9%)	<b>0.008</b>	<b>0.004</b>
Myocardial infarction	89 (20.3%)	83 (19.0%)	86 (19.7%)	100 (23.0%)	0.49	0.10
Prior HF hospitalization	234 (53.4%)	242 (55.4%)	268 (61.5%)	284 (65.3%)	<b>0.001</b>	<b>&lt;0.0001</b>
Clinical profile						
NYHA III + IV, <i>N</i> (%)	128 (29.3%)	131 (30.0%)	150 (34.3%)	202 (46.7%)	<b>&lt;0.0001</b>	<b>&lt;0.0001</b>
Orthopnea, <i>N</i> (%)	110 (25.5%)	107 (24.9%)	149 (34.3%)	173 (40.0%)	<b>&lt;0.0001</b>	<b>&lt;0.0001</b>
Jugular venous distention, <i>N</i> (%)	63 (15.3%)	65 (15.6%)	77 (18.8%)	92 (22.6%)	<b>0.02</b>	<b>0.03</b>
Leg edema, <i>N</i> (%)	285 (65.2%)	316 (72.3%)	318 (72.8%)	329 (75.6%)	<b>0.006</b>	<b>0.001</b>
Systolic BP, mmHg	126.4±15.0	128.4±16.5	126.6±15.8	128.6±16.1	0.08	0.18
Heart rate, bpm	69.5±11.5	69.2±11.0	68.5±11.5	68.7±12.2	0.54	0.39
LVEF, %	58.1±7.6	58.0±8.1	57.9±7.5	58.8±7.9	0.36	0.24
Medications, <i>N</i> (%)						
ACEi/ARB	349 (79.7%)	332 (76.0%)	335 (76.7%)	352 (80.9%)	0.23	0.27
Beta-blocker	332 (75.8%)	327 (74.8%)	344 (78.7%)	360 (82.8%)	<b>0.02</b>	<b>0.003</b>
Calcium channel blocker	139 (31.7%)	182 (41.6%)	163 (37.3%)	185 (42.5%)	<b>0.004</b>	<b>0.009</b>
Loop diuretics	374 (85.4%)	380 (87.0%)	402 (92.0%)	391 (89.9%)	<b>0.01</b>	<b>0.007</b>
Spirinolactone	212 (48.4%)	234 (53.5%)	221 (50.6%)	210 (48.3%)	0.36	0.38
Laboratory findings						
Hemoglobin, g/dL	15.0±0.9	13.4±0.4	12.3±0.4	10.8±0.8	<b>&lt;0.0001</b>	<b>&lt;0.0001</b>
Sodium, mmol/L	139.8±3.0	139.9±3.0	139.5±3.1	139.5±3.4	0.22	0.09
Potassium, mmol/L	4.2±0.4	4.2±0.4	4.2±0.4	4.2±0.4	0.61	0.63
Blood urea nitrogen, mg/dL	17.0±13.6	19.3±13.5	23.0±15.0	25.6±15.9	<b>&lt;0.0001</b>	<b>&lt;0.0001</b>
eGFR, ml/min/1.73m <sup>2</sup>	69.4±21.1	67.1±22.4	61.7±20.3	59.3±20.7	<b>&lt;0.0001</b>	<b>&lt;0.0001</b>
Natriuretic peptide z score* ( <i>N</i> =1,046)	-0.2±1.0	-0.0±0.9	0.0±1.0	0.2±1.1	<b>0.003</b>	<b>0.001</b>
BNP, pg/ml ( <i>N</i> =690)	242 (140–410)	258 (154–423)	246 (154–441)	305 (163–566)	0.09	<b>0.041</b>
NT-proBNP, pg/mL ( <i>N</i> =356)	903 (500–1404)	882 (528–1665)	918 (604–2424)	1451 (631–2582)	<b>0.01</b>	0.08
Echocardiography						
LVM index, g/m <sup>2</sup> ( <i>N</i> =635)	110.0±30.1	108.9±33.5	109.2±30.4	112.6±30.9	0.69	0.20
LAV index, mm <sup>3</sup> /m <sup>2</sup> ( <i>N</i> =575)	30.4±10.5	32.5±16.0	31.0±13.7	30.9±13.5	0.61	0.76
<i>E</i> / <i>A</i> ratio ( <i>E</i> / <i>e</i> =397)	1.3±0.8	1.4±0.7	1.4±0.7	1.4±0.7	0.85	0.75
<i>E</i> / <i>e</i> ' ratio ( <i>N</i> =275)	11.7±5.4	15.2±6.9	14.1±5.8	16.0±5.5	<b>0.0005</b>	<b>0.0007</b>
GLS ( <i>N</i> =333)	-15.1±3.2	-15.1±3.8	-15.2±3.4	-16.4±3.3	<b>0.047</b>	0.09
KCCQ overall score	62.1±23.4	59.9±23.1	57.8±22.5	52.8±23.7	<b>&lt;0.0001</b>	<b>&lt;0.0001</b>

Values are expressed as mean ± SD, *n* (%) or median (25th-to-75th percentile)

Bold represent significant values (*p* < 0.05)

*ePVS* estimated plasma volume status; *HF* heart failure; *NYHA* New York Heart Association; *BP* blood pressure; *LVEF* left-ventricular ejection fraction; *ACEi* angiotensin-converting enzyme inhibitor; *ARB* angiotensin receptor blocker; *eGFR* estimated glomerular filtration rate; *BNP* brain natriuretic peptide; *NT-proBNP* N-terminal-pro brain natriuretic peptide; *LVM* left-ventricular mass; *LAV* left atrial volume; *GLS* global longitudinal strain; *KCCQ* Kansas City Cardiomyopathy Questionnaire

\* *p* value adjusted for age and sex at entry

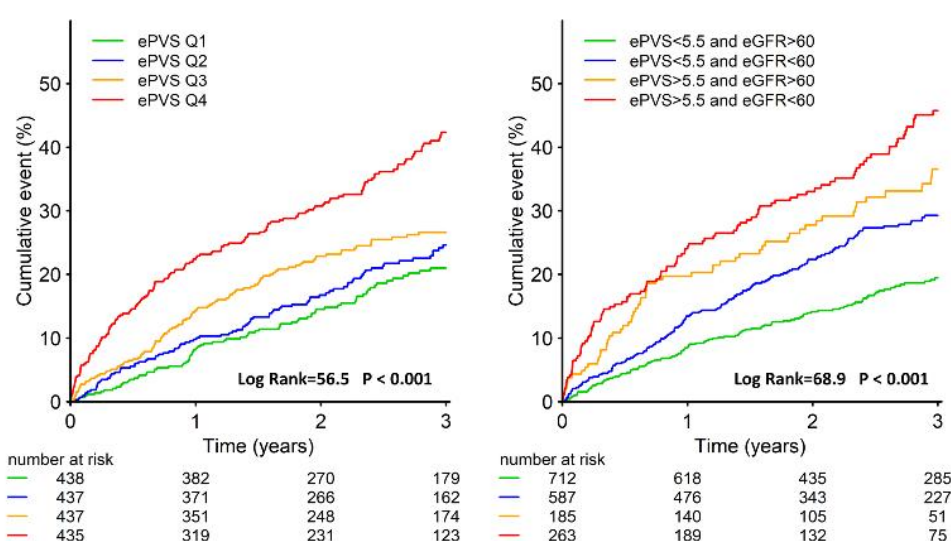
\*\* Natriuretic peptide z-score was calculated using both BNP and NT-proBNP



**Table 2** Multivariable model of the association between clinical profiles and estimated plasma volume status (per 1 mL/g)

	Beta	95% CI	$R^2 = 0.16$ $p$ value
(Constant)	4.41	3.76–5.05	<0.001
Age, yrs (per 5 years)	0.04	0.01–0.07	0.006
Female gender	0.42	0.32–0.52	<0.001
Body mass index	−0.01	−0.02 to 0.003	0.004
Diabetes	0.32	0.22–0.43	<0.001
Atrial fibrillation	−0.13	−0.23 to 0.03	0.009
Prior HF hospitalization	0.25	0.15–0.35	<0.001
Coronary artery revascularization	0.15	0.04–0.25	0.008
NYHA III or IV	0.13	0.02–0.24	0.018
Orthopnea	0.13	0.02–0.24	0.019
Jugular venous distention	0.17	0.04–0.30	0.011
Leg edema	0.16	0.06–0.27	0.003
Use of Beta-blocker	0.17	0.05–0.29	0.005
eGFR, mL/min/1.73m <sup>2</sup> (per 5 mL/min/1.73m <sup>2</sup> )	−0.03	−0.04 to 0.02	<0.001
KCCQ overall summary score (per 5)	−0.02	−0.03 to 0.01	<0.001

CI confidence interval; HF heart failure; NYHA New York Heart Association; eGFR estimated glomerular filtration rate; KCCQ Kansas City Cardiomyopathy Questionnaire

**Fig. 1** Kaplan–Meier survival curves for the primary outcome according to estimated plasma volume status. Higher ePVS increases the risk of major cardiovascular events, and the combination of ePVS and eGFR was associated with a higher risk of cardiovascular events. Estimated plasma volume status (ePVS): Quartile 1, <4.15 mL/g; Quartile 2, 4.15–4.79 mL/g; Quartile 3, 4.79–5.50 mL/g; Quartile 4, >5.50 mL/g. ePVS, estimated plasma volume status; eGFR, estimated glomerular filtration rate

HR = 1.06 (0.98–1.16)  $p = 0.17$  for the primary endpoint]. In a previous report assessing the association between Duarte-derived ePVS and the composite of HF hospitalization or all-cause mortality in 449 patients with HFpEF [19], after a median follow-up of 10.7 years, the best-cut off point, ePVS > 5.5 mL/g, was found to be associated with poor outcomes (21.6% of patients died and 24.7% had HF hospitalization) [19]. However, the analyses were not adjusted for natriuretic peptide, which could result in residual confounding.

To the best of our knowledge, the present study is the first to assess the prognostic/risk-stratification value of

Duarte-derived ePVS and Hakim-derived ePVS on top of clinical and routine biological covariates (including natriuretic peptides). By demonstrating a significant reclassification improvement of ePVS derived from Duarte formula but not Hakim formula, our findings suggest a better prognostic utility of Duarte-derived ePVS in patients with HFpEF. The main difference in the aforementioned ePVS formulas is the use of dry body weight in the Hakim formula. Given the complex interplay between congestion and cardiac cachexia in patients with HF [30, 31], dry body weight may represent a difficult variable to assess and could introduce major bias in the formula.

**Table 3** Cox proportional hazard model of Duarte-derived estimated plasma volume status for the primary outcome

Primary endpoint	Model 1			Model 2			Model 3		
	HR	95% CI	p value	HR	95% CI	p value	HR	95% CI	p value
ePVS Continuous (per 1 ml/g)	1.33	1.24–1.44	<b>&lt;0.001</b>	1.27	1.18–1.37	<b>&lt;0.001</b>	1.23	1.10–1.37	<b>&lt;0.001</b>
ePVS Categorical									
Q1		(Reference)			(Reference)			(Reference)	
Q2	1.02	0.78–1.35	<b>0.87</b>	1.07	0.81–1.41	0.63	1.15	0.80–1.65	0.44
Q3	1.40	1.08–1.82	<b>0.01</b>	1.39	1.07–1.80	<b>0.01</b>	1.25	0.88–1.78	0.22
Q4	2.16	1.69–2.75	<b>&lt;0.001</b>	2.00	1.55–2.59	<b>&lt;0.001</b>	1.79	1.28–2.50	<b>&lt;0.001</b>
ePVS and eGFR interplay									
ePVS <5.5 ml/g & eGFR >60 ml/min/1.73m <sup>2</sup>		(Reference)			(Reference)			(Reference)	
ePVS <5.5 ml/g & eGFR <60 ml/min/1.73m <sup>2</sup>	1.53	1.23–1.89	<b>&lt;0.001</b>	1.28	0.94–1.75	0.12	1.99	1.31–3.00	<b>0.001</b>
ePVS >5.5 ml/g & eGFR >60 ml/min/1.73m <sup>2</sup>	1.90	1.41–2.55	<b>&lt;0.001</b>	1.83	1.35–2.47	<b>&lt;0.001</b>	2.00	1.36–2.92	<b>&lt;0.001</b>
ePVS >5.5 ml/g & eGFR <60 ml/min/1.73m <sup>2</sup>	2.65	2.08–3.37	<b>&lt;0.001</b>	2.13	1.51–3.00	<b>&lt;0.001</b>	2.59	1.63–4.11	<b>&lt;0.001</b>
PValue for interaction with eGFR									
Continuous			0.45						
Categorical			0.65						

Bold represent significant values ( $p < 0.05$ )

HR hazard ratio; CI confidence interval; ePVS estimated plasma volume status; eGFR estimated glomerular filtration rate

Model 1, univariable model

Model 2, adjusted for age, female gender, body mass index, previous myocardial infarction, left-ventricular ejection fraction, New York Heart Association III or IV, potassium and estimated glomerular filtration rate at baseline

Model 3, adjusted for covariables in Model 2 plus natriuretic peptide (BNP or NT-proBNP) transformed by z-score

The previous reports have shown different fluid profiles between patients with HFpEF and HFrEF [32, 33]. Miller et al. compared body fluid profiles measured using the <sup>131</sup>I-labeled albumin method between patients with HFpEF and HFrEF [17]. Their results showed that patients with HFpEF had a higher interstitial fluid volume with higher body weight compared with those with HFrEF, suggesting greater extravascular volume distribution in patients with HFpEF. These results may explain why dry body weight is less associated with PV in patients with HFpEF, leading to the limited prognostic value of the Hakim-derived ePVS in this setting.

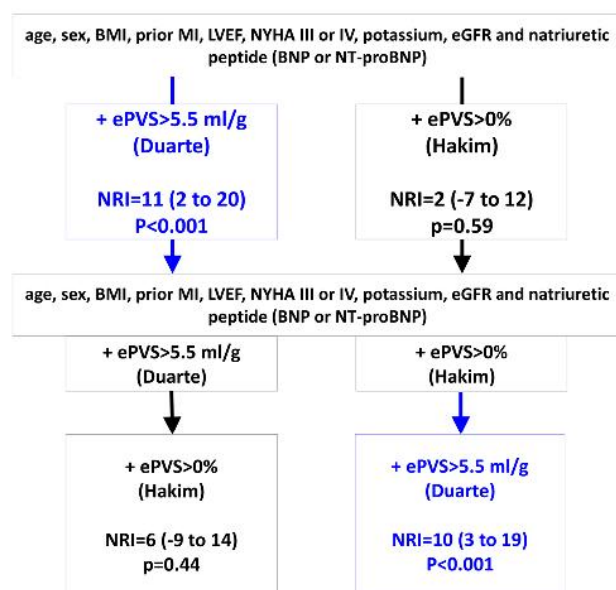
### Duarte-derived ePVS as a congestion marker and its interplay with renal function

In the current study, patients with higher Duarte-derived ePVS were associated with a more severe congestion status as assessed by clinical variables (NYHA III or IV, orthopnea, jugular venous distention, and leg edema), NT-proBNP and *E/e'*. These results support the premise that ePVS derived from hemoglobin/hematocrit is an integrative congestion marker in HFpEF. The previous studies assessing the change in hemoglobin or hematocrit showed an association with clinical assessments of congestion [34–36]. Recent reports also showed a significant

association of hemoglobin with biological, ultrasound, or radiographic measures of congestion in ambulatory HF patients with fewer signs/symptoms of congestion [37, 38]. Hemoglobin itself is thus likely to be the preferred marker with high sensitivity for the assessment or monitoring of congestion in conjunction with lung ultrasound or natriuretic peptide [1, 39]. Furthermore, a recent meta-analysis assessed the association between clinical profiles and measured blood volume components in 368 patients with HF. Their results showed that hemoglobin was significantly associated with measured PV, but not with blood volume [40]. These findings further strengthen that Duarte-derived ePVS could potentially become an easy-to-use and promising assessment tool for evaluating congestion/plasma volume in patients with HF.

Renal functional deterioration enhances neurohormonal activation, leading to increased PV values [41]. Renal venous congestion due to increased PV has been implicated in the pathogenesis of renal impairment [42], whereas decreased PV, similar to hemoconcentration, is also associated with worsening renal function [34–36]. Despite this reported intimate relationship between PV and renal function, we did not find any statistical interaction between ePVS and eGFR with regard to study outcomes. Our observations thus suggest that Duarte-derived ePVS





**Fig. 2** Comparison of the discriminative values of plasma volume estimated from the Duarte and Hakim formulas for the primary outcome. PV estimated from Duarte formula improved prognostic performance on top of clinical and routine variables (including renal function and natriuretic peptides), whereas PV estimated from Hakim formula did not. BMI, body mass index; MI, myocardial infarction; LVEF, left-ventricular ejection fraction; NYHA, New York Heart Association; eGFR, estimated glomerular filtration rate; BNP, B-type natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide; ePVS, estimated plasma volume status; NRI, net reclassification improvement

may help clinicians in better identifying patients at higher risk of cardiovascular events regardless of renal function.

## Clinical perspective

Hemodynamic congestion begins gradually and ultimately results in symptomatic congestion and/or urgent hospitalization. Close biological monitoring of congestion may, therefore, provide a better stratification of patient risk. Accordingly, plasma volume, estimated from hemoglobin/hematocrit using Duarte's formula, may represent an easy-to-use marker in patients with HFpEF in clinical routine.

In the present study, the highest quartile of PV estimated from Duarte's formula ( $\geq 5.5$  mL/g) appeared to drive a higher risk of study outcomes regardless of renal function. This threshold for the prognostic value of ePVS ( $\geq 5.5$  mL/g) is in keeping with the recent data regarding ePVS in patients with acute or chronic HF [12, 13, 19]. Further studies are needed to determine whether this threshold may help to optimize decongestion therapy and the monitoring of ambulatory patients.

## Limitations

The present study has several limitations. This is a post hoc analysis of the TOPCAT trial, and thus, given its inherent limitations, we are unable to infer causality nor exclude residual confounders. First, no direct measurement of PV was performed by the conventional radioisotope-labeled albumin or red blood cell assays, although these techniques are relatively impractical in routine clinical practice given their high cost and technical requirements. Second, we did not have access to serial hemoglobin/hematocrit measurements. Changes in ePVS, especially by the effect of mineralocorticoid receptor antagonist, may also provide good patient risk stratification [43]. Third, we cannot exclude analytical or laboratory variability introduced by natriuretic peptide measured at the clinical site laboratories.

## Conclusion

Duarte-derived ePVS appears as an integrative congestion variable capable of improving patient risk stratification, whereas the Hakim-derived ePVS did not. Duarte-derived ePVS provided prognostic information irrespective of renal function. Our findings suggest that ePVS derived from hemoglobin/hematocrit alone could be clinically useful for quantifying congestion status in patients with HFpEF.

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## Compliance with ethical standards

**Conflict of interest** P.R. reports grants and personal fees from AstraZeneca, grants and personal fees from Bayer, grants and personal fees from CVRx, personal fees from Fresenius, grants and personal fees from Novartis, personal fees from Grunenthal, personal fees from Servier, personal fees from Stealth Peptides, personal fees from Vifor Fresenius Medical Care Renal Pharma, personal fees from Idorsia, personal fees from NovoNordisk, personal fees from Ablative Solutions, personal fees from G3P, personal fees from Corvidia, personal fees from Relypsa, outside the submitted work; and Cofounder: CardioRenal, a company developing a telemonitoring loop in heart failure (including potassium measurements). B.P. reports personal fees (consulting) from Bayer, KBP Pharmaceuticals, AstraZeneca, Relypsa/Vifor, Sanofi, sc Pharmaceuticals, Sarfex pharmaceuticals, Stealth Peptides, Cereno Scientific, SQinnovations, G3 pharmaceuticals, Ardelyx and Tricida; stock options from KBP Pharmaceuticals, sc Pharmaceuticals, Sarfex pharmaceuticals, Relypsa, Cereno scientific, SQinnovations, G3 pharmaceuticals, Ardelyx and Tricida; patent for site specific de-



livery of eplerenone to the myocardium US patent Number 9931412. N.G. reports honoraria from Novartis and Boehringer. All other authors have no conflicts to disclose.

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#### **5.2.4. Estimated plasma volume status in heart failure: Clinical implications and future directions (6<sup>th</sup> paper)**

In our previous research projects, we showed that PV estimated from hemoglobin/hematocrit may be a reliable surrogate of congestion and its clinical utilities in patients with HF. Following these advances, we summarized the recent evidence supporting the association of ePVS with clinical congestion and outcome(s) in a narrative review and discusses future directions for monitoring ePVS in HF.

In this review, we acknowledged the limited correlation between estimated and measured PV<sup>82, 83, 85, 90</sup>. Complex underlying factors related to patients, comorbidities and fluid distribution of HF may influence these results. We showed that evidence points toward higher Duarte- and Hakim-derived PVS with older age, ischemic heart disease, more severe clinical congestion, poorer renal function and higher natriuretic peptide<sup>84-87</sup>. Available evidence (including ours) support ePVS as a clinically relevant congestion marker. Furthermore, accumulating evidence showed the robust associations between ePVS and decongestion therapy (loop diuretics, mineralocorticoid receptor antagonists, SGLT2i and ultrafiltration) in various HF settings<sup>85, 88, 90, 155, 157-160</sup>. Despite reported different fluid distribution across a wide HF spectrum (acute/chronic, HFpEF/HFrEF)<sup>77, 135, 155, 161, 162</sup>, increased Duarte- or Hakim-derived ePVS is strongly associated with a higher risk of clinical outcomes in these phenotypes of HF<sup>81, 84, 85, 88, 159, 163-167</sup>. An actionable threshold of >5.5dl/g in Duarte-derived ePVS is proposed in this review, based on an integrative approach of the available literature, to define an excessive congestive status, which has been repeatedly shown to be associated with poor outcomes<sup>156, 159, 168</sup>.

Recent published data also showed that pulmonary pressure-based HF monitoring led to optimized titration in diuretic doses and subsequent favorable outcomes in ambulatory HF patients<sup>139</sup>. The access to this invasive monitoring, however, may be difficult in most outpatients with HF in the context of elderly, high comorbidity burden and/or economic concerns. We believe that the large-scale monitoring of congestion status, using estimation of PV, based on serial hemoglobin/hematocrit may hence represent an inexpensive, widely and readily available congestion monitoring strategy.



# European Journal of Heart Failure

## Monitoring Congestion with Hemoconcentration/Hemodilution in Heart Failure

--Manuscript Draft--

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<b>Abstract:</b>	Congestion is one of the main predictors of poor outcome in patients with heart failure (HF). Assessing and monitoring congestion is essential for optimizing HF therapy. Among the various available methods, serial measurements of estimated plasma volume (ePVS) using routine blood count and/or body weight (e.g. the Strauss, Duarte, Hakim formulas) may be suitable for optimizing decongesting therapy (loop diuretics, mineralocorticoid receptor antagonists, SGLT2i) in various HF settings. This narrative review summarizes the recent evidence supporting the association of ePVS with clinical congestion and outcome(s) and discusses future directions for monitoring ePVS in HF.



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January 22, 2020

Prof. Macro Metra

Editor-in-Chief

*European Journal of Heart Failure*

Dear Prof. Metra,

We are respectfully submitting our review manuscript entitled " Monitoring Congestion with Hemoconcentration/Hemodilution in Heart Failure" to the *European Journal of Heart Failure*.

This narrative review summarizes the recent evidence supporting the association of plasma volume estimated from hemoglobin/hematocrit with or without body weight with clinical congestion and study-outcomes, and discusses future directions for monitoring plasma volume estimation in HF in various settings (acutely decompensation, chronic setting, HFpEF, HFrEF). Among the various available methods, serial measurements of estimated plasma volume status derived from Strauss, Duarte, Hakim formulas may be suitable for optimizing decongesting therapy (loop diuretics, mineralocorticoid receptor antagonists, SGLT2i) in various HF settings.

We feel this authoritative review is extremely important with regard to future studies and the clinical care of these patients. For this reason, the co-authors and I felt that *European Journal of Heart Failure* was the most suitable journal, because of its broad, global readership and its ability to bring the needed attention to these issues by reaching large numbers of researchers and clinicians in the field.

The co-authors and I will be open to the editors' suggestions on areas where the paper could be improved for publication in *European Journal of Heart Failure*. All authors contributed to the drafting and revising of this manuscript for intellectual content. All authors have read and approved the final submitted version of this manuscript. I will serve personally as the corresponding author for this manuscript.

Thank you for the opportunity to submit our work to *European Journal of Heart Failure*. We look forward to receiving the reviewers' comments. Should you have any questions, or require more information, please do not hesitate to contact me.

Yours sincerely,

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## **Monitoring Congestion with Hemoconcentration/Hemodilution in Heart Failure**

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**Abbreviations and Acronyms**

PV=plasma volume

ePVS=estimated plasma volume status

HF=heart failure

CHF=chronic heart failure

AHF=acute heart failure

HFrEF=heart failure with reduced ejection fraction

HFpEF=heart failure with preserved ejection fraction

HFmrEF=heart failure with mid-range ejection fraction



**Abstract**

Congestion is one of the main predictors of poor outcome in patients with heart failure (HF). Assessing and monitoring congestion is essential for optimizing HF therapy. Among the various available methods, serial measurements of estimated plasma volume (ePVS) using routine blood count and/or body weight (e.g. the Strauss, Duarte, Hakim formulas) may be suitable for optimizing decongesting therapy (loop diuretics, mineralocorticoid receptor antagonists, SGLT2i) in various HF settings. This narrative review summarizes the recent evidence supporting the association of ePVS with clinical congestion and outcome(s) and discusses future directions for monitoring ePVS in HF.

## Introduction

Congestion is one of the main mechanisms underlying worsening heart failure (HF) and is associated with poor outcome. Insufficient decongestion is associated with higher rates of HF re-admission and death.(1) Therefore, it is of paramount importance to better detect and monitor congestion before progression to decompensation (2) and to assess the intensity of decongestion for an optimal tailoring of HF therapy. International guidelines have long recommended assessing “volume status” in order to adapt diuretic doses (3). However, congestion can be difficult to assess, especially when extrapulmonary signs of congestion are mild, or in patients with residual congestion at discharge from a HF hospitalization (2).

According to the principle of total body volume distribution, body volume is approximately 60% of body weight, all fluid compartments are balanced, and a change in plasma volume (PV) would be accompanied by an equal change in the interstitial and intracellular compartment (4-7). Volume expansion in patients with HF is associated with changes in fluid volume. PV in patients with decompensated HF may increase by 40% compared with that in healthy controls (8). An increase in PV due to redistributed or accumulated fluid volume contributes to HF symptoms, subsequently leading to urgent HF hospitalization (2,4,9). It may thus be clinically useful to monitor PV in order to detect worsening HF. This however warrants a reliable and actionable assessment of PV.

Hemoconcentration (or hemodilution) gauged by a change in hemoglobin or hematocrit concentrations as an indirect marker of changes in PV has been shown to trend with clinical assessments of congestion (10-12). For instance, an analysis of the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) trial investigated baseline-to-discharge increases in hematocrit, albumin and total protein values. Patients with 2 or more of the 3 aforementioned variables with values in the top tertile were considered to have evidence of hemoconcentration, which was found to be associated with greater net weight or fluid loss and greater reduction in right atrial pressure and pulmonary capillary wedge pressure, along with a substantially lower risk of mortality (10). More recently, hemoglobin was found to be significantly

negatively correlated with all tested biological and ultrasound measurements of congestion in a chronic HF patient population across a large spectrum of ejection fractions (13). In a meta-analysis from a systematic review including 18 studies and a total of 368 patients with HF, hemoglobin was found negatively associated with measured plasma volume (Beta=-6.66 ; SE=2.53, p=0.008)(14). While direct quantification of PV accurately depicts the severity of congestion in patients with chronic HF (15,16), direct measurements of PV unfortunately use methods which are technically-demanding, costly and not readily available to clinicians or suitable for serial monitoring. Therefore, PV estimated from a routine blood count and/or body weight may be more clinically relevant for repeat use given its low cost and practicability. Estimated PV status (ePVS) might provide a phenotypic characteristic to tailor personalized therapy in the different settings of HF.

This narrative review summarizes the recent evidence supporting the association of ePVS with clinical congestion and outcome and discusses future directions for monitoring ePVS in HF.

## **Estimated and Measured Plasma Volume Status**

### **Formulae for Estimating Plasma Volume**

Among recent reports in HF settings, two representative methods are available for estimating PV. Both express relative values of PV and use routinely available variables (*i.e.*, hemoglobin and body weight).

#### **Strauss Formula**

The concept of estimating PV was first reported by Strauss et al. in 1951 (17). This seminal research of the Strauss formula demonstrated the association between the infusion of saline into human bodies and rapid changes in their estimated PV. In 1970's, Dill et al. reported the association of a decrease in body weight after exercise with a steep decrease in ePVS using hemoglobin and hematocrit (18). This formula was validated against a radiolabeled gold standard method and has been routinely used over decades for the estimation of plasma volume in patients scheduled for plasma exchanges (19,20).

To estimate relative changes in PV between 2 time points, the Strauss formula uses changes in hemoglobin and hematocrit (17):

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

In a recent report, Duarte et al. used an instantaneous-derived measurement of plasma volume (Duarte's formula) for estimating PV derived from the Strauss formula as follows (21):

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

### **Hakim Formula**

The Hakim formula is also used for calculating actual and ideal PV and ePVS derived from hematocrit and dry body weight using the following equations (22):

$$\text{actual PV} = (100 - \text{hematocrit (\%)}) / 100 \times [a + (b \times \text{weight (kg)})]$$

$$\text{ideal PV} = c \times \text{weight (kg)}$$

(males: a=1530, b=41, c=39; females; a=864, b=47.9, c=40),

Relative PV status, an index of the extent to which patients have deviated from their ideal PV, was subsequently calculated from the following equation:

$$ePVS = [(\text{actual PVS} - \text{ideal PV}) / \text{ideal PV}] \times 100\%$$

One caveat with the Hakim formula is that it warrants dry body weight which is a major potential confounder in the HF setting, where there is a complex interplay between congestion and loss in body weight ("cachexia"), both associated with poor prognosis (23).

### **Measured Plasma Volume**

Radioisotope assays are considered as the gold-standard, as they accurately assess PV status along with red blood cell and total blood volume, using the concomitant determination of hematocrit. The



latter provides relevant information, since red blood cell abnormalities (non-hemodilutional anemia or polycythemia) may coexist with PV abnormalities in patients with HF and may challenge its isolated interpretation (7,24). Notwithstanding, the radioisotope assays are expensive and impractical for serial monitoring, due to the need of frequent venous blood sampling and processing delays (25) .

#### **131I-labeled albumin method (24)**

The 131I-labeled albumin method (Volumex, Daxor Corporation, New York) is a validated and standardized clinically available technique. Low-dose iodinated I-131-labeled albumin is injected, and from a contralateral forearm venous catheter, blood samples are collected at time 0 (pre-injection), and at 12, 18, 24, 30, and 36 min post-injection. Hematocrit is determined from each sample, and the plasma radioactivity of each sample is measured (in duplicate) in a semi-automated counter (Food and Drug Administration approved BVA-100 Blood Volume Analyzer, Daxor Corporation). Subsequent to an initial assessment in patients with acutely decompensated HF, it was proposed that the readily available peripheral hematocrit test results may provide an updated view of the patients' volume status, such that, in those cases where it could be assumed that the red blood cell volume was reasonably stable (absent bleeding or interventions to correct anemia), an increase in peripheral hematocrit could be interpreted as a true (decongestive) decrease in plasma volume (24).

#### **125I-HSA method (26)**

The International Committee for Standardization in Hematology recommends the 125I-HSA method (26). A 125I-labeled albumin is injected peripherally, and blood is collected from a different vein (usually the opposite arm) at 10, 20 and 30min post-injection. The radioactivity of the plasma samples and the standard are determined in a scintillation counter. Plasma volume is calculated by the following equation:

$$PV = \frac{\text{Radioactivity of standard (cpm/ml)} \times \text{dilution of standard} \times \text{volume injected (ml)}}{\text{Radioactivity of postinjection sample (cpm/ml, adjusted to time zero)}}$$

### **<sup>99m</sup>Tc-HSA method (7,25)**

Technetium(<sup>99m</sup>Tc)-labeled red blood cells is injected peripherally after 60min in supine position. Thereafter, blood is collected at 10-min intervals for 30minutes. Radioactivity is measured in an automated counter. PV is calculated from the measured blood volume, venous hematocrit, corrected for the trapped plasma and mean body hematocrit.

### **IV-administered visible fluorescent injectate (VFI)<sup>TM</sup> (FAST BIOMedical) (27)**

Recently, a non-isotopic (fluorescent) method to rapidly quantify PV and renal function was developed. The method consists of 12mg of a 150-kDa carboxy-methylated dextran, conjugated to a rhodamine dye (plasma volume marker), and 35mg of a 5-kDa carboxy-methylated dextran, conjugated to fluorescein (renal clearance marker), in a total volume of 3.0mL. As the large molecule is retained in the intravascular space, its concentration reflects real-time plasma volume, and since the small molecule is freely filtered across the glomerulus, its change represents the glomerular filtration rate. The injectate is infused intravenously over 30s. Dye concentrations are quantified 15min after the injections for initial PV measurements using the indicator-dilution principle. Blood volumes are calculated based on PV and the subject's hematocrit. Samples are also taken at 60 and 170 min for determination of glomerular filtration rate by the FAST BioMedical technique (27). Validation results were recently published using data from 16 healthy subjects and 16 subjects with chronic kidney disease. Additionally, this technique accurately tracked dynamic changes in PV induced by a volume challenge following an intravenous bolus of 350mL of a 5% albumin solution in normal saline in 8 healthy subjects (27). The ongoing EMPAKT-CHF (Estimating versus Measuring Plasma Volume and Kidney Function in Acute Decompensated Congestive Heart Failure) study is a one-armed, phase 2 clinical trial using (VFI)<sup>TM</sup> to assay and assess measured PV and measured glomerular filtration rate in hospitalized patients with acute decompensated congestive HF (NCT03808948).

## **Estimated Plasma Volume Status as a Congestion Marker**

### **Comparison between Estimated Plasma Volume Status and Direct Plasma Volume**

Several reports have assessed the correlation between ePVS and conventional radioisotope-labeled albumin or red blood cell assays. Ling et al. compared ePVS derived from the Hakim formula and actual PV using the gold standard  $^{125}\text{I}$ -labeled human serum albumin method (28). Results showed a moderate correlation between measured PV and estimated PV ( $r=0.51$ ,  $p=0.006$ ) in 30 patients with CHF ( $r=0.68$ ,  $p<0.001$  in 119 healthy subjects). Martens et al. also compared ePVS derived from Hakim and PV expansion using Technetium ( $^{99}\text{Tc}$ )-labeled red blood cells in stable patients with CHF and HFrEF, showing moderate to good correlation ( $r=0.71$ ,  $p<0.001$ ) and a good agreement between measured and calculated plasma volume (25). Furthermore, Fudim et al. compared ePVS and measured PV in 110 stable CHF patients with NYHA class III or IV (29). The authors used both the Hakim formula and Strauss formulae (change and instantaneous), compared to low-dose  $^{131}\text{I}$ -labeled albumin intravenously. They reported moderate-to-strong correlation of the Hakim formula with the measured quantitative PV ( $r=0.51$ ,  $p=0.006$  and  $r=0.64$ ,  $p<0.001$ ), while the Strauss formula ePVS was weakly correlated with measured PV ( $r=0.29$ ,  $p=0.003$ ). A recent report comparing Strauss-derived ePVS and measured PV by  $^{125}\text{I}$ -human serum albumin in 10 patients with type 2 diabetes showed good correlation (Lin's concordance index of 0.6 ( $p<0.01$ ) between both PV measurements) (30).

### **Association between Clinical Congestion Markers and Estimated Plasma Volume Status**

Clinical predictors of higher ePVS, including demographics, comorbidities, ultrasound/hemodynamic parameters and biomarkers are presented in **Table 1**. Similar clinical determinants have been reported for ePVS calculated by the Strauss and Hakim formulae. Patients with higher ePVS were older, had more frequent ischemic heart disease, more severe clinical congestion, poorer renal function, higher natriuretic peptide and were less likely to be on HF medications (28,31-33). Of note, some available data in the HF cohort studies demonstrated good correlations between instantaneous and/or changes in

ePVS and natriuretic peptide. Using data from the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) trial, Rossignol et al. showed a relatively weak correlation between baseline to 1-month changes in ePVS and BNP ( $r = 0.284$ ;  $p < 0.001$ ), independently of study drug and renal function variations (34). Not surprisingly, significant associations between ePVS and congestion markers such as natriuretic peptide were also observed in patients with HFpEF (33).

These findings therefore strengthen the concept that ePVS is a clinically relevant congestion marker (**Central Illustration**).

### **Association of Estimated Plasma Volume Status with Clinical Outcomes in the Different Settings of Heart Failure**

Patients with acute heart failure (AHF) have more interstitial fluid volume due to fluid accumulation/re-distribution compared to those with chronic heart failure (CHF) (9,35,36), whereas fluid volume profiles show a different distribution between patients with HFpEF and HFrEF (37,38). Androne et al. showed that increased measured blood volume, as assessed by intravenous administration of iodine 131–labeled albumin, was associated with an increased risk of death or urgent cardiac transplantation (15).

A number of other reports also found independent associations between an increase in estimated PV level and a higher risk of clinical outcomes, consistently and across a wide HF spectrum (acute/chronic, HFpEF/HFrEF) (**Table 2**).

### **Chronic Heart Failure**

The associations of ePVS with clinical outcomes have been well documented in patients with CHF irrespective of LV systolic function.



Rossignol et al. investigated the prognostic value of changes in PV using the Strauss formula in 6,820 patients with HFrEF in the Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca-Heart Failure (GISSI-HF trial) (39). During a median follow-up of 3.9 years, increased PV (>0%) from baseline was independently associated with a higher incidence of all-cause mortality [adjusted HR (95%CI)=1.010 (1.002-1.018), p=0.017] and cardiovascular mortality [adjusted HR (95%CI)=1.012 (1.003-1.020), p=0.007], independent of a significant decrease in body weight. A post-hoc analysis of the Valsartan Heart Failure Trial (Val-HeFT) assessed ePVS derived from the Hakim formula in 5,002 patients with HFrEF (28). After a median follow-up of 716 days (during which 20.0% of patients died), patients with the highest ePVS quartiles were associated with increased all-cause mortality after adjusting for clinical covariates including BNP [adjusted HR (95%CI)=1.26 (1.05-1.52), p=0.01]. Similar prognostic implication of Strauss-derived or Hakim-derived ePVS is in line with reports in HFpEF patients (33,40). In a post-hoc analysis of Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT), ePVS derived from the Hakim formula was assessed in 3,414 patients with HFpEF, in which increased ePVS was associated with a higher risk of the composite of all-cause death or HF re-hospitalization (33).

### **Heart Failure with Reduced Ejection Fraction and Post-myocardial Infarction**

In 6,080 patients with HFrEF following acute myocardial infarction from the EPHESUS study database, after a mean follow-up of 16 months, a significant decrease in ePVS as assessed by the Strauss-formula (delta ePVS) from baseline to 1 month was associated with a lower risk of clinical outcomes (34). Furthermore, in another report of the EPHESUS, Duarte et al. assessed the prognostic value of instantaneous ePVS at 1 month as well as ePVS change from baseline to 1 month (21). They found that instantaneous ePVS at 1 month was a better predictor of cardiovascular events than change in ePVS from baseline to 1 month over a follow-up period of 6 months. The fact that the Hakim formula was not associated with outcomes in this analysis may arise from the integration of body weight in this formula. Indeed, Hakim-derived ePVS increases when hematocrit decreases and conversely decreases when weight decreases, whereas patients with events displayed lower weight and

hemoglobin. Ideally, dry weight (i.e., the body weight measured in non-congested patients), which was not assessed in this latter study and is difficult to estimate in routine practice because of frequently persisting edema in HF patients, should have been used to run this formula (21).

### **Acute Heart Failure**

A study assessing change in Strauss-derived ePVS from admission to discharge in 712 patients with AHF (41) found that an increase in ePVS at discharge was associated with poor prognosis, and provided a significant improvement in prognostic reclassification, on top of standard clinical prognostic models. This is in keeping with findings of several smaller studies, in patients with AHF, showing the prognostic value of discharge ePVS and of ePVS change from admission and discharge, likely depicting residual congestion (42-44). Other reports showed that patients with increased in admission ePVS also have worse prognosis (31,45). In a large cohort of 1,369 patients with acute dyspnea admitted to the emergency department, the highest tertiles of admission Strauss-derived ePVS was associated with the diagnosis of AHF [adjusted OR (95%CI)=1.64(1.16–2.33), p=0.005] (46) as the main cause of dyspnea. A value of ePVS >5.12 dl/g identified patients who, concomitant with infection or chronic renal failure, were diagnosed with AHF in the emergency department. In addition, higher ePVS was associated with a higher risk of in-hospital mortality.

### **Hemoconcentration and Worsening Renal Function**

Aggressive decongestion as documented by a decrease in PV and hemoconcentration, improves clinical outcomes in patients with HF (10-12,47,48). Incident hemoconcentration, across a large range of definitions, is frequently associated with worsening renal function (10-12,47,49-52)(**Supplementary table 1**), which has little negative prognostic influence (50,53,54). Importantly, in contrast, worsening renal function without hemoconcentration, i.e. with persistent congestion, is associated with worse outcomes (55,56). Importantly, in most of the aforementioned studies, hemoconcentration was derived from changes in hemoglobin or hematocrit.

## **Plasma Volume as an Actionable Biomarker to Guide (De)congestion Therapeutic Strategies in Heart Failure**

Half a century ago, furosemide infusion was shown to consistently increase hematocrit and decrease estimated (Strauss formula) and measured (isotopic) plasma volume (57). In the 1990's, ultrafiltration in chronic heart failure was found to decrease estimated plasma volume (hematocrit-based formula) (58) along with pulmonary wedge pressure and right atrial pressure, two established biomarkers of congestion. Importantly, immediately after ultrafiltration, mean pulmonary wedge pressure decreased by 29% and right atrial pressure decreased by 46%. Both variables remained unchanged in the next two days. Plasma volume was reduced by 22% immediately after the procedure and by 10% after 24 hours, and subsequently fully recovered in the next 24 hours. This differential kinetics may reflect a modest correlation between ePVS changes and pulmonary wedge pressure changes. However, more importantly, changes in ePVS and pulmonary wedge pressure were directionally and consistently concordant and were simultaneously reduced by the ultrafiltration process. Ultimately, in HF, hemoconcentration, which is easily and continuously measured by an in-line hematocrit sensor during ultrafiltration therapy, is considered as an appropriate surrogate indicating when the plasma refill rate is exceeded by the rate of fluid removal (59). More recently, several contemporary HF cohort studies showed correlations between volume depletion due to diuretic response and decreases in ePVS (28,38,41).

The EPHESUS data in HF patients post-MI showed that the mineralocorticoid receptor antagonist (MRA) eplerenone induced a diuretic-like effect compared to placebo, as assessed by decreased ePVS (Strauss Formula) after one month, an effect associated with improved clinical outcomes (34). In patients with chronic HF, a higher dose of renin-angiotensin-antagonist-blocker (RAS-blocker; ACE-I or ARB) and a higher dose of a MRA have moreover been associated with an independent higher odds of having an optimal estimated plasma volume status in HF<sub>r</sub>EF and HF<sub>m</sub>rEF (25).

SGLT2 inhibitors are likely to become part of the life-saving drug armamentarium in HF, downstream of the DAPA-HF trial in HFrEF (60), while HFpEF trials are ongoing (61). In a randomized, placebo-controlled, double-blind trial, 75 subjects with type 2 diabetes were assigned either placebo, the SGLT2 inhibitor dapagliflozin 10mg/day, or hydrochlorothiazide 25mg/day. SGLT2 inhibitor dapagliflozin treatment resulted in a 7.3% reduction in measured (isotopic) PV from baseline, with parallel consistent increases in hematocrit and hemoglobin (62). In a pooled database of 13 phase 2b/3 placebo-controlled clinical trials involving 4,533 patients with type 2 diabetes and randomized to dapagliflozin 10mg daily or matched placebo, dapagliflozin decreased estimated plasma (Strauss Formula) by 9.6% (95% confidence interval 9.0 to 10.2) compared to placebo after 24 weeks (30). Of note, the increase in hematocrit, consistent with the rise in serum albumin levels, mediated a major part of the beneficial effect in the EMPA-REG cardiovascular outcome trial (60,62).

Whether monitoring PV, hematocrit or hemoglobin may enable optimization of HF therapy and therefore improve cardiovascular outcomes warrants dedicated randomized clinical trials. Interestingly, a provocative retrospective analysis of a single center database supported both the short (30-day readmission and mortality) and long-term benefit (365-day mortality), unrestricted by ejection fraction category, of a volume-guided HF therapy versus propensity-matched controls in patients hospitalized for HF. The HF treatment strategy was individualized and guided by initial blood volume analysis with DAXOR results on an ad hoc basis with the consistent goal of normalizing measured total blood volume and/or red blood cell volume disturbance, using a rise in peripheral hematocrit in relation to the patients' peripheral hematocrit as a surrogate marker of interstitial fluid volume decongestion or increase in red blood cell volume, depending on the primary treatment strategy. As rightly pointed out by W. Tang in an accompanying editorial (63), "Such hypothesis-generating insights require independent validation with a randomized controlled trial design to demonstrate rigor and reproducibility of the findings. Translating in clinical practice, the blood volume analysis is not an inexpensive test, and requires logistic solutions for its administration. Hence, beyond demonstrating incremental benefits by a BVA guided approach in ADHF management, clinical adaptability and

practical use of such a strategy will also depend on its cost-benefit assessment at a time when there is growing concerns regarding the increasing costs of health care”.

### **Clinical Perspectives. Monitoring Plasma Volume for Therapy Optimization**

The CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients (CHAMPION) trial highlighted the benefit of HF management according to pulmonary pressure data derived from wireless devices on HF re-hospitalization in ambulatory patients with HF (64). Importantly, in this trial, changes in treatment prompted by persistent hemodynamic congestion were overwhelmingly dominated by an increase in diuretic doses (64). This invasive outpatient monitoring, however, may not be widely available in all patients with HF in the context of elderly, high comorbidity burden and economic concerns. Monitoring congestion status, using plasma volume estimation, based on changes in serial hemoglobin/hematocrit measurements could hence represent a low-cost and easy-to-use alternative.

On the basis of the available retrospective data, specific target hemoconcentration goals have yet to be defined, and it is unclear whether the same targets should be applied to different patient subsets (65). Based on the latest published data with the Duarte’s Strauss-derived instantaneous assessment of ePVS (Strauss-Duarte) in acutely decompensated or chronic HF, an actionable threshold of  $>5.5\text{dl/g}$  may be proposed to define an excessive congestive status, associated with poor outcomes (40,41,46), which may allow prospective evaluation as a trigger for therapeutic action. Interestingly, in a recent study, capillary blood samples were drawn by study nurses at home 5 days a week for two months after an acute decompensation in 15 patients with HFrEF. Hematocrit and hemoglobin (along with creatinine and potassium) were measured using an approved home-based device (ABOTT iSTAT). An ePVS  $>5.5\text{dl/g}$ , suggestive of undiagnosed residual congestion, was observed at discharge in 3 out the 15 patients. It was possible to document a number of episodes of re-congestion (mean  $\pm$  standard deviation;  $1.4 \pm 1.5$  for an ePVS rise  $>10\%$ ,  $2.3 \pm 2.4$  for an ePVS rise  $>15\%$ ,  $1.8 \pm 2.6$  for an



ePVS>5.5dl/g) (70). Adequately powered prospective clinical trials using hematocrit/hemoglobin and ePVS are however needed to investigate this hypothesis.

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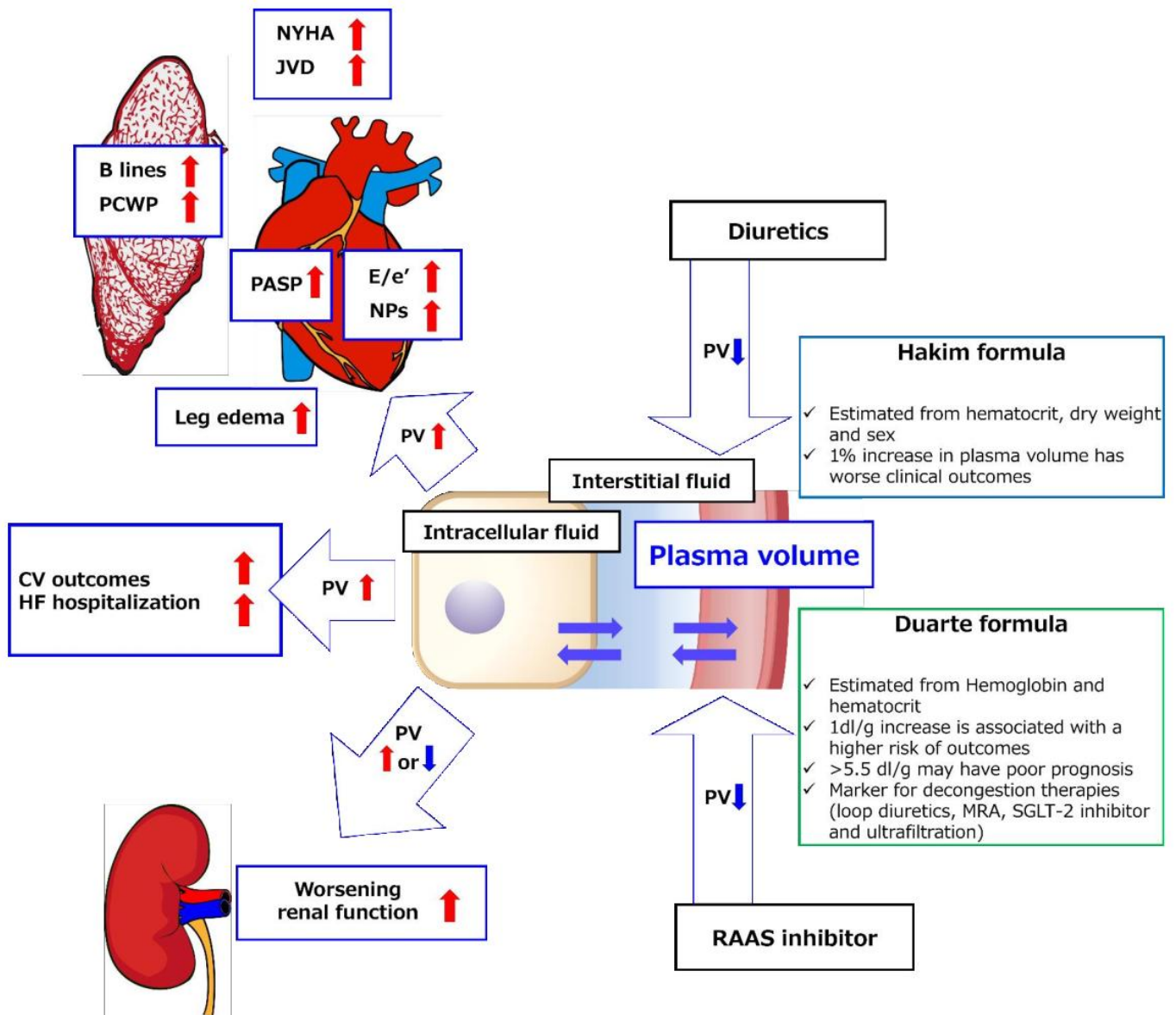


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### **Central Illustration. Associations of Estimated Plasma Volume Status with Clinical Profiles, Treatment Response and Clinical Outcomes**

PV, plasma volume; NYHA, New York Heart Association; JVD, jugular venous distention; PCWP, pulmonary capillary wedge pressure; PASP, pulmonary artery systolic pressure;  $E/e'$ , the ratio between early mitral inflow velocity and mitral annular early diastolic velocity; NPs, natriuretic peptides (brain type natriuretic peptide or N-terminal pro-B-type natriuretic peptide); WRF, worsening renal function; RAAS, renin-angiotensin-aldosterone-system; CV, cardiovascular; HF, heart failure; MRA, mineralocorticoid receptor antagonist; SGLT-2, sodium-glucose co-transporter-2.

**Central Illustration. Associations of Estimated Plasma Volume Status with Clinical Profiles, Treatment Response and Clinical Outcomes**



**Table 1. Clinical Determinants for Higher Plasma Volume**

NYHA, New York Heart Association; JVD, jugular venous distention; BP, blood pressure; RAAS, renin-angiotensin-aldosterone-system; ADHF, acutely decompensated heart failure; TRV, tricuspid regurgitation velocity; PASP, pulmonary artery systolic pressure; EF, ejection fraction; TAPSE, tricuspid annular plane systolic excursion; PCWP, pulmonary capillary wedge pressure; BNP, brain natriuretic peptide; NT-proBNP, N-terminal pro-brain natriuretic peptide; eGFR, estimated glomerular filtration rate.

**Table 2. Prognostic Value of Estimated Plasma Volume Status**

BS: baseline; M: month; HF, heart failure; ePVS, estimated plasma volume status; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; CHF, chronic heart failure; ADHF, acutely decompensated heart failure; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; MI, myocardial infarction; ACM, all-cause mortality; CVM, cardiovascular mortality; LVAD, left ventricular assistance device.

Table 1. Clinical Determinants for Higher Plasma Volume

Predictor category	Factors	Strauss/ Duarte	reference	Hakim	reference	I-131 labeled albumin	reference	Comments
Clinical parameters	older	○	(40,41,45,46)	○	(31,33,66)			
	female sex	○	(41,46)					
	higher body weight	○	(32)					
	lower body mass index			○	(28,31,66)			
	prior history of HF	○	(46)					patients with acute dyspnea and higher ePVS had more frequent prior HF hospitalizations (46)
Echo/ hemodynamics	ischemic heart disease	○	(40,41,44)	○	(33)			
	more severe congestion (NYHA, JVD and leg edema)	○	(40,41,46)	○	(28,31)			
	lower systolic BP	○	(46)	○	(28,31,33,66)	○	(15)	
	no use of RAS inhibitor			○	(31)			
	no use of beta-blocker					○	(15)	
	no use of aldosterone antagonist	○	(41)					
	use or higher dose of furosemide	○	(41,46)	○	(28)			association between higher ePVS and increased furosemide doses at discharge in patients with ADHF (41)
	higher TRV or PASP	○	(41)	○	(33)			association between higher ePVS and higher TRV in patients with CHF and preserved EF (33)
	higher TAPSE	○	(45)					
	higher E/e'	○	(67)	○	(31)			ePVS derived from Duarte formula was significantly associated with E/e', whereas ePVS derived from Hakim was not (67)
Biomarkers	higher PCWP					○	(15,58)	PCWP was significantly higher in hypervolemic subjects than in other subjects (p=0.01), was significantly correlated with measured blood volume (r=0.69, p 0.01), and was associated with an increased risk of death or urgent cardiac transplantation during a median follow-up of 719 days (1-year event rate 39% vs. 0%, p <0.01 by log-rank test) (15).
	higher BNP or NT-proBNP	○	(21,34,41,46,68)	○	(28,31,33)	○	(15)	correlation b/w change BNP and ePVS (r=0.28) (34); correlation b/w instantaneous ePVS and BNP (r=0.23 or 0.25) (21); correlation between baseline ePVS and BNP (r=0.21, p<0.01) (28)
	lower eGFR (or higher creatinine)	○	(32,41,44-46)	○	(33,66)			
	lower sodium			○	(31,33)			
	Lower albumin			○	(66)			



Table 2. Prognostic Value of Estimated Plasma Volume Status

Author/year	n	HF phenotype	ePVS timing	Age (yrs)	NYHA III/IV (%)	LVEF (%)	Follow-up	Outcome	Comments
<b>Strauss/Duarte (change or instantaneous)</b>									
Rossignol 2015 (39)	6,820	CHF with HF+EF	Change from BS to follow-up visit (within 1 yr)	67	36	33	3.9 yrs (median)	ACM, CVM	PVS change>0 was associated with a higher incidence of outcomes
Rossignol 2011 (34)	6,080	HF+EF and post-MI	Change from BS to IM	64	—	33	16 months (median)	ACM, CVM or HF hospitalization etc	decreased ePVS was associated with 11 % to 19% to better outcomes
Duarte 2015 (21)	4,957	HF+EF and post-MI	BS, 1 mo. and change from BS to 1 mo. Admission, discharge and change from admission to discharge	65	17	35	within 6 months	CVM or HF hospitalization	ePVS at 1 month is a better predictor than ePVS change
Kobayashi 2018 (41)	712	ADHF	Admission, discharge and change from admission to discharge	73	69	41	1 yr	ACM or HF hospitalization	higher ePVS at discharge had worse prognosis in three separate cohorts from three countries (Japan, France and Portugal)
Kobayashi 2019 (45)	117	ADHF	Admission	74	55	40	90 days	ACM or HF hospitalization	combination of higher ePVS and higher congestion score assessed by chest X-ray had 5-fold higher risk of outcome
Balderston 2018 (42)	218	ADHF	Discharge and 1st visit at outpatient clinic	68	—	34	90 days	ACM or HF hospitalization	ePVS at post-discharge had prognostic value of outcome
Hudson 2016 (43)	967	ADHF	Change from admission to discharge	74	93	—	from 4.9 to 8.7 yrs	ACM, ACM or HF hospitalization	highest ePVS tertile was associated with a higher risk of outcomes
Bilchick 2017 (44)	324	ADHF	Change from admission to discharge	56	—	—	within 6 months	ACM, cardiac transplantation or LVAD	increased ePVS was associated with a higher risk of outcomes
Massari 2019 (68)	436	184 AHF + 252 CHF	Admission	75	56	42	463 days (median)	ACM	ePVS>5.3dl/g had worse prognosis
Chouhied 2018 (69)	1,369	Acute dyspnea (including 288 AHF)	Admission	77	—	—	in-hospital	In-hospital mortality	higher ePVS tertiles were associated with higher incidence of in-hospital mortality
Huang 2019 (40)	449	CHF with HFpEF	BS and change from BS to date of event (or end of follow-up period)	66	42	69	10.7 yrs (median)	ACM or HF hospitalization	ePVS>5.5dl/g at baseline or an increase in ePVS was associated with a higher risk of outcomes
<b>Hakim</b>									
Ling HZ 2015 (28)	5,002	CHF with HF+EF	BS	61	36	27	716 days	ACM or HF re-hospitalization	ePVS> -4% was associated with a higher risk of primary outcome
Grodin 2019 (33)	3,414	CHF with HFpEF	BS	69	33	61		CVM, HF re-hospitalization or aborted cardiac arrest	higher ePVS was associated with a higher risk of HF hospitalization
Martens 2018 (25)	1,173	CHF	BS	70	58	32	33 months (mean)	ACM or HF re-hospitalization	ePVS>0% was associated with a higher risk of primary outcome
Yoshihisa 2018 (31)	1,115	AHF	Admission	67	16	50	1007 days (mean)	ACM, CVM, CVM or HF re-hospitalization	Highest ePVS tertile was associated with a higher risk of clinical outcomes
Okonko 2019 (66)	459	CHF with HF+EF	BS, weeks 4, 12 and 24	68	83	32	within 24 weeks	ACM or HF hospitalization	<ul style="list-style-type: none"> <li>a decrease in ePVS from BS to week 24 was associated with an increase in 6-min walk and improvement of NYHA class.</li> <li>ePVS&gt; -4% at baseline was an independent predictor of outcome.</li> </ul>

Tamaki 2019 (70)	384	ADHF	Admission, discharge and change from admission to discharge (Strauss formula)	76	28	39	743 days (median)	ACM or HF hospitalization	ePVS both at admission and discharge had worse prognosis
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### **5.3. Radiographic congestion score index and estimated plasma volume status**

#### **5.3.1. Chest X-ray Quantification of Admission Lung Congestion as a Prognostic Factor in Patients Admitted for Worsening Heart Failure from the ICALOR Cohort Study (7<sup>th</sup> paper)**

Pulmonary congestion evaluated from radiographic CSI and systemic congestion assessed by Duarte-derived ePVS are individually associated with the risk for cardiovascular outcomes. However, whether the combined assessment of these congestion markers is further helpful to predict post-discharge outcome in patients hospitalized for worsening HF has been poorly studied.

From the data of the ICALOR HF disease management program, we studied the association of radiographic CSI, Duarte-derived ePVS and their interplay with length of stay and the composite of death or HF re-hospitalization at 90 days in patients hospitalized for worsening HF.

In a total of 117 patients included in this study (mean age  $74 \pm 14$  years; males 57%; mean LVEF  $40 \pm 16\%$ ), patients were stratified according to the levels of CSI (median=2.20) and ePVS (median=5.38). Multivariable analysis showed that High CSI/high ePVS was associated with a 6-day longer length of stay [adjusted-OR (95%CI)=6.78 (1.82-29.79),  $p < 0.01$ ] and a 5-fold higher risk of primary outcome [adjusted-OR (95%CI)=5.13 (1.26-25.11)  $p = 0.03$ ] compared to low CSI/low ePVS, while other configurations (either isolated high CSI or high ePVS) yielded neutral associations. Furthermore, CSI and ePVS significantly improved reclassification on top of clinical prognostic model for the composite outcome (NRI=37.3%, 0.52-87.0,  $p = 0.046$ ).

Our results proposed that the combination of pulmonary and systemic congestion based on chest radiography and hemoglobin/hematocrit may identify a cluster of high-risk patients at short-term outcomes.



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# Chest X-ray quantification of admission lung congestion as a prognostic factor in patients admitted for worsening heart failure from the ICALOR cohort study

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## ABSTRACT

**Introduction:** Chest X-ray (CXR) widely used, but the prognostic value of congestion quantification using CXR remains uncertain. The main objective of the present study was to assess whether initial quantification of lung congestion evaluated by CXR [and its interplay with estimated plasma volume status (ePVS)] in patients with worsening heart failure (WHF) is associated with in-hospital and short-term clinical outcome.

**Methods:** We studied 117 patients hospitalized for WHF in the ICALOR HF disease management program. Pulmonary congestion was estimated using congestion score index (CSI, range 0 to 3) evaluated from 6 lung areas on CXR. Systemic congestion was assessed by ePVS. Logistic regression analysis was used to assess length of stay and the composite of all-cause death or HF re-hospitalization at 90 days.

**Results:** Patients were divided according to the median of admission CSI (median = 2.20) and ePVS (median = 5.38). Higher CSI was significantly associated with higher pulmonary arterial systolic pressure in multivariable models. Multivariable models showed patients with high CSI/high ePVS had a 6-day longer length of stay [OR (95% CI) = 6.78 (1.82–29.79),  $p < 0.01$ ] and 5-fold higher risk of 90-day composite outcome [OR (95% CI) = 5.13 (1.26–25.11)  $p = 0.03$ ] compared to patients with low CSI/low ePVS, while other configurations (either isolated high CSI or high ePVS) yielded neutral associations. Furthermore, CSI and ePVS significantly improved reclassification on top of clinical covariates for the composite outcome [Net reclassification index = 37.3% (0.52–87.0),  $p = 0.046$ ].

**Conclusion:** An admission assessment of pulmonary and systemic congestion in WHF patients using CSI and ePVS can identify a cluster of high-risk patients at short-term outcomes.

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## 1. Introduction

Worsening heart failure (WHF) is a frequent cause of hospitalization worldwide and is associated with a high short-term risk of HF re-hospitalization and death [1,2]. Most hospitalizations in patients with HF are the consequence of congestion [3]. Our group [3–5] and others [6–8] have demonstrated that residual congestion is strongly associated with outcome. The value of congestion quantification at admission is however less well documented and its evaluation remains difficult

[3,5] despite the advent of new tools including lung ultrasound [5,9]. Importantly, two major components of congestion should be distinguished: i) pulmonary congestion which is associated with increased left ventricular filling pressure [10] and pulmonary artery systolic pressure [11] and ii) systemic (peripheral) congestion which is associated with increased right atrial pressure [12]. However, the interplay between these two congestion components is yet to be determined.

Chest X-ray (CXR), which was until the 1980s the only test performed to help the diagnosis of WHF, is almost considered nowadays to be an obsolete tool and has been replaced in many indications. However, in addition to the diagnostic value recommended by the current guidelines [13], recent studies showed the prognostic values of quantification of congestion using CXR in patients with acute decompensated HF [14] and chronic HF [15]. In contrast, systemic and right sided congestion can be measured by a number of variables, although typically rely on the assessment of peripheral edema and inferior vena cava

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measurements, respectively [16]. Estimated plasma volume status (ePVS) has recently been proposed by our group as a useful marker of congestion [17,18] which, by essence, evaluates systemic congestion.

Our main objectives were to assess whether initial CXR quantification of lung congestion 1) is correlated with other methods of congestion assessment (i.e. clinical, biological and echocardiographic), 2) is associated with in-hospital and clinical outcomes at 90 days, and 3) interacts with ePVS (the latter assessing different dimensions of congestion) in terms of short-term outcomes.

## 2. Methods

### 2.1. Study population

Patients from the HF disease management program entitled Insuffisance Cardiaque en LORaine (ICALOR) [19,20] hospitalized in the Cardiology department, Nancy University Hospital, France from January 2010 to December 2013 were studied. Of 460 patients, 117 patients aged 18 or older were admitted for WHF, as defined by the ESC guidelines [21], which was not caused by acute myocardial infarction and had available laboratory findings at admission and usable echocardiographic data [performed at 1.0 (1st quartile 1.0–2nd quartile 2.0) days from admission] (Supplementary Fig. 1). The study was approved by the Commission nationale de l'informatique et des libertés (CNIL). Under French law, no formal Institutional Review Board approval is required for data extraction from patients' medical records.

### 2.2. Outcome

The primary outcome was the composite of all-cause mortality or re-hospitalization for HF at 90 days, which was prospectively collected in the database as part of the disease management surveillance program. Five patients (4.3%) were lost to follow-up.

### 2.3. Clinical profiles

Clinical data including demographic characteristics, comorbidities, physical examination and blood pressure at admission were prospectively collected and used in this analysis. The clinical classifications were defined by the absence or presence of signs of congestion and hypoperfusion as previously shown [13,22]. Indications of congestion included orthopnea, jugular venous distention, rales or peripheral edema, whereas compromised perfusion was assessed by the presence of a narrow proportional pulse pressure ((systolic - diastolic blood pressure)/systolic blood pressure (SBP)  $\leq 25\%$ ) [22].

### 2.4. Echocardiography

Echocardiographic examinations were performed using Vivid 7 or Vivid 9 (GE Vingmed Ultrasound, Horten, Norway) with a 2.5 MHz transducer and analyzed offline using dedicated automated software (Echo PAC PC version 110.1.0, GE Healthcare). All images were acquired at a frame rate of 50 to 70 frames/s. In the present study, all echocardiographic parameters were re-analyzed by two operators blinded to clinical parameters (SP and MB).

Left ventricular (LV) volumes were measured from 2D standard views and LV ejection fraction (LVEF) estimated by the biplane Simpson's method according to the recommendations of the American Society of Echocardiography [23]. LV volumes measures were indexed to body surface area.

Severity of mitral regurgitation was evaluated and inferior vena cava (IVC) and tricuspid annulus plane systolic excursion (TAPSE) were obtained as recommended [23]. Pulmonary arterial systolic pressure (PASP) was estimated using tricuspid velocity and inferior vena cava compliance and diameter [24]. Diastolic function was assessed from the pattern of mitral inflow and  $e'$  velocity measured by pulsed-wave Doppler and tissue Doppler imaging respectively, enabling the calculation of E/A and E/ $e'$  ratios [25,26].

### 2.5. Radiographic congestion score index

The severity of lung congestion was quantified using the previously published congestion score index (CSI) [14,15]. After dividing the lung field into six topographical areas, each area was evaluated as follows: Score 0, normal; Score 1, cephalization (superior area), perihilar haze or perivascular/peribronchial cuffing or Kerley's A lines (middle area), Kerley's B or C lines (inferior area); Score 2, interstitial or local or mild alveolar pulmonary edema; Score 3, intense alveolar pulmonary edema (Fig. 1).

To enhance the reproducibility of this scoring with regard to the degree of confluent edema, a part of the divided lung field which visually occupied a density similar to cardiac silhouette was regarded as an intense area whereas the field with weaker density was considered to be a mild area. Lung areas were not scored when they were occupied by more than one third pleural effusion (including vanishing tumor), atelectasis or cardiac silhouette. CSI was calculated as the sum of the scores in each area divided by the number of available areas.

CXR was analyzed by a single physician (MB), blinded from clinical data and outcome, with no previous training in congestion quantification on CXR prior to this study. After a short training using a 20-patient sample with a CXR congestion quantification expert

(MK), intra-observer and inter-observer (with MK) were tested on 30 randomly selected patients, blinded to clinical status and CXR timing (i.e. at admission, at discharge or intermediate). Intra-class correlation coefficients showed good reproducibility [0.86 (0.68–0.93) and 0.83 (0.62–0.93) for intra and inter-observer reproducibility, respectively].

### 2.6. Estimated plasma volume (ePVS) status

The ePVS was calculated from the Strauss-derived Duarte formula using hematocrit and hemoglobin values at admission as follows [17,27,28] and expressed in dl/g [29]:

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

### 2.7. Statistical methods

Continuous data are expressed as means  $\pm$  standard deviation or as medians (inter-quartile range) and categorical variables as frequencies (percentage). Patients with WHF were divided into four groups according to median CSI (2.20) and median ePVS (5.38) at admission; low CSI/low ePVS, low CSI/high ePVS, high CSI/low ePVS and high CSI/high ePVS. Group differences were assessed using Kruskal-Wallis tests for continuous variables and chi-square test for categorical variables, while unadjusted correlations were expressed using Pearson's correlation coefficients. Inter-observer and intra-observer agreements of CSI were assessed with the intraclass correlation coefficient (ICC).

Linear regression analyses and binary logistic regression analyses were performed to assess the associations between clinical, biological, echocardiographic variables and admission CSI. All variables with a  $p < 0.10$  by univariable analysis were used as candidate variables in the multivariable model.

Associations of CSI and ePVS with length of hospital stay and composite outcome were derived from univariable and multivariable logistic regression analyses. Adjusted variables were selected from clinically relevant variables including age, SBP, LVEF, blood urea nitrogen (BUN), estimated glomerular filtration rate (eGFR) [30] and brain natriuretic peptide (BNP) at admission. An interaction test was performed to determine whether there would be interaction between CSI and ePVS on the 90-day composite outcome. In addition, the increase in discriminative value with the addition of CSI and ePVS to predict the 90-day composite outcome on top of aforementioned clinical variables was evaluated using continuous net reclassification improvement (NRI) and integrated diagnostic improvement (IDI) as previously used by our group [4,31].

A  $p$ -value  $< 0.05$  was considered significant. No imputation was performed. Statistical analyses were performed using the R statistical software (3.4.0) including ICC and continuous NRI and IDI (ICC and survIDINRI packages).

## 3. Results

### 3.1. Baseline characteristics

The patient characteristics of the 117 included WHF patients are reported in Table 1. Most patients were male, had hypertension, and frequently had ( $>20\%$ ) diabetes, ischemic cardiac disease or chronic kidney disease. LVEF was  $<40\%$  in a majority of patients.

### 3.2. Association between admission CSI and other congestion variables

Mean CSI at admission was  $2.1 \pm 0.8$ . Admission CSI was moderately correlated with oxygen flow and poorly correlated with ePVS, body mass index and echocardiographic variables with regard to right-sided function: PASP and TAPSE (Supplementary Table 1). No other noteworthy correlations were identified, including with E/ $e'$  and IVC.

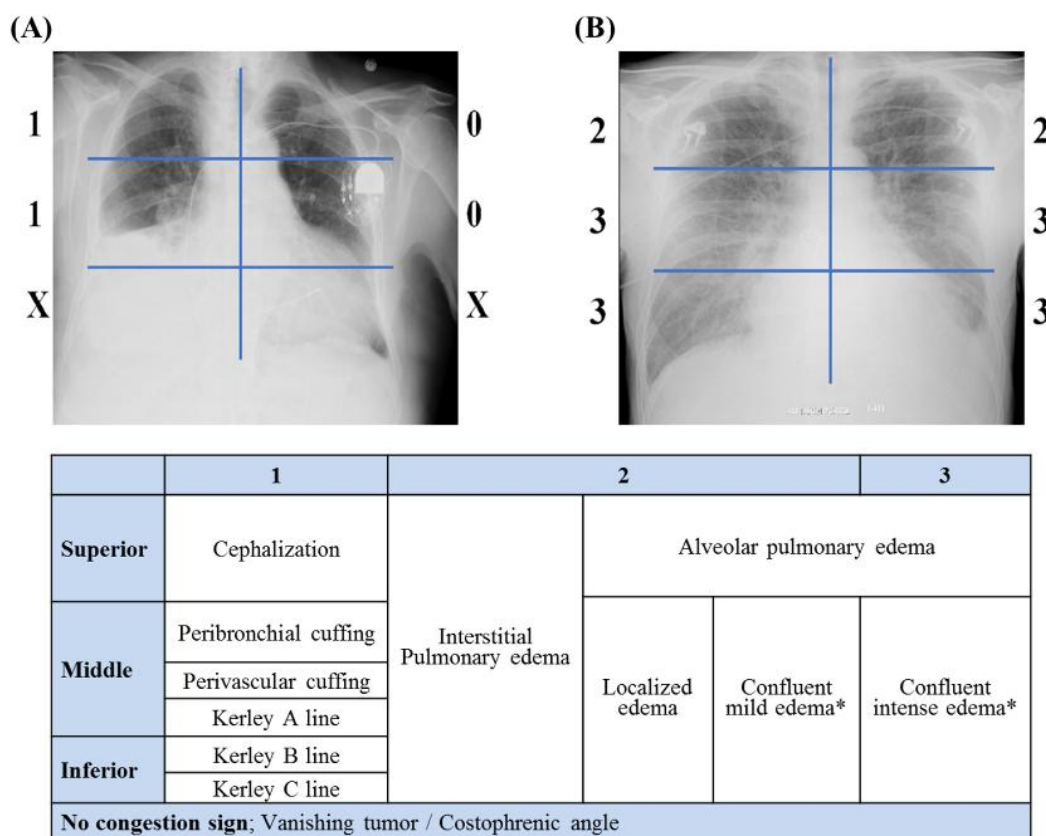
Univariable linear regression analysis revealed significant associations of higher ePVS, TAPSE and PASP with higher CSI (Table 2). There was no significant association with CSI in multivariable model.

In considering CSI to be a dichotomized variable (according to the median), higher eGFR and PASP remained significantly associated with higher CSI in multivariable logistic regression analysis (Table 2).

### 3.3. Interplay between admission CSI and ePVS

When considering subsets of patients divided according to CSI and ePVS medians (Table 1), patients with high CSI and low ePVS were younger than other subsets whereas TAPSE was higher in patients with high ePVS, with or without high CSI. Similarly, higher PASP was observed in patients with high ePVS, with or without high CSI, although





**Fig. 1.** Radiographic congestion scoring. A) Example of low CSI: CSI = 0.5. Cephalization and perihilar haze are visible in the right field. Inferior fields are not available due to pleural effusion. B) Example of high CSI: CSI =  $(2 + 3 + 3 + 2 + 3 + 3)/6 = 2.67$ . There is diffuse alveolar edema, appearing as mild in superior fields and intense in other fields. No available segment was defined in lung-field areas when occupied greater than one third by pleural effusion, atelectasis or cardiac silhouette. \*With regard to confluent edema, when the density in a part of divided lung field was visually similar to that of cardiac silhouette, the field was regarded as intense edema. CSI, congestive score index.

the highest values were observed in the high CSI/high ePVS group. BNP values were not significantly different across groups.

### 3.4. Survival analysis

The mean length of hospital stay was  $12.5 \pm 8.0$  days. At 90 days, 30 (25.4%) patients reached the primary outcome with 13 (11.0%) and 22 (18.6%) for all-cause death and/or HF re-hospitalization, respectively.

Multivariable cox models showed that high admission CSI was significantly associated with a >4-day longer length of stay and a 3-fold higher 90-day risk of the composite outcome (Supplementary Table 2). Association of ePVS with either length of stay or 90-day outcome yielded borderline significance *p*-values. The *p*-value for interaction between ePVS and CSI for the 90-day composite outcome was 0.05, leading to a further examination of the association between subtypes derived from both CSI and ePVS and clinical outcomes.

In univariable analyses, compared to patients with low CSI/low ePVS, patients with high CSI/high ePVS had a significantly longer length of stay [OR (95% CI) = 3.35 (1.12–10.01), *p* = 0.03] and higher risk of the composite outcome [OR (95% CI) = 4.36 (1.09–17.54), *p* = 0.04]. After adjusting for clinical confounders, patients with high CSI/high ePVS retained at higher risk of prolonging hospital stay and the incidence of the composite outcome (Fig. 2). In contrast, other configurations (either isolated high CSI or isolated high ePVS) had non-statistically significant associations with length of stay and 90-day composite outcome.

With regard to the composite outcome, the addition of admission CSI and ePVS on top of age, SBP, reduced LVEF, BUN, eGFR and BNP at admission improved significantly reclassification [NRI (95% CI) = 37.3 (0.5–87.0), *p* = 0.046 and IDI (95% CI) = 3.3 (0.4–14.9), *p* = 0.03].

## 4. Discussion

The main findings of this study are that 1) quantification of admission pulmonary congestion with CXR is significantly associated with PASP; 2) patients with concomitant high CSI and high ePVS have a marked increase in both length of stay and 90-day risk of death or HF re-hospitalization whereas patients with only one of these features appear to have a much less detrimental prognosis and; 3) the combined use of CSI and ePVS improves patient's risk-stratification beyond clinical profiles.

### 4.1. Is it worth assessing and how to assess pulmonary congestion in patients admitted for worsening heart failure?

It is well known that both the level and the distribution of congestion matter [3]. Many algorithms have been proposed to grade congestion [3] using clinical, biological and imaging variables. However, most algorithms propose a "qualitative" congestion assessment or require specific clinical training and/or expertise. The present work shows that a readily available semi-quantitative pulmonary congestion assessment using CXR is associated with PASP and short-term outcomes. Indeed, one of the few variables associated with CSI in multivariable models was PASP, suggesting that CSI can accurately assess pulmonary congestion which is the consequence of rising intravascular pressure in pulmonary arteries. In contrast, BNP was not significantly (and strongly) different across CSI/ePVS groups, probably because of its incapacity to identify the congestion profile of patients; All of the patients included in this analysis had worsening HF and consequently raised BNP [32,33]. In addition, we found that higher eGFR was also associated with increased CSI. Fluid re-distribution rather than accumulation,



Table 1

Patient characteristics for the whole cohort and according to CSI/ePVS subsets.

	Overall (N = 117)	Low CSI Low ePVS (N = 30)	Low CSI High ePVS (N = 33)	High CSI Low ePVS (N = 22)	High CSI High ePVS (N = 32)	p-Value
Age, yrs	73.7 ± 14.4	73.4 ± 14.7	75.2 ± 11.8	66.1 ± 16.4	77.2 ± 15.2	<b>0.045</b>
Male, n (%)	75 (56.8%)	18 (58.1%)	18 (54.5%)	15 (68.2%)	15 (46.9%)	0.48
Body mass index, kg/m <sup>2</sup>	26.4 ± 6.0	25.0 ± 6.2	25.5 ± 4.7	29.3 ± 5.4	26.4 ± 5.9	0.12
Heart failure etiology, n (%)						
Ischemic	42 (35.9%)	11 (37.9%)	10 (34.5%)	5 (25.0%)	16 (55.2%)	0.17
Valvular	28 (21.2%)	10 (32.3%)	5 (15.2%)	5 (22.7%)	4 (12.5%)	0.46
Medical history, n (%)						
Hypertension	89 (67.4%)	22 (71.0%)	20 (60.6%)	14 (63.6%)	23 (71.9%)	0.86
Diabetes mellitus	46 (34.8%)	10 (32.3%)	13 (39.4%)	4 (18.2%)	14 (43.8%)	0.36
COPD	28 (21.2%)	8 (25.8%)	5 (15.2%)	6 (27.3%)	7 (21.9%)	0.82
Chronic kidney disease	28 (21.2%)	5 (16.1%)	9 (27.3%)	2 (9.1%)	11 (34.4%)	0.21
Physical examinations						
NYHA class ≥ III, n (%)	65 (55.1%)	20 (64.5%)	16 (48.5%)	10 (45.5%)	17 (53.1%)	0.29
Rales, n (%)	83 (71.6%)	14 (58.3%)	22 (71.0%)	15 (71.4%)	22 (81.5%)	0.35
Systolic blood pressure, mm Hg	119.4 ± 20.2	118.5 ± 16.4	117.0 ± 25.8	114.0 ± 15.2	126.8 ± 21.3	0.12
Heart rate, bpm	74.6 ± 15.3	75.9 ± 16.4	71.4 ± 11.3	78.2 ± 19.0	72.9 ± 14.5	0.38
Physical profiles, n (%)						<b>0.04</b>
Warm/wet	99 (89.2%)	25 (86.2%)	29 (96.7%)	17 (77.3%)	28 (93.3%)	
Warm/dry	8 (7.2%)	4 (13.8%)	0 (0%)	2 (9.1%)	2 (6.7%)	
Cold/wet	4 (3.6%)	0 (0%)	1 (3.3%)	3 (13.6%)	0 (0%)	
Cold/dry	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Laboratory findings						
Sodium, mmol/l	139.6 ± 3.8	139.5 ± 2.7	140.1 ± 4.1	138.7 ± 3.7	139.6 ± 4.2	0.66
BUN, mg/dl	33.7 ± 16.5	36.4 ± 18.3	36.7 ± 16.6	29.1 ± 16.2	33.5 ± 16.4	0.41
eGFR, ml/min/1.73 m <sup>2</sup>	53.7 ± 22.1	49.3 ± 21.3	45.2 ± 17.1	64.3 ± 17.9	50.7 ± 21.9	<b>&lt;0.01</b>
BNP, pg/ml	900 (477–1477)	970 (392–1933)	1055 (586–1864)	561 (419–915)	1031 (589–1438)	0.09
ePVS, dl/g	5.4 ± 1.3	4.4 ± 0.6	6.3 ± 0.8	4.3 ± 0.6	6.6 ± 1.0	<b>&lt;0.01</b>
Echocardiography						
LVDVI, ml/m <sup>2</sup>	79.0 ± 34.0	80.2 ± 28.9	73.2 ± 29.6	75.6 ± 32.9	88.9 ± 45.8	0.49
LVEF, %	40.1 ± 16.0	36.3 ± 16.6	43.2 ± 17.3	38.4 ± 16.5	43.4 ± 15.4	0.24
LVEF < 40%, n (%)	68 (51.5%)	18 (58.1%)	16 (48.5%)	12 (54.5%)	13 (40.6%)	0.54
TMF E/A ratio	2.0 ± 1.2	2.3 ± 1.0	2.2 ± 1.4	1.4 ± 1.1	1.9 ± 0.9	0.21
TMF E deceleration time, ms	174.9 ± 66.9	180.1 ± 64.0	170.6 ± 69.4	175.8 ± 95.2	174.0 ± 54.6	0.96
E/e' ratio	13.6 ± 5.8	11.9 ± 5.1	14.4 ± 6.2	14.0 ± 6.7	15.1 ± 6.2	0.26
TAPSE, cm	15.5 ± 4.6	13.6 ± 4.5	16.2 ± 4.8	14.2 ± 3.3	17.6 ± 4.3	<b>&lt;0.01</b>
IVC, mm	22.1 ± 6.2	22.4 ± 7.4	23.8 ± 5.0	23.9 ± 6.0	20.1 ± 4.7	0.13
PASP, mm Hg	37.3 ± 12.9	33.3 ± 12.4	36.5 ± 12.8	33.7 ± 9.3	43.3 ± 13.6	<b>0.02</b>
MR grade, 0/1/2/3/4	34/32/38/10/3	12/8/6/3/1	10/10/10/2/1	6/7/8/0/1	6/7/14/5/0	0.51
Congestion score index	2.1 ± 0.8	1.5 ± 0.5	1.5 ± 0.7	2.8 ± 0.2	2.8 ± 0.2	<b>&lt;0.01</b>
Medication at discharge, n (%)						
ACEi or ARB	96 (83.5%)	23 (76.7%)	25 (75.8%)	22 (100%)	26 (86.7%)	0.07
Beta-blocker	93 (80.2%)	22 (71.0%)	29 (87.9%)	15 (68.2%)	27 (90.0%)	0.08
MRA	19 (16.4%)	6 (19.4%)	4 (12.1%)	6 (27.3%)	3 (10.0%)	0.33
Loop diuretics	103 (88.8%)	25 (80.6%)	31 (93.9%)	19 (86.4%)	28 (93.3%)	0.30

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

CSI, congestion score index; ePVS, estimated plasma volume; COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide; LVDVI, left ventricular diastolic volume index; LVEF, left ventricular ejection fraction; TMF, transmitral flow; E/A ratio, ratio of peak early and late diastolic velocities; E/e', ratio of early mitral inflow velocity and mitral annular early diastolic velocity; TAPSE, tricuspid annular plane systolic excursion; IVC, inferior vena cava; PASP, pulmonary artery systolic pressure; MR, mitral regurgitation; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist.

Values in bold style represent significant difference ( $p < 0.05$ ).

which is an important contributor of worsening renal function [34], may lead to pulmonary congestion [35].

We previously showed that lung congestion quantified by lung ultrasound imaging (LUS) within days of admission [5] or at discharge [4] was associated with short-term outcome following discharge. In the present study, we demonstrated that lung congestion assessed by CSI is significantly associated with longer length of stay as well as with higher incidence of primary outcome when used in conjunction with ePVS. These findings are congruent with the results of Melenovsky et al. [15] who demonstrated that CSI was associated with pulmonary vascular disease, right ventricular overload/dysfunction and increased mortality in chronic HF. We believe the present results may encourage to perform CXR more systematically in patients admitted for suspected WHF.

#### 4.2. Interplay between CSI and ePVS

In the current cohort, we identified that patients with both increased CSI and ePVS had a marked increase in the risk of 90-day HF readmission

or all-cause death. In contrast, patients with only one abnormal congestion component (*i.e.* only pulmonary congestion assessed using CXR or only systemic congestion assessed with ePVS) had a less stringent increased risk of clinical events. Moreover, addition of admission CSI and ePVS yielded a significant improvement on top of traditional clinical covariates at admission (*e.g.* SBP, LVEF, eGFR and BNP). This suggests that patients with both systemic and pulmonary congestion are at the utmost risk of events. Isolated pulmonary congestion, especially in the setting of hypertension, is often perceived as a less severe form of WHF although has not been extensively studied [36–41]. Likewise, the clinical prognosis of patients with isolated systemic/intravascular congestion has yet to be comprehensively studied. The novelty of the present study lines in assessing the interplay between these two components of congestion and identifying that the specific phenotype of generalized congestion is associated with a markedly increased risk of event and could represent an integrative marker of more severe HF.

Residual congestion is typically the focus of risk-stratifying tools [16,42]. However, there is a likely link between admission and discharge



Table 2

Association of admission radiographic congestion score index with clinical, echocardiographic and biological congestive variables.

Linear regression analysis	Univariable analysis			Multivariable analysis		
	$\beta$	95% CI	p-Value	$\beta$	95% CI	p-Value
Age, yrs (per 5 yrs)	0.01	−0.05–0.06	0.80			
Male	−0.02	−0.33–0.28	0.88			
NYHA class	0.06	−0.23–0.35	0.67			
Systolic BP, mm Hg (per 10 mm Hg)	0.06	−0.01–0.14	0.10	0.03	−0.07–0.13	0.59
Serum sodium, mEq/l	0.004	−0.04–0.05	0.86			
BUN, mg/dl (per 5 mg/dl)	−0.03	−0.07–0.02	0.27			
eGFR, ml/min/1.73 m <sup>2</sup> (per 5 ml/min/1.73 m <sup>2</sup> )	0.04	0.00–0.07	0.052	0.05	−0.004–0.10	0.07
BNP, pg/ml (per 100 pg/ml)	−0.01	−0.02–0.01	0.28			
ePVS, dl/g	0.12	0.002–0.23	<b>0.047</b>	0.06	−0.13–0.25	0.53
LVEF, % (per 5%)	0.01	−0.04–0.06	0.66			
MR ≥ moderate	−0.27	−0.74–0.21	0.28			
E/e'	0.01	−0.02–0.03	0.66			
TAPSE, cm	0.04	0.01–0.08	<b>0.02</b>	0.01	−0.05–0.07	0.73
PASP, mm Hg (per 10 mm Hg)	0.14	0.01–0.27	<b>0.03</b>	0.05	−0.15–0.25	0.64
IVC, mm	−0.03	−0.06–0.003	0.08	−0.02	−0.05–0.02	0.37
Logistic regression analysis	Univariable analysis			Multivariable analysis		
	OR	95% CI	p-Value	OR	95% CI	p-Value
Age ≥ 70 yrs	1.28	0.60–2.76	0.53			
Male	1.00	0.48–2.08	0.99			
NYHA class III or IV	0.44	0.08–1.94	0.29			
Systolic BP ≥ 140 mm Hg	0.97	0.29–3.13	0.96			
Serum sodium ≤ 135 mEq/l	0.99	0.31–3.27	0.98			
BUN ≥ 20 mg/dl	0.87	0.29–2.69	0.81			
eGFR ≤ 45 ml/min/1.73 m <sup>2</sup>	0.40	0.19–0.84	<b>0.02</b>	0.40	0.17–0.93	<b>0.04</b>
BNP ≥ 200 pg/ml	1.47	0.53–4.32	0.47			
ePVS ≥ (median)	1.32	0.64–2.77	0.46			
LVEF ≤ 40%	0.74	0.35–1.52	0.41			
MR ≥ moderate	1.00	0.30–3.21	0.99			
E/e' ≥ 15	1.04	0.45–2.37	0.93			
TAPSE ≥ 15 cm	0.62	0.27–1.38	0.24			
PASP ≥ 40 mm Hg	2.80	1.19–6.79	<b>0.02</b>	2.72	1.13–6.74	<b>0.03</b>
IVC ≥ 20 mm	0.68	0.27–1.69	0.40			

Logistic regression analysis was performed for dichotomized variables determined by CSI of 2.20 (median).

CSI, congestion score index; NYHA, New York Heart Association; BP, blood pressure; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; TMF, transmitral flow; TAPSE, tricuspid annular plane systolic excursion; PASP, pulmonary artery systolic pressure; IVC, inferior vena cava.

Values in bold style represent significant difference ( $p < 0.05$ ).

congestion since patients with the most overt admission congestion are the most likely to experience discharge congestion. Discharge CXR was only available in a minority of patients in our study and consequently we were unable to measure the in-hospital changes in congestion profiles. We can hypothesize that discharge CSI could have been a more relevant prognostic marker although this particular aspect would need to be studied in future analyses.

#### 4.3. Pathophysiology of pulmonary congestion: PASP and RV function

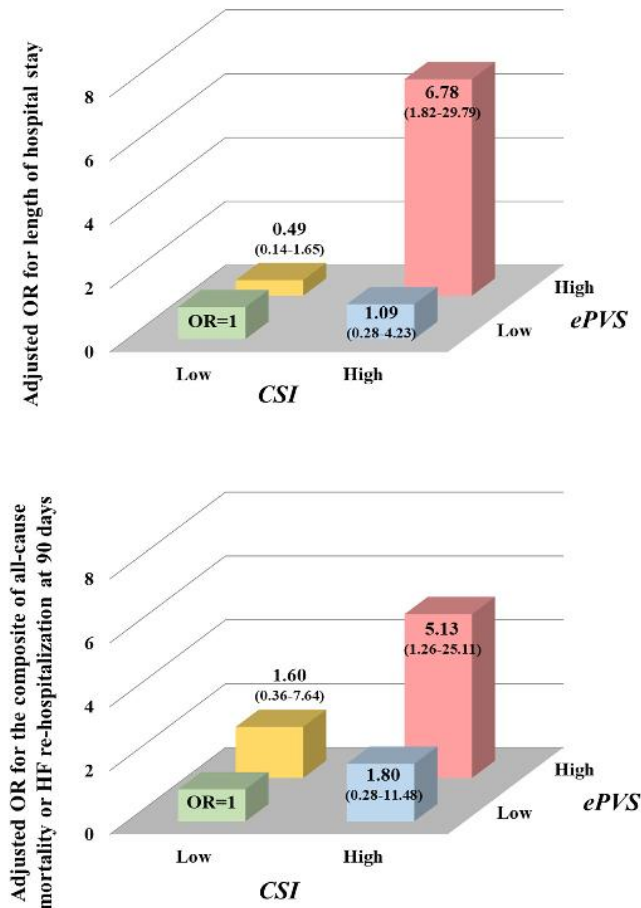
Our results target some pathophysiological features that have not been often previously addressed. McIver et al. advocated the notion that RV function was volume dependent and that an increase in RV function may actually contribute to pulmonary congestion development [43]. In contrast, other authors rather promote the concept of increased LV filling pressure that eventually increase pulmonary congestion, overload the RV and result in decreased RV function [44]. In the present study, higher TAPSE was associated overall with a higher CSI level (*i.e.* pulmonary congestion) as highlighted in the univariable linear regression analysis which would favor the first aforementioned postulate. However, when dividing the cohort according to both CSI and ePVS, an intriguing association pattern was observed, notably that patients with high CSI but low ePVS had a lower TAPSE than patients with high ePVS regardless of CSI status. This could be the result of an increase in RV contractility following increased RV volumes as recently suggested by McIver [43].

We identified the association between PASP and CSI in the multivariable model. Nevertheless, this association could be perceived as weak since patients with both high ePVS and high CSI had approximately 10 mm Hg higher in a mean PASP compared to patients with low ePVS and low CSI. However, it should be emphasized that equivocal associations of pulmonary congestion and elevated wedge pressure have been reported in the past [11,45]. In addition, the reported association between LUS with invasive wedge pressure [11] appeared of similar magnitude to that observed in the present study.

#### 4.4. Clinical perspectives

Patients admitted for WHF have a high-risk of death and/or re-hospitalization either during or after their index hospitalization. A better risk stratification is likely to help tailoring the monitoring of identified high-risk patients. Our results suggest that the combined assessment of admission pulmonary congestion using CSI and systemic congestion using ePVS has an important prognostic value. This simple categorization of patients, performed at admission, does not require highly specialized exams while conversely providing relevant information regarding PASP. This simple evaluation method could hence be very useful in hospitals or units where an expert evaluation by a cardiologist is not easily available 24 h a day, 7 days a week: We believe that looking carefully at CXR to quantify congestion remains a viable tool in a number of clinical settings. In addition, an automated evaluation of congestion using CXR could ultimately be implemented in radiographic information software, which would greatly promote the utilization of CSI to quantify





**Fig. 2.** Odd ratio for length of hospital stay and composite of all-cause mortality or heart failure re-hospitalization at 90 days. Multivariable logistic regression models were adjusted for age, systolic blood pressure, left ventricular ejection fraction, blood urea nitrogen, estimated glomerular filtration rate and brain natriuretic peptide at admission. OR, odd ratio; LOS, length of hospital stay; CSI, congestion score index; ePVS, estimated plasma volume status.

congestion. As a consequence, large-scale multicenter studies should explore whether this simple assessment of CXR and hemoglobin/hematocrit could help identifying risk-stratification of patients with worsening HF admitting to the hospitals.

#### 4.5. Limitations

This is a single-center cohort study derived from a disease management program: thus, residual confounding may ultimately exist and generalizability is not certain. In addition, some patients were lost to follow-up (approximately 5%) and patients were including in this management program at hospital discharge, which prevented the analysis of in-hospital mortality. However, patients included in this cohort were followed within a HF disease management program, which ensure some standardization in patients' care and follow-up. In addition, the moderate size of our cohort only yielded moderate statistical power and patients in each CSI/ePVS subgroups were small, which made difficult the use of survival analysis (including Kaplan-Meier curves). Moreover, given the size of the cohort, only median were considered as cut-offs; Other cutoff points might have resulted in different associations. Moreover, patients with only one abnormal congestion component (*i.e.* isolated increased CSI or ePVS) could have significantly increased risk of events in larger datasets. Certain important variables, *e.g.* factors precipitating to WHF and diastolic dysfunction grade (because of the absence of available LA volume), were not available and consequently

could not be adjusted for. We had no direct measurement of plasma volume; Recent data suggest that the association of plasma volume measurements and estimation can differ [46].

CSI was measured retrospectively; 50 had no CXR at admission as part of routine care. Nevertheless, all analyses were performed blinded from other parameters and outcomes. The CSI method also has some intrinsic limitations: it is a semi-quantitative tool which necessarily features some subjectivity. Despite our efforts in CSI quantification, scoring CSI was at times challenging, especially when CXR was of average quality or when patients had acute or chronic pulmonary comorbidities. These difficulties reflect real-life circumstances, which may alleviate the applicability of our results. Lastly, it is important to emphasize that CSI quantification requires a short training period of about 2–3 h before accurate scoring of congestion can be achieved and in a reproducible manner. CSI scoring thus requires more effort than routine CXR reading in an acute setting.

#### 5. Conclusion

A combined assessment of pulmonary and systemic congestion at admission using CSI and ePVS can help in identifying a cluster of patients who have a higher risk of short-term outcomes. These patients would demand particular monitoring during decongestion therapy as well as closer surveillance in the post-discharge term. CXR should hence still be systematically performed in patients admitted for WHF.

#### Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcard.2019.06.062>.

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## 6. Discussion of the thesis

In this thesis, we showed that quantification of radiographic pulmonary congestion has a good diagnostic value for AHF in patients with dyspnea in the emergency department and good prognostic value in patients hospitalized for worsening HF. In addition, we showed that PV estimated from hemoglobin and hematocrit is associated with left-sided congestion markers (i.e., natriuretic peptide, E/e' and LV filling pressure) and have a good prognosis value in different settings of HF (acutely decompensated HF and HFpEF). Furthermore, the combination of CSI and ePVS was associated with outcomes in patients admitted for worsening HF. All our papers strengthened the paramount importance of these readily available congestion variable in clinical routine. Nonetheless, these studies had several limitations.

### 6.1. Limitations

All reports on CSI/ePVS shown herein consist of observational data, in which we cannot exclude several potential biases. The PARADISE cohort in which we explored diagnostic value of CSI, despite being large, is of single-center and retrospective nature. Other cohorts from Tokyo, Nancy and Porto are of moderate size and consequently have limited statistical power. Previous prospective randomized clinical trials using congestion markers such as NPs and invasive hemodynamic monitoring failed to show their potential benefits compared with standard care alone<sup>136, 147-149</sup>. However, intriguingly, three recent randomized trials comparing LUS-based management plus standard of care vs standard of care alone in ambulatory patients with HF or patients discharged from HF hospitalization<sup>169-171</sup> showed a significant protective effect of LUS-based management. Indeed, the results concordantly showed LUS-guided management reduced the risks of urgent HF visits and/or HF (re) hospitalization as well as decreased BNP levels and improved quality of life. Following these promising success of small LUS trial, adequately powered randomized prospective study are warranted to investigate the diagnostic and prognostic performances of CSI and ePVS.

In our cohorts, only a few congestion markers were available. However, we should emphasize that each component of congestion profiles (i.e., intravascular congestion, pulmonary congestion and

systemic congestion) may interact with one another. We were not able to evaluate the interplay of all congestion variables (p.e. LUS and echocardiography) during this thesis as these data were not available in the datasets. This lack of data precludes positioning our findings within the overall scope of congestion evaluation in HF.

## 6.2. Strengths

The PARADISE cohort, which we extensively used during this PhD, have a large size and a relatively homogenous management and adjudicated AHF diagnosis (which is currently the gold standard of diagnostic studies). In addition, we could use external data to validate some of our findings (including the diagnostic value of CSI). Importantly, in the PARADISE cohort, the hospital's electronic charts (Resurgences®) were systematically reviewed by investigators to search for the records of all patients admitted for acute dyspnea in the emergency department; therefore, selection bias likely did not occur. We consequently believe, despite its single-center data, that the PARADISE cohort already have many assets.

We were able to assess the prognostic value of CSI in three independent cohorts arising from very different settings from cardiology departments in Tokyo and Nancy and an emergency department in Porto. Despite these heterogenous settings, we were able to show concordant prognostic value of CSI, which considerably strengthen the clinical importance of CSI in the HF management on a global scale. We believe that these cohorts, even if of moderate size, synergize efficiently and ensure important external validity of our findings.

Changes in PV estimated from hemoglobin and hematocrit has been (scarcely) used in the five decades following its validation with a radiolabeled gold standard method. Our team is promoting the concept of ePVS being an instantaneous measurement of plasma volume, a measurement that has been showed to have important prognostic value in patients with HF following myocardial infarction<sup>81</sup>. Based on the data accumulated during this PhD, we now have evidence for its important clinical value. Of note we expanded the knowledge regarding its prognostic value in very different settings of HF (from acute

HF to HFpEF). The important concordance between our studies, performed in various setting, is probably the strongest strength of our PhD.

To the best of our knowledge, our work regarding the value of the combined assessment of CSI and ePVS is novel and, to some extent, pave the way for more mechanistic studies, exploring different components of congestion (left- and right-sided congestion). The diagram we introduced in the first part of this thesis, providing a 3D evaluation of congestion, is yet to implement in the literature and a dedicated evaluation of its value is to be performed.

## 7. Perspectives

Despite progressively improved diagnostic and prognostic performances of congestion measurements, in current clinical practice guidelines, no evaluation tool for congestion is recommended as a Class I, Level of Evidence: A. This lack of standardized assessment may be explained by the proposed complex underlying profiles of congestion (intravascular, systemic and pulmonary congestion). Therefore, assessing patient profile using one single congestion maker may be conceptually challenging. In particular, natriuretic peptides are a widely available and biologically plausible marker to express the severity of congestion and is very often used in clinical practice. These parameters, however, are considered an intravascular congestion marker and may reflect left-sided congestion rather than right-sided congestion. Right-sided congestion is nonetheless central for risk-stratification and possibly for therapeutic management. Therefore, the integration of all source of information (including ePVS and CSI which we focused on during this PhD) related to congestion may provide better insights and opportunities for personalized management of congestion.

Following the results gathered during the course of this PhD, the following points appear of central interest to further favor the incorporation of ePVS and CSI in clinical practice.

1. The first point is related to the nature of available data. The diagnostic and prognostic performance of the integration of the several components of congestion profiles should be assessed in large-size multicenter retrospective and prospective studies to convince the HF community that congestion evaluation using new imaging and biological evaluation tools are useful. This step appears mandatory to promote a multiparameter “integrated” approach. To this purpose, the multi-center version of the PARADISE study and the (Pathway and Urgent care of dyspneic Patient at the emergency department in Lorraine district) PURPLE study will be used, along with the Acute Heart Failure -COngestion Repeated Evaluation (AHF-CORE).
2. The second point is related to the best strategy to be used to identify the most relevant congestion variables in HF as well as the best strategy to favor the use of congestion evaluation tools in routine practice. We believe that, to be used on a global scale, integrated congestion scoring has to be generated from an AI based algorithm. This approach would favor the personalization of algorithm

to patients' background, including comorbidities in a more flexible way than “classical” statistical approaches.

3. The third point, given the complex nature of AI based algorithms, is the necessity of a subsequent embedding in the electronic medical records of the algorithms, providing real-time useful personalized information in clinical practice.

### **7.1 Cohorts to be used within the integration process**

To achieve our goal, we will need to use data permitting to evaluate both the diagnostic and prognostic value of our approach to congestion. The PARADISE and PURPLE cohort will give access to patients with and without acute HF, admitted for acute dyspnea in the ED. These cohorts will be used both for diagnostic (in the entire cohorts) and prognostic (in the subset of acute HF patients) purposes. For prognostic purposes, we will also use the AHF-CORE cohort and a pooled patient dataset from several European countries (with available lung ultrasound data in all patients).

Regarding the nature of available data,

- clinical and biological data will be available in all cohorts,
- radiographic data will be available in the PARADISE and PURPLE studies,
- echocardiographic data will be available in all patients from the AHF-CORE cohort, a majority of patients from the European pooled patient dataset and some patients in the updated version of the PARADISE and PURPLE studies.
- lung ultrasound data will be available in all patients from the AHF-CORE cohort and European pooled patient dataset

These cohorts will consequently enable us to cover both diagnostic and prognostic aspects using a range of congestion variables of various natures.



### 7.1.1 The Pathway of dyspneic patients in Emergency (PARADISE)

The PARADISE cohort is a retrospective cohort study including patients aged  $\geq 18$  years admitted in the emergency department of the Nancy University Hospital (France) between January 1, 2015 and December 31, 2015<sup>168, 179</sup>. Investigators systematically reviewed the hospital's electronic charts (Resurgences<sup>®</sup>), and identified all patients admitted for acute dyspnea. All patients with signs or symptoms of dyspnea, or requiring oxygen treatment during their emergency department stay were included. Patients with shock or cardiac arrest were excluded. Demographic parameters, medical history, physical examination, laboratory findings and treatment received in the ED were retrieved from the patients' electronic records. The primary outcome was in-hospital mortality. The PARADISE cohort was approved by the Commission d'Informatique et Libertés (CIL) (Number R2016-08) and registered on "clinicaltrials.gov" (NCT02800122).

We are currently extending this cohort to have access to data on a 10-year period in a multicenter setting. This would gather the data from more than 80 000 patients. To do so, we validated an identification algorithm that can automatically spot patients meeting the inclusion criteria of the initial PARADISE cohort. In addition, the CIC-P team has been working over the past 3 years on text mining procedures able to assess the presence/absence of comorbidities, symptoms and clinical signs from the electronic records. Promising results are emerging following this important work. This "expanded" version of the PARADISE cohort will importantly improve the statistical power and expand the possible hypothesis that can be tested on this cohort. In addition, in the version we worked on of the dataset from the PARADISE cohort, echocardiographic data was not available, although these parameters are known important factors for the diagnosis and prognosis of HF. Our updated dataset will incorporate echocardiographic parameters in patients in whom an echocardiography was performed during the hospital stay, and consequently likely provide better modeling.

Importantly, the CIC-P has already retrieved the 1-year mortality of patients from the 2015 PARADISE cohort, and as already exported the vital status of 8 000 patients from the "extended" cohort. This additional data will obviously be used in prognostic analysis.

### **7.1.2 Pathway and Urgent caRe of Dyspneic Patient at the Emergency Department in Lorraine District (PURPLE)**

The PURPLE cohort is an ongoing observational prospective multicenter study of patients admitted for acute dyspnea in an emergency department of the participating centers in the Lorraine district since November 2017. The main objective is to assess clinical outcomes of this population according to the cause of acute dyspnea as well as determine the predictors of these outcomes, both overall and according to each acute dyspnea cause. As for the PARADISE cohort, all patients aged  $\geq 18$  years with acute dyspnea, or requiring oxygen treatment during their emergency department stay are included and patients with shock or cardiac arrest were excluded. Demographic parameters, medical history, initial treatments, physical examination and laboratory findings were prospectively assessed. The primary outcome is in-hospital mortality. The secondary outcomes are all-cause mortality within 1 year or changes during hospital index in demographic, clinical, treatment, biological parameters. All patients recruited in PURPLE study were given written informed non-opposition documents to verify their willingness to participate in the study (ClinicalTrials.gov Identifier: NCT03194243).

This diversity of data nature, mixing imaging and biological data, in large multi-center datasets from the PARADISE and PURPLE cohorts, will permit to provide a true integration of congestion variables for both diagnostic and prognostic analyses. In addition, the multiplicity of centers will provide opportunities to implement derivation/validation strategies.

### **7.1.3 Acute Heart Failure -COngestion Repeated Evaluation (AHF-CORE)**

The AHF-CORE study is an ongoing prospective multicenter regional cohort targeting to include 80 patients hospitalized for acute HF and assess numerous congestion markers (clinical, biological and ultrasound) on admission and discharge. Patients aged  $\geq 60$  years hospitalized for left-sided or global AHF due to exacerbation of CHF within 72 hours of admission to hospital are eligible for enrollment. The main exclusion criteria is comorbidity reducing life expectancy to  $\leq 3$  months, diagnosis of HF made less than 3 months prior to inclusion, exacerbation of HF attributed to acute coronary syndrome, and estimated glomerular filtration rate  $< 15$  ml/min/m<sup>2</sup> at baseline, history of

pulmonary lobectomy or pneumonectomy, severe pulmonary or pleural disease preventing the reliable acquisition of pulmonary ultrasound images. All patients recruited in AHF-CORE study give written informed consent to participate in the study (ClinicalTrials.gov Identifier: NCT03327532).

Patients undergo a complete evaluation of congestion at inclusion and discharge, including echocardiography, lung ultrasound, renal venous doppler and jugular vein evaluation. In addition a complete biological is performed.

The primary outcome is the composite of all-cause death and/or HF re-hospitalization within 3 months. The second outcomes are changes from admission to discharge in clinical (i.e. rales, JVD, edema, fatigue, dyspnea, orthopnea), biological (i.e. BNP, hemoglobin and hematocrit) and ultrasound congestion markers (i.e., B lines, pleural effusion, E/e', tricuspid regurgitation velocity, jugular diameter and renal venous blood flow pattern).

This study, given the extensive congestion evaluation performed both at admission and discharge will permit to determine which are the most important congestion variable, namely the most associated with subsequent outcome in patients hospitalized for worsening HF. The AHF-CORE cohort will permit the integration of congestion measurements in a cardiology environment, with a special emphasis on imaging of congestion, whereas the PARADISE and PURPLE cohort will have less detailed information and will give insights for the emergency department management (rather than cardiology ward as in the AHF-CORE study). The focus of the AHF-CORE study will be prognosis analyses.

#### **7.1.4 Pooled patient data from the European countries (Nancy, Perugia, Pisa and Siena cohorts)**

We recently performed a patient-level meta-analysis combining datasets from four independent international cohort studies of patients admitted for worsening HF.

- The Nancy cohort study <sup>180</sup>; The Nancy cohort study included 50 patients who were hospitalized for ADHF at the Institut Lorrain du Coeur et des Vaisseaux in France from April 2014 to August

2015. Physical examination and laboratory data were assessed on admission, and LUS was performed during the first 3 days following admission.

- The Perugia cohort study <sup>120</sup>; The Perugia cohort study included 60 patients who were hospitalized for ADHF at the Division of Cardiologia e Fisiopatologia Cardiovascolare in Perugia from April 2014 to October 2014. Physical examination, laboratory data, and LUS were assessed at discharge.
- The Pisa cohort study <sup>121</sup>; The Pisa cohort study included 268 patients who were hospitalized for ADHF in the Cardiology Department in Pisa from October 2004 to October 2008. Physical examination, laboratory data and LUS were assessed on admission.
- The Siena cohort study <sup>181</sup>; The Siena cohort study included 162 patients with ADHF in sinus rhythm. All patients underwent echocardiography within 12 hours from admission. Clinical, biological and LUS data were assessed both on admission, and at discharge.

Main exclusion criteria in the merged population were; (i) poor acoustic window, (ii) pulmonary fibrosis, previous pneumectomy or lobectomy, pulmonary cancer or metastases, breast prosthesis; (iii) acute myocardial infarction, (iv) cardiogenic shock and (v) severe sepsis.

The primary outcome was the composite of all-cause mortality and/or HF re-hospitalization. All patients were systematically followed after discharge in each institution. The median follow-up periods of each cohort study were 90.0 [64.3–71.3] days in the Nancy study, 90.0 [61.0–90.0] days in the Perugia study, 416.0 [233.0–923.0] days in the Pisa study, and 180.0 [98.0–180.0] days in the Siena study.

Each cohort study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Committees.

This meta-analysis is valuable as it gathers LUS Data along with echocardiography data in a sizeable number of patients. Again, congestion variable integration will be efficiently performed in this cohort given the variety of data nature available, with a special emphasis on imaging variables. This dataset will be used in prognostic analyses.



## 7.2. Integration of all evaluation tools of congestion using machine learning approach

### 7.2.1 Outline of the machine learning approach

A number of congestion variables exist, covering different dimensions of congestion as proposed in the first part of this thesis (**Figure 5**). There is an overlap of some variables with one another. In addition, it is very probable that some variables interact between each other, p.e. that one congestion variable is relevant in patients with determined clinical characteristics and not in other patients. At last, multicollinearity can be an issue as some variables do investigate the same “dimension” of congestion.

Usual statistical methods will usually have important difficulties to unravel this complexity. First, multicollinearity is an important issue in multivariable modelling. In addition, interaction is a concept that is difficult to tackle in the setting of model building given the low statistical power of interaction tests. At last, statistical methods have to assess associations with predefined relevant outcome and cannot identify profiles or patterns, which would nonetheless be useful in our understanding of congestion, as highlighted in our introduction to our thesis.

To tackle the high dimensional and possibly nonlinear effects of congestion variables, which can represent true “big data” in the setting of integrated multiple congestion markers evaluation, we propose to use machine learning (ML). ML can provide better information over conventional statistical techniques as it can learn rules and identify patterns progressively from data, without any a priori assumptions. This technique has been used in cardiovascular medicine to find novel phenotyping of existing diseases<sup>182, 183</sup>, improve the quality of healthcare service<sup>184</sup> and predict mortality and cardiovascular events<sup>185, 186</sup>. As for other high dimensional information regarding biomedical science such as proteomics, metabolomics, lipidomics and genetics, the integration of all clinical, biological and imaging congestion data may provide new discoveries.

ML is categorized into supervised and unsupervised learning approaches (**Table 2**). Supervised ML is applied for classification and regression models, using labeled dataset to predict known outcomes. This technique has been successfully applied to build the models for the diagnosis, prediction and treatment of cardiovascular disease as well as cardiovascular imaging analysis. A recent intriguing paper in the TOPCAT trial compared five methods (i.e. machine learning and conventional

statistical techniques) to determine the best prediction model for assessing risks of cardiovascular outcomes in patients with HFpEF<sup>185</sup>. A total of 86 clinical variables were included in these models, and their data showed that random forest (a supervised ML method) was the best performing model.

Unsupervised ML is used to identify novel mechanisms, phenotypes or genotypes from hidden patterns presented in the dataset. Cluster analysis is classified as an unsupervised ML technique which determines the hidden patterns of unlabeled data to create homogenous groups without a priori knowledge and assumption. Data are grouped into categories (cluster group) based on some measures of similarity or distance. In cardiovascular research, cluster analysis is used to characterize the homogenous patient profiles, for example, patients with HFpEF<sup>183</sup> or those with cardiac alterations due to diabetes mellitus<sup>182</sup>.

A major concern for this technique is its external validity. After an algorithm has been identified, an important next step is to confirm whether this algorithm remains accurate when new data are applied. Generally, data are required for both training data (for developing the algorithm) and testing data (new data, for applying this algorithm) to validate this algorithm. When external validation is not feasible, the same dataset is subdivided, and the validation is performed iteratively on data not used for derivation (x-fold cross validation).

Importantly, ML approach depends on the quality of supplied data, incorporated variables and the appropriateness of method/software used. In the following, we propose examples (i.e., cohorts, parameters and methods) to explore diagnostic and prognostic values of an integrated congestion approach using ML.

**Table 2. Machine learning approach (Adapted from Dey et al. <sup>187</sup>)**

<b>Supervised</b>		
<b>Support machines</b>	<b>vector</b>	Whereas regression analysis may identify linear associations, support vector machines provide nonlinear models by defining “planes” in higher-dimension that best separate out features into groups that predict outcomes.
<b>Random forests</b>		Identify the best cut point values in different features of individual groups of related data to be able to separate them out to predict a particular outcome.
<b>Convolved networks (CNN)</b>	<b>neural</b>	A multilayered network, often applied to image processing, simulating some of the properties of the human visual cortex. A mathematical model is used to pass on results to successive layers.
<b>Deep learning (often described as CNN)</b>	<b>as</b>	This technique is defined as a class of artificial neural network algorithms, in which more internal layers are used than in traditional neural network approaches (“deep” merely describes a multilayered separation approach).
<b>Unsupervised</b>		
<b>Principal analysis</b>	<b>component</b>	Simple form of unsupervised learning in which the features that account for the most variation in a dataset can be identified.
<b>Hierarchical clustering</b>		<p>Creates a hierarchical decomposition of the data based on similarity with another cluster by aggregating them (an agglomerative approach) or dividing them as it moves down in hierarchy (a divisive approach).</p> <p>*Strength - easy comprehension and illustration using dendrograms, insensitive too utliers.</p> <p>*Difficulty - arbitrary metric and linkage criteria, does not work with missing data, may lead to misinterpretation of the dendrogram, difficulty finding optimal solution.</p>
<b>Partition algorithms (K-means clustering)</b>		<p>Form of cluster analysis that identifies degree of separation of different features within a dataset and tries to find groupings in which features are most differentiated. It does this by defining similarity on the basis of proximity to the centroid (mean, median, or medoid) of the cluster. The algorithm modulates the data to build the cluster by iteratively evaluating the distance from the centroid.</p> <p>*Strengths - simple and easy to implement, easy to interpret, fast, and efficient. Has remained relatively underutilized in cardiology despite its simplicity in implementation and interpretation.</p> <p>*Difficulty - uniform cluster size, may work poorly with different densities of clusters, difficult to find k, sensitive to outliers.</p>
<b>Model-based algorithm</b>		<p>This clustering algorithm makes a general assumption that the data in each cluster is generated from probabilistic (primarily Gaussian) model.</p> <p>*Strengths - distributional description for components, possible to assess clusters-within-clusters, can make inference about the number of clusters.</p> <p>*Difficulties - computationally intensive, can be slow to converge</p>

## **7.2.2 Diagnosis value for acute heart failure of machine learning based integration of congestion markers**

### **7.2.2.1 Included cohorts**

PARADISE cohort and PURPLE cohort.

### **7.2.2.2 Candidate variables**

- Demographic data  
age, sex, body mass index
- Medical history  
hypertension, diabetes, prior HF hospitalization, coronary artery disease, myocardial infarction, atrial fibrillation/flutter, chronic obstructive pulmonary disease
- Physical examinations  
systolic blood pressure, heart rate, respiratory rate, saturated oxygen
- Clinical congestion data  
leg edema, jugular venous distention, rales, dyspnea pattern, hepatomegaly, NYHA class
- Biological congestion data  
hemoglobin, hematocrit, sodium, potassium, blood urea nitrogen, estimated glomerular filtration rate, NPs, ePVS
- Imaging congestion data  
CSI  
Lung ultrasound (when available)  
Echocardiographic data (when available)

### **7.2.2.3 Outcomes**

- Discharge diagnosis of AHF

### **7.2.2.4 Machine learning approach**

As a first approach, logistic regression with a lasso regularization for variable selection

Then, supervised ML based on random forests will be used to build diagnostic model for AHF in the derivation cohort (PARADISE). This random forest model will be validated in the PURPLE cohort. All candidate variables with low missing data (<10%) will be incorporated in this model. Random forest will permit a classification of most important variables. In addition, decision trees could be constructed to provide a tool that could be readily used in clinical practice, based on all available data in the emergency department.

### **7.2.3 Prognostic value of integrated congestion approach derived from machine learning methods**

#### **7.2.3.1 Included cohorts**

AHF-CORE (derivation cohort), Pooled patient data from the European countries (validation cohort)

#### **7.2.3.2 Candidate variables**

- Demographic data  
age, sex, body mass index
- Medical history  
hypertension, diabetes, prior HF hospitalization, coronary artery disease, myocardial infarction, atrial fibrillation/flutter, chronic obstructive pulmonary disease
- Physical examinations (admission and discharge)  
systolic blood pressure, heart rate, respiratory rate
- Clinical congestion data (admission and discharge)  
leg edema, jugular venous distention, rales, hepatomegaly, NYHA class
- Biological congestion data (admission and discharge)  
hemoglobin, hematocrit, sodium, potassium, blood urea nitrogen, estimated glomerular filtration rate, NPs, ePVS
- Imaging congestion data (admission and discharge)  
Detailed echocardiography and lung ultrasound data

#### **7.3.3.3 Outcomes**

- the composite of cardiovascular mortality and/or HF (re) hospitalization
- the composite of all-cause mortality and/or HF (re) hospitalization
- cardiovascular mortality
- all-cause mortality
- HF (re) hospitalization

#### **7.3.3.4 Machine learning approach**

Random forest will be used to build prognostic model in derivation (AHF-CORE) and validation (pooled European database) cohorts. All candidate variables with low missing data (<10%) will be incorporated in this model. In addition, a decision tree taking into account survival analysis (p.e. the CART algorithm) constructed in the AHF-CORE cohort could be applied in the pooled European database to ensure its external validity.



### 7.3. Artificial intelligence approach to Congestion Score index

An important issue of novel imaging techniques is related to their generalizability. This obviously remains true for imaging congestion markers since these markers may be limited by the somewhat subjective and qualitative nature of their interpretation. However, recently, deep learning, a branch of ML, has been used to analyze cardiovascular imaging to measure cardiac function, assess coronary artery stenosis and predict incident HF<sup>189-191</sup>. This novel approach may confer an objective and quantitative evaluation of imaging, and previous studies showed the possibility that deep learning-based assessment may provide better diagnostic values than experienced clinicians<sup>192, 193</sup>.

We intend to first use this approach on chest radiography and determine whether neural networks applied on chest radiography can identify new approaches to this imaging technique to better diagnose AHF. This could be readily performed from the “initial” version of the PARADISE cohort. In addition, the correlation between artificial intelligence evaluation and CSI could be evaluated. This approach would use artificial intelligence not in the integration of data measured by men, but would actually measure directly, from raw data, relevant information that can predict the presence of AHF in the emergency department.

### 7.4. Integration of congestion markers in electronic healthcare records

Random forests derived models, that cannot be applied following a simple rule in each patient, will likely have better intrinsic performance than decision tree models in the analysis described above. This could greatly limit the implementation of these ML-based tools in clinical practice. However, creating online apps on which physician would enter the data to obtain the prediction of the model could overcome this difficulty. Yet, this solution could be very time consuming and constitute an important barrier in the development of these approaches.

Beyond these implementation difficulties, Cook et al. reported, based on guidelines, the overestimation of the pooled cohort equations in primary prevention external cohorts, and suggested the possibility of real-time calibration of risk prediction equations with big data analytics<sup>188</sup>. This suggests that an evolution of the model is advisable, to prevent mid-term mismatch with changes in medical practice.

To overcome these difficulties, it is likely that embedding the ML-based models within health records will both decrease the time needed for physicians/health professionals to obtain model outputs and prevent model mismatch. In clinical practice, there are large amounts of accessible data including electronic medical records (i.e. health records, prescribing and outcome data), patient data (i.e. life style, activity and diet) and image-derived data (i.e., chest radiography, echocardiography and lung ultrasound). In the future, we will be able to recode unstructured data from patient files into structured data (as in the dataset of a cohort study) using text mining. Following this step, algorithms could incorporate these “big” clinical data to provide diagnostic score of AHF and prognostic score in patients with HF (**Figure 6**). Moreover, this prediction score may be improved by the accumulating evidence from the literature, and such personalized medicine could help and perhaps guide clinicians manage patients with HF in the similar way that a proficient expert would.

The increasing availability of automated real-time evaluation in electronic health records (EHRs) could provide in the future more precise and clinically relevant patient information about congestion assessment, while not increasing the workload of doctors and nurses (data entry, modeling and calculation being imbedded within the routine healthcare file). We believe this could constitute the future of congestion evaluation, and possibly, more generally of medicine.



## 8. Conclusion

We showed the clinical utility of readily and widely available congestion markers evaluated from chest radiography and hemoglobin/hematocrit. Estimated Plasma Volume, Congestion Score indexed evaluated from chest radiography and their combination provide better diagnostic performance and patient risk-stratification in patients with HF, while reflecting the severity of congestion. Sequential assessments of these congestion markers may help clinicians determine the “best” timing of (re-) hospitalization for HF and discharge in patients with HF in the future. Additional research, probably targeting the integration of all congestion evaluation, are needed.

## 9. Articles

9.1. Congestion Score Index Evaluated from Chest Radiography for Diagnosing Acute Heart Failure in the Emergency Department: insights from the PARADISE cohort (submitted in PLOS Medicine)

9.2. Mid-term prognostic impact of residual pulmonary congestion assessed by radiographic scoring in patients admitted for worsening heart failure (published in Int J Cardiol)

9.3. Association of Estimated Plasma Volume Status with Hemodynamic and Echocardiographic Parameters (published in Clin Res Cardiol)

9.4. Prognostic value of estimated plasma volume in acute heart failure in three cohort studies (published in Clin Res Cardiol)

9.5. Prognostic Impact of Plasma Volume Estimated from Hemoglobin and Hematocrit in Heart Failure with Preserved Ejection Fraction (published in Clin Res Cardiol)

9.6. Estimated plasma volume status in heart failure: Clinical implications and future directions (submitted in European Journal Heart Failure)

9.7. Chest X-ray Quantification of Admission Lung Congestion as a Prognostic Factor in Patients Admitted for Worsening Heart Failure from the ICALOR Cohort Study (published in Int J Cardiol)



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### Abstract (English version)

Congestion generally expresses systemic and pulmonary edema associated with elevated intracardiac pressure and is a major predictor of poor prognosis in patients with heart failure (HF). Therefore, it is of paramount importance to best assess and monitor congestion at each point of patient management (i.e., before progression to decompensation, emergency department (ED), hospital stay, prior discharge assessment and outpatient clinic). Accumulated data highlighted that several evaluation tools of congestion derived from clinical, biological, imaging and hemodynamic markers/parameters can help clinicians diagnose acute HF, understand the underlying causes and manage optimally patients with chronic HF or acutely decompensated HF. However, the availability of these congestion markers may limit their clinical utility. Readily and widely available evaluation tool is warranted to quantify and/or monitor congestion and eventually improve risk-stratification. Congestion score evaluated from chest radiography and plasma volume (PV) estimated from hemoglobin and hematocrit may provide relevant information in patients with HF.

Our specific aims were; 1) to evaluate the diagnostic and prognostic performance of radiographic pulmonary congestion quantification in patients with acute dyspnea; 2) to evaluate the clinical and prognostic implications of estimated PV quantification in patients with HF; and 3) to assess the prognostic value of the combination of these congestion markers in patients hospitalized for worsening HF.

In this PhD, we showed that radiographic congestion score improve diagnostic performance for acute HF in dyspneic patients in the ED on top of clinical variables and have a diagnostic accuracy of similar magnitude to natriuretic peptide. In addition, we showed that residual radiographic pulmonary congestion (rather than admission congestion) convey a worse prognosis in patients admitted for acute HF in Cardiology and ED.

We investigated the associations of estimated PV with well-known biological, echocardiographic and hemodynamic markers of congestion and showed that estimated PV acts rather as a left-sided congestion marker and is an independent prognostic marker in acutely decompensated HF (in three international cohorts) and ambulatory HF with preserved ejection fraction (in the TOPCAT trial). Furthermore, the prognostic value of the combination of radiographic congestion score and estimated PV on admission in patients hospitalized for worsening HF in cardiology department appears as a promising prognostic approach for in-hospital outcomes and post-discharge short-term outcomes.

Our work shows the clinical relevance of radiographic-based pulmonary congestion scoring, estimated PV and their combination (exploring different components of congestion) in patients with HF. The integration of multiple congestion markers may provide, in the future, more pragmatic, useful and personalized congestion profiling in HF.

### Abstract (Version française)

La congestion réfère aux œdèmes pulmonaires et systémiques habituellement observés dans un contexte d'augmentation des pressions intracardiaques. C'est un prédicteur majeur de mauvais pronostic en insuffisance cardiaque (IC). Une meilleure évaluation et quantification de la congestion au cours du parcours de soins (en amont d'une décompensation, aux urgences, en cours d'hospitalisation et en contexte ambulatoire) est souhaitable pour améliorer la stratification du risque et le management de ces patients. Des outils d'évaluation de la congestion facilement accessibles et d'utilisation simple seraient utiles dans ce contexte.

Au cours de ce doctorat, nous avons étudié un score de congestion estimé à partir de la radiographie pulmonaire ainsi que le volume plasmatique estimé à partir de l'hémoglobine et de l'hématocrite sanguine. Notre but était d'évaluer la pertinence de ces paramètres de congestion en IC. Nous avons donc évalué 1) la capacité diagnostique et pronostique du score de congestion pulmonaire radiologique dans le contexte de la dyspnée aigue, 2) les implications cliniques et pronostiques de la quantification du volume plasmatique estimé en IC et 3) l'utilité de la combinaison de ces 2 variables en IC décompensée.

Nous avons dans un premier temps montré que le score radiologique de congestion pulmonaire améliore la performance diagnostique pour l'IC chez des patients admis pour dyspnée aigue aux urgences, en plus de l'utilisation de variables cliniques et que la capacité diagnostique atteinte égale celle des peptides natriurétiques. Nous avons aussi observé que la congestion pulmonaire radiologique résiduelle (plutôt que la congestion initiale) était associée au pronostic de patients admis pour IC décompensée.

Nous avons évalué l'association du volume plasmatique estimé avec des variables biologiques, échographiques et hémodynamiques de congestion et montré que le volume plasmatique estimé est un marqueur de congestion préférentiellement gauche (comme les peptides natriurétiques et les pressions de remplissage ventriculaire). Nous avons montré que le volume plasmatique estimé était indépendamment associé au pronostic des patients en IC décompensée (dans 3 cohortes internationales) et en IC ambulatoire avec fraction d'éjection préservée (dans l'essai clinique TOPCAT). Nous avons aussi montré qu'une approche combinée du score radiologique de congestion pulmonaire et du volume plasmatique estimé chez des patients IC avait une valeur importante pour la stratification du risque intra-hospitalier et dans les suites de l'hospitalisation.

Notre travail souligne l'utilité clinique du score radiologique de congestion pulmonaire, du volume plasmatique estimé et de leur évaluation conjointe dans le champ de l'IC. Dans la lignée de ces travaux, une intégration des marqueurs de congestion au sein d'une démarche multi-paramétrique pourrait apporter une meilleure caractérisation du profil congestif individuel des patients insuffisants cardiaques.

**Keywords,** heart failure, congestion, chest radiography, plasma volume, prognosis.